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BURNS COUNTRY

Everything you wanted to know about Robert Burns, Scotland's national bard (and lots more besides). Please let us know if anything's missing, wrong, or just plain wonderful

AULD LANG SYNE
Words | **Karaoke!**

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Complete Works

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To A Mouse, On Turning Her Up In Her Nest With The Plough

1785
Type: **Poem**

Wee, sleekit, cow'rin, tim'rous beastie,
O, what a panic's in thy breastie!
Thou need na start awa sae hasty,
Wi' bickering brattle!
I wad be laith to rin an' chase thee,
Wi' murd'ring pattle!

I'm truly sorry man's dominion,
Has broken nature's social union,
An' justifies that ill opinion,
Which makes thee startle
At me, thy poor, earth-born companion,
An' fellow-mortal!

I doubt na, whiles, but thou may thieve;
What then? poor beastie, thou maun live!
A daimen icker in a thrave
'S a sma' request;

I'll get a blessin wi' the lave,
An' never miss't!

Thy wee bit housie, too, in ruin!
It's silly wa's the win's are strewin!
An' naething, now, to big a new ane,
O' foggage green!
An' bleak December's winds ensuin,
Baith snell an' keen!

Thou saw the fields laid bare an' waste,
An' weary winter comin fast,
An' cozie here, beneath the blast,
Thou thought to dwell-
Till crash! the cruel coulter past
Out thro' thy cell.

That wee bit heap o' leaves an' stibble,
Has cost thee mony a weary nibble!
Now thou's turn'd out, for a' thy trouble,
But house or hald,
To thole the winter's sleety dribble,
An' cranreuch cauld!

But, Mousie, thou art no thy lane,
In proving foresight may be vain;
The best-laid schemes o' mice an 'men
Gang aft agley,
An'lea'e us nought but grief an' pain,
For promis'd joy!

Still thou art blest, compar'd wi' me
The present only toucheth thee:
But, Och! I backward cast my e'e.
On prospects drear!
An' forward, tho' I canna see,
I guess an' fear!

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International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 77

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9); Resolution EB115.R4 (EB115/2005/REC/1)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–113) and Recommended (1–74) International Nonproprietary Names can be found in *Cumulative List No. 16, 2015* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 77

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9); résolution EB115.R4 (EB115/2005/REC/1)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–113) et recommandées (1–74) dans la *Liste récapitulative No. 16, 2015* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 77

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9); Résolution EB115.R4 (EB115/2005/REC/1) EB115.R4 (EB115/2005/REC/1)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–113) y Recomendadas (1–74) se encuentran reunidas en *Cumulative List No. 16, 2015* (disponible sólo en CD-ROM).

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

adegramotidum

adegramotide — human Wilms tumor protein (WT33)-(34-51)-peptide

adégramotide — protéine tumorale de Wilms humaine (WT33)-(34-51)-peptide

adegramotida — proteína tumoral de Wilms humana (WT33)-(34-51)-péptido

$C_{87}H_{123}N_{19}O_{24}$

H—Trp—Ala—Pro—Val—Leu—Asp—Phe—Ala—Pro—
—Pro—Gly—Ala—Ser—Ala—Tyr—Gly—Ser—Leu—OH
10 18

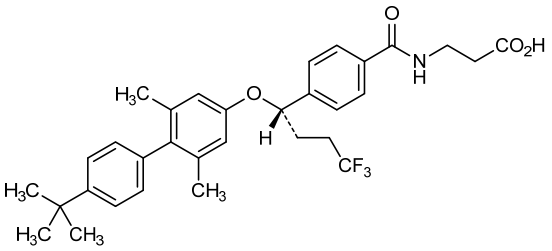
adomeglivantum

adomeglivant — 3-(4-{(1*S*)-1-[(4'-*tert*-butyl-2,6-dimethyl[1,1'-biphenyl]-4-yl)oxy]-4,4,4-trifluorobutyl}benzamido)propanoic acid

adoméglivant — acide 3-(4-{(1*S*)-1-[(4'-*tert*-butyl-2,6-diméthyl[1,1'-biphényl]-4-yl)oxy]-4,4,4-trifluorobutyl}benzamido)propanoïque

adomeglivant — ácido 3-(4-{(1*S*)-1-[(4'-*terc*-butil-2,6-dimetil[1,1'-bifenil]-4-il)oxi]-4,4,4-trifluorobutil}benzamido)propanoico

$C_{32}H_{36}F_3NO_4$



afabicinum

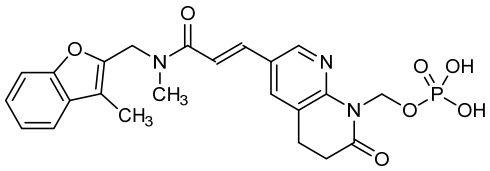
afabicin — {6-[(1*E*)-3-{methyl[(3-methyl-1-benzofuran-2-yl)methyl]amino}-3-oxoprop-1-en-1-yl]-2-oxo-3,4-dihydro-1,8-naphthyridin-1(2*H*)-yl}methyl dihydrogen phosphate

afabicine — dihydrogénophosphate de {6-[(1*E*)-3-{méthyl[(3-méthyl-1-benzofuran-2-yl)méthyl]amino}-3-oxoprop-1-én-1-yl]-2-oxo-3,4-dihydro-1,8-naphtyridin-1(2*H*)-yl}méthyle

afabicina

dihidrogenofosfato de {6-[(1*E*)-3-{metil[(3-metil-1-benzofuran-2-il)metil]amino}-3-oxoprop-1-en-1-il]-2-oxo-3,4-dihidro-1,8-naftiridin-1(2*H*)-il}metilo

$C_{23}H_{24}N_3O_7P$



alicapistatum

alicapistat

(2*R*)-1-benzyl-*N*-[(2*RS*)-4-(cyclopropylamino)-3,4-dioxo-1-phenylbutan-2-yl]-5-oxopyrrolidine-2-carboxamide

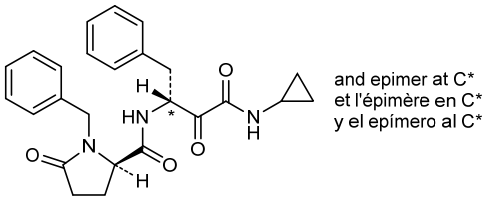
alicapistat

(2*R*)-1-benzyl-*N*-[(2*RS*)-4-(cyclopropylamino)-3,4-dioxo-1-phénylbutan-2-yl]-5-oxopyrrolidine-2-carboxamide

alicapistat

(2*R*)-1-bencil-*N*-[(2*RS*)-4-(ciclopropilamino)-1-fenil-3,4-dioxobutan-2-il]-5-oxopirrolidina-2-carboxamida

$C_{25}H_{27}N_3O_4$



and epimer at C*
et l'épimère en C*
y el epímero al C*

alidornasum alfa #

alidornase alfa

N$^{2.1}$-glycyl-deoxyribonuclease I (DNase I), human, produced in *Nicotiana tabacum* cell culture, glycoform alfa, chemically amidated by condensation of an average of about 10-12 molecules of ethane-1,2-diamine per enzyme molecule with free carboxy groups to give *N*-(2-aminoethyl) carboxamide groups (about 7 per molecule on average) and intramolecularly *N*,*N*'-(ethane-1,2-diyl)-bridged pairs of carboxamide groups

alidornase alfa

N$^{2.1}$-glycyl-déoxyribonucléase I (DNase I), humaine, produite par cultures de cellules de *Nicotiana tabacum*, glycoforme alfa, formant des fonctions amides par condensation chimique d'en moyenne environ 10-12 molécules d'éthane-1,2-diamine par molécule d'enzyme avec des groupes carboxy libres pour donner des groupes *N*-(2-aminoéthyl) carboxamide (environ 7 par molécule en moyenne) et des ponts intramoléculaires de groupes *N*,*N*'-(éthane-1,2-diyl) entre des paires de groupes carboxamides

alidornasa alfa

$N^{2.1}$-glicil-desoxiribonucleasa I (DNasa I), humana, producida en cultivos de células de *Nicotiana tabacum*, glicoforma alfa, glicoforma alfa, formadora de funciones amidas por condensación química por término medio de 10-12 moléculas de etano-1,2-diamina por molécula de enzima con grupos carboxi libres para proporcionar grupos *N*-(2-aminoetil) carboxamida (aproximadamente 7 por molécula por término medio) y los puentes intramoleculares de grupos *N,N'*-(etano-1,2-diil) entre pares de grupos carboxamidas

```
GLKIAAFNIQ TFGETKMSNA TLVSYIVQIL SRYDIALVQE VRDSHLTAVG 50
KLLDNLNQDA PDTYHYVVSE PLGRNSYKER YLFVYRPDQV SAVDSYYYDD 100
GCEPCGNDTF NREPAIVRFF SRFTEVREFA IVPLHAAPGD AVAEIDALYD 150
VYLDVQEKWG LEDVMLMGDF NAGCSYVRPS QWSSIRLWTS PTFQWLIPDS 200
ADTTATPTHC AYDRIVVAGM LLRGAVVPDS ALPFNFQAAY GLSDQLAQAI 250
SDHYPVEVML K                                          261
```

Disulfide bridges location / position des ponts disulfure / posiciones de los puentes disulfuro
102-105, 174-210
N-glycosylation sites / sites de N-glycosylation / sitios de N-glicosilación
Asn 19, Asn 107
Ethane-1,2-diamine modification sites: Asp and Glu residues and C-terminal

andecaliximabum #

andecaliximab

immunoglobulin G4-kappa, anti-[*Homo sapiens* MMP9 (matrix metallopeptidase 9, gelatinase B)], chimeric monoclonal antibody;
gamma4 heavy chain (1-442) [chimeric VH (*Mus musculus* IGHV2-9*02 -(IGHD) -*Homo sapiens* IGHJ4*01) [8.7.9] (1-115), *Homo sapiens* IGHG4*01 (CH1 (116-213), hinge S10>P (223) (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)) (116-442)], (129-214')-disulfide with kappa light chain (1'-214') [chimeric V-KAPPA (*Mus musculus* IGKV6-17 -*Homo sapiens* IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (221-221":224-224")-bisdisulfide

andécaliximab

immunoglobuline G4-kappa, anti-[*Homo sapiens* MMP9 (matrice métallopeptidase 9, gélatinase B)], anticorps monoclonal chimérique;
chaîne lourde gamma4 (1-440) [VH chimérique (*Mus musculus* IGHV2-9*02 -(IGHD) -*Homo sapiens* IGHJ4*01) [8.7.9] (1-115), *Homo sapiens* IGHG4*01 (CH1 (116-213), charnière S10>P (223) (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)) (116-442)], (129-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA chimérique (*Mus musculus* IGKV6-17 -*Homo sapiens* IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (221-221":224-224")-bisdisulfure

andecaliximab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* MMP9 (matriz metalopeptidasa 9, gelatinasa B)], anticuerpo monoclonal quimérico;
cadena pesada gamma4 (1-440) [VH quimérico (*Mus musculus* IGHV2-9*02 -(IGHD) -*Homo sapiens* IGHJ4*01) [8.7.9] (1-115), *Homo sapiens* IGHG4*01 (CH1 (116-213), bisagra S10>P (223) (214-225), CH2 (226-335), CH3 (336-440), CHS (441-442)) (116-442)], (129-214')-disulfuro con

la cadena ligera kappa (1'-214') [V-KAPPA quimérico (*Mus musculus* IGKV6-17 -*Homo sapiens* IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (221-221":224-224")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSETLSL TCTVSGFSLL SYGVHWVRQP PGKGLEWLGV  50
IWTGGTTNYN SALMSRFTIS KDDSKNTVYL KMNSLKTEDT AIYYCARYYY 100
GMDYWGQGTL VTVSSASTKG PSVFPLAPCS RSTSESTAAL GCLVKDYFPE 150
PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV 200
DHKPSNTKVD KRVESKYGPP CPPCPAPEFL GGPSVFLFPP KPKDTLMISR 250
TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTYRVVSV 300
LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE PQVYTLPPSQ 350
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF 400
LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL GK         442
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQDVR NTVAWYQQKP GKAPKLLIYS  50
SSYRNTGVPD RFSGSGSGTD FTLTISSLQA EDVAVYYCQQ HYITPYTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-95 142-198 256-316 362-420
22"-95" 142"-198" 256"-316" 362"-420"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (CH1 10-CL 126) 129-214' 129"-214"'
Inter-H-H (h 8, h 11) 221-221" 224-224"

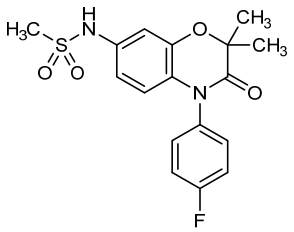
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
292, 292"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

apararenonum
apararenone — *N*-[4-(4-fluorophenyl)-2,2-dimethyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl]methanesulfonamide

apararénone — *N*-[4-(4-fluorophényl)-2,2-diméthyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl]méthanesulfonamide

apararenona — *N*-[4-(4-fluorofenil)-2,2-dimetil-3-oxo-3,4-dihidro-2*H*-1,4-benzoxazin-7-il]metanosulfonamida

$C_{17}H_{17}FN_2O_4S$

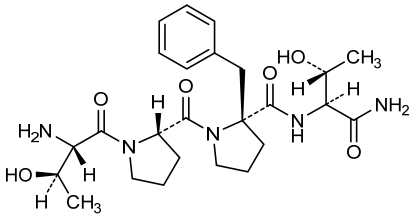


apimostinelum
apimostinel — L-threonyl-L-prolyl-2-benzyl-L-prolyl-L-threoninamide

apimostinel — L-thréonyl-L-prolyl-2-benzyl-L-prolyl-L-thréoninamide

apimostinel — L-treonil-L-prolil-2-bencil-L-prolil-L-treoninamida

$C_{25}H_{37}N_5O_6$



aprutumabum #

aprutumab	immunoglobulin G1-lambda1, anti-[*Homo sapiens* FGFR2 (fibroblast growth factor receptor 2, keratinocyte growth factor receptor, KGFR, CD332)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), hinge (221-235), CH2 (236-345), CH3 (346-450),CHS K>del (451)) (123-451)], (225-215')-disulfide with lambda1 light chain (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dimer (231-231'':234-234'')-bisdisulfide
aprutumab	immunoglobuline G1-lambda1, anti-[*Homo sapiens* FGFR2 (récepteur 2 du facteur de croissance des fibroblastes, récepteur du facteur de croissance des kératinocytes, KGFR, CD332)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), charnière (236-345), CH2 (236-345), CH3 (346-450), CHS K>del (451)) (123-451)], (225-215')-disulfure avec la chaîne légère lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dimère (231-231'':234-234'')-bisdisulfure
aprutumab	inmunoglobulina G1-lambda1, anti-[*Homo sapiens* FGFR2 (receptor 2 del factor de crecimiento de los fibroblastos, receptor del factor de crecimiento de los queratinocitos, KGFR, CD332)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), bisagra (236-345), CH2 (236-345), CH3 (346-450), CHS K>del (451)) (123-451)], (225-215')-disulfuro con la cadena ligera lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dímero (231-231'':234-234'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA  50
ISGSGTSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARVR 100
YNWNHGDWFD PWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
G                                                       451
```

Light chain / Chaîne légère / Cadena ligera

```
QSVLTQPPSA SGTPGQRVTI SCSGSSSNIG NNYVSWYQQL PGTAPKLLIY  50
ENYNRPAGVP DRFSGSKSGT SASLAISGLR SEDEADYYCS SWDDSLNYWV 100
FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV 150
AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT 200
HEGSTVEKTV APTECS                                       216
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 149-205 266-326 372-430
22"-96" 149"-205" 266"-326" 372"-430"
Intra-L (C23-C104) 22'-89' 138'-197'
22'"-89'" 138'"-197'"
Inter-H-L (h 5-CL 126) 225-215' 225"-215"
Inter-H-H (h 11, h 14) 231-231' 234-234"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

aprutumabum ixadotinum #

aprutumab ixadotin

immunoglobulin G1-lambda1, anti-[*Homo sapiens* FGFR2 (fibroblast growth factor receptor 2, keratinocyte growth factor receptor, KGFR, CD332)], *Homo sapiens* monoclonal antibody conjugated to an auristatin W derivative;
gamma1 heavy chain (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), hinge (221-235), CH2 (236-345), CH3 (346-450),CHS K>del (451)) (123-451)], (225-215')-disulfide with lambda1 light chain (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dimer (231-231":234-234")-bisdisulfide; conjugated, on an average of 4 lysyl, to *N*-(5-carboxypentyl)-*N*-demethyl-auristatin W (AW) $C^{1.5}$-(1,2-oxazinan-2-yl) derivative

aprutumab ixadotine

immunoglobuline G1-lambda1, anti-[*Homo sapiens* FGFR2 (récepteur 2 du facteur de croissance des fibroblastes, récepteur du facteur de croissance des kératinocytes, KGFR, CD332)], *Homo sapiens* anticorps monoclonal conjugué à un dérivé de l'auristatine W;
chaîne lourde gamma1 (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), charnière (236-345), CH2 (236-345), CH3 (346-450), CHS K>del (451)) (123-451)], (225-215')-disulfure avec la chaîne légère lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dimère (231-231":234-234")-bisdisulfure; conjugué, sur 4 lysyl en moyenne, au dérivé $C^{1.5}$-(1,2-oxazinan-2-yle) de *N*-(5-carboxypentyl)-*N*-desméthyl-auristatine W (AW)

aprutumab ixadotina

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* FGFR2 (receptor 2 del factor de crecimiento de los fibroblastos, receptor del factor de crecimiento de los queratinocitos, KGFR, CD332)], *Homo sapiens* anticuerpo monoclonal conjugado a un derivado de la auristatina W; cadena pesada gamma1 (1-451) [*Homo sapiens* VH (IGHV3-23*01 (98.00%) -(IGHD) -IGHJ5*02) [8.8.15](1-122) -IGHG1*01, Gm17,1 (CH1 (123-220), bisagra (236-345), CH2 (236-345), CH3 (346-450), CHS K>del (451)) (123-451)], (225-215')-disulfuro con la cadena ligero lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (90.70%) -IGLJ3*02) [8.3.11] (1'-110') -IGLC2*01 (111'-216')]; dímero (231-231":234-234")-bisdisulfuro; conjugado, en 4 grupos lisil por término medio, con el derivado $C^{1.5}$-(1,2-oxazinan-2-ilo) de *N*-(5-carboxipentil)-*N*-desmetil-auristatina W (AW)

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA  50
ISGSGTSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARVR 100
YNWNHGDWFD PWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
G                                                       451
```

Light chain / Chaîne légère / Cadena ligera

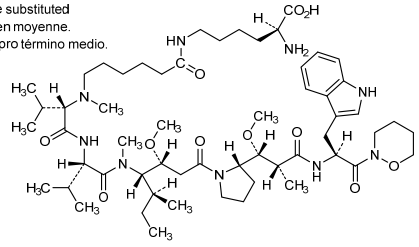
```
QSVLTQPPSA SGTPGQRVTI SCSGSSSNIG NNYVSWYQQL PGTAPKLLIY  50
ENYNRPAGVP DRFSGSKSGT SASLAISGLR SEDEADYYCS SWDDSLNYWV 100
FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV 150
AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT 200
HEGSTVEKTV APTECS                                      216
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	149-205	266-326	372-430
	22"-96"	149"-205"	266"-326"	372"-430"
Intra-L (C23-C104)	22'-89'	138'-197'		
	22'"-89'"	138'"-197'"		
Inter-H-L (h 5-CL 126)	225-215'	225"-215'"		
Inter-H-H (h 11, h 14)	231-231'	234-234"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales
An average of 4 lysyl are substituted
4 lysyls sont substitués en moyenne.
4 lisils estan sustituidos pro término medio.



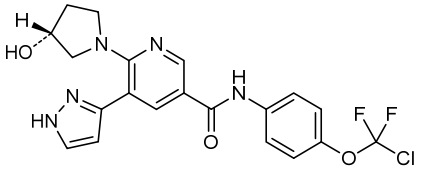
asciminibum

asciminib — *N*-[4-(chlorodifluoromethoxy)phenyl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl)pyridine-3-carboxamide

asciminib — *N*-[4-(chlorodifluorométhoxy)phényl]-6-[(3*R*)-3-hydroxypyrrolidin-1-yl]-5-(1*H*-pyrazol-3-yl)pyridine-3-carboxamide

asciminib — *N*-[4-(clorodifluorometoxi)fenil]-6-[(3*R*)-3-hidroxipirrolidin-1-il]-5-(1*H*-pirazol-3-il)piridina-3-carboxamida

$C_{20}H_{18}ClF_2N_5O_3$



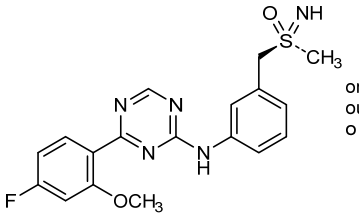
atuveciclibum

atuveciclib — (+)-[(3-{[4-(4-fluoro-2-methoxyphenyl)-1,3,5-triazin-2-yl]amino}phenyl)methyl](imino)(methyl)-λ^6-sulfanone

atuvéciclib — (+)-[(3-{[4-(4-fluoro-2-méthoxyphényl)-1,3,5-triazin-2-yl]amino}phényl)méthyl](imino)(méthyl)-λ^6-sulfanone

atuveciclib — (+)-[(3-{[4-(4-fluoro-2-metoxifenil)-1,3,5-triazin-2-il]amino}fenil)metil](imino)(metil)-λ^6-sulfanona

$C_{18}H_{18}FN_5O_2S$



or enantiomer
ou énantiomère
o enantiómero

audencelum

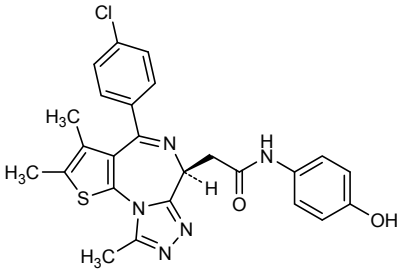
audencel — autologous interleukin (IL)-12-secreting dendritic cells (DCs), loaded with autologous tumour lysate, comprising >70% of total immune cells. The cells are differentiated from autologous monocytes by culturing in the presence of interleukin (IL)-4 and GM-CSF (granulocyte-macrophage colony-stimulating factor), following which they are exposed to the patient's tumor protein/tumor-associated antigen (TAA), and subsequently to lipopolysaccharide (LPS) in the presence of interferon gamma (IFN-γ) to enable IL-12 secretion.

audencel	cellules dendritiques autologues secrétant de l'interleukine-12 (IL-12), chargées avec un lysat de tumeur autologue, comprenant plus de 70% du total des cellules immunitaires. Les cellules sont différenciées à partir de monocytes autologues par une culture en présence d'interleukine-4 (IL-4) et de facteur de stimulation des colonies de granulocytes et de macrophages (GM-CSF), ensuite elles sont exposées à la protéine tumorale/antigène associé à la tumeur du patient, puis au lipopolysaccharide (LPS) en présence d'interféron gamma (IFN- γ) afin de permettre la sécrétion d'IL-12.
audencel	células dendríticas autólogas que secretan la interleukina-12 (IL-12), cargadas con un lisado de tumor autólogo, que comprende más del 70% del total de células inmunitarias. Las células se diferencian a partir de monocitos autólogos a través de un cultivo en presencia de interleukina-4 (IL-4) y del factor de estimulación de las colonias de granulocitos y de macrófagos (GM-CSF), a continuación ellas se exponen a la proteína tumoral/antigénica asociada al tumor del paciente (TAA), y después al lipopolisacárido (LPS) en presencia del interferón gamma (IFN-γ) para permitir la secreción de la IL-12.

birabresibum

birabresib	2-[(6*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl]-*N*-(4-hydroxyphenyl)acetamide
birabrésib	2-[(6*S*)-4-(4-chlorophényl)-2,3,9-triméthyl-6*H*-thiéno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazépin-6-yl]-*N*-(4-hydroxyphényl)acétamide
birabresib	2-[(6*S*)-4-(4-clorofenil)-2,3,9-trimetil-6*H*-tieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-il]-*N*-(4-hidroxifenil)acetamida

$C_{25}H_{22}ClN_5O_2S$



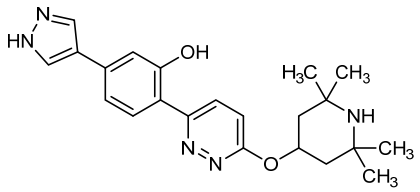
branaplamum

branaplam	5-(1*H*-pyrazol-4-yl)-2-{6-[(2,2,6,6-tetramethylpiperidin-4-yl)oxy]pyridazin-3-yl}phenol
branaplam	5-(1*H*-pyrazol-4-yl)-2-{6-[(2,2,6,6-tétraméthylpipéridin-4-yl)oxy]pyridazin-3-yl}phenol

branaplam

5-(1*H*-pirazol-4-il)-2-{6-[(2,2,6,6-tetrametilpiperidin-4-il)oxi]piridazin-3-il}fenol

$C_{22}H_{27}N_5O_2$



brazikumabum #

brazikumab

immunoglobulin G2-lambda, anti-[*Homo sapiens* IL23A (interleukin 23 subunit alpha, IL-23A, IL-23 subunit p19, IL23p19)], *Homo sapiens* monoclonal antibody; gamma2 heavy chain (1-450) [*Homo sapiens* VH (IGHV3-33*01 (99.00%) -(IGHD)-IGHJ3*02) [8.8.17] (1-124) -IGHG2*01, G2m.. (CH1 (125-222), hinge (223-234), CH2 (235-343), CH3 (344-448), CHS (449-450)) (125-450)], (138-216')-disulfide with lambda light chain (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-40*01 (96.00%) -IGLJ3*02) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimer (226-226'':227-227'':230-230'':233-233'')-tetrakisdisulfide

brazikumab

immunoglobuline G2-lambda, anti-[*Homo sapiens* IL23A (interleukine 23 sous-unité alpha, IL-23A, IL-23 sous-unité p19, IL23p19)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma2 (1-450) [*Homo sapiens* VH (IGHV3-33*01 (99.00%) -(IGHD)-IGHJ3*02) [8.8.17] (1-124) -IGHG2*01, G2m.. (CH1 (125-222), charnière (223-234), CH2 (235-343), CH3 (344-448), CHS (449-450)) (125-450)], (138-216')-disulfure avec la chaîne légère lambda (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-40*01 (96.00%) -IGLJ3*02) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimère (226-226'':227-227'':230-230'':233-233'')-tétrakisdisulfure

brazikumab

inmunoglobulina G2-lambda, anti-[*Homo sapiens* IL23A (interleukina 23 subunidad alfa, IL-23A, IL-23 subunidad p19, IL23p19)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma2 (1-450) [*Homo sapiens* VH (IGHV3-33*01 (99.00%) -(IGHD)-IGHJ3*02) [8.8.17] (1-124) -IGHG2*01, G2m.. (CH1 (125-222), bisagra (223-234), CH2 (235-343), CH3 (344-448), CHS (449-450)) (125-450)], (138-216')-disulfuro con la cadena ligera lambda (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-40*01 (96.00%) -IGLJ3*02) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dímero (226-226'':227-227'':230-230'':233-233'')-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SYGMHWVRQA PGKGLEWVAV  50
IWYDGSNEYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARDR 100
GYTSSWYPDA FDIWGQGTMV TVSSASTKGP SVFPLAPCSR STSESTAALG 150
CLVKDYFPEP VTVSWNSGAL TSGVHTFPAV LQSSGLYSLS SVVTVPSSNF 200
GTQTYTCNVD HKPSNTKVDK TVERKCCVEC PPCPAPPVAG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVQFNW YVDGVEVHNA KTKPREEQFN 300
STFRVVSVLT VVHQDWLNGK EYKCKVSNKG LPAPIEKTIS KTKGQPREPQ 350
VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPM 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 450
```

Light chain / Chaîne légère / Cadena ligera

```
QSVLTQPPSV SGAPGQRVTI SCTGSSSNTG AGYDVHWYQQ VPGTAPKLLI  50
YGSGNRPSGV PDRFSGSKSG TSASLAITGL QAEDEADYYC QSYDSSLSGW 100
VFGGGTRLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT 150
VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV 200
THEGSTVEKT VAPTECS                                     217
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	151-207	264-324	370-428
	22"-96"	151"-207"	264"-324"	370"-428"
Intra-L (C23-C104)	22'-90'	139'-198'		
	22'"-90'"	139'"-198'"		
Inter-H-L (CH1 10-CL 126)	138-216'	138"-216'"		
Inter-H-H (h 4, h 5, h 8, h 11)	226-226"	227-227"	230-230"	233-233"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
300, 300"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés

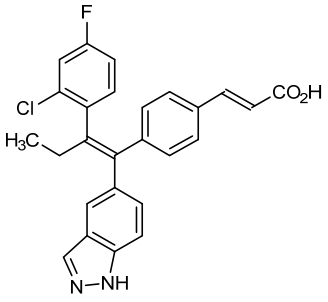
brilanestrantum

brilanestrant — (2*E*)-3-{4-[(1*E*)-2-(2-chloro-4-fluorophenyl)-1-(1*H*-indazol-5-yl)but-1-en-1-yl]phenyl}prop-2-enoic acid

brilanestrant — acide (2*E*)-3-{4-[(1*E*)-2-(2-chloro-4-fluorophényl)-1-(1*H*-indazol-5-yl)but-1-én-1-yl]phényl}prop-2-énoïque

brilanestrant — ácido (2*E*)-3-{4-[(1*E*)-2-(2-cloro-4-fluorofenil)-1-(1*H*-indazol-5-il)but-1-en-1-il]fenil}prop-2-enoico

$C_{26}H_{20}ClFN_2O_2$



burosumabum #

burosumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* FGF23 (fibroblast growth factor 23)], *Homo sapiens* monoclonal antibody;

gamma1 heavy chain (1-447) [*Homo sapiens* VH (IGHV1-46*01 (94.90%) -(IGHD) -IGHJ3*02) [8.8.10] (1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447))(118-447)], (220-213')-disulfide with kappa light chain (1'-213') [*Homo sapiens* V-KAPPA (IGKVD1-13*01 (97.90%) -IGKJ3*01) [6.3.8] (1'-106') -IGKC*01, Km3 (107'-213')]; dimer (226-226'':229-229'')-bisdisulfide

burosumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* FGF23 (facteur de croissance des fibroblastes 23)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-447) [*Homo sapiens* VH (IGHV1-46*01 (94.90%) -(IGHD) -IGHJ3*02) [8.8.10] (1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), charnière (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-213')-disulfure avec la chaîne légère kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV1-13*02 (97.90%) -IGKJ3*01) [6.3.8] (1'-107') -IGKC*01, Km3 (107'-213')]; (226-226'':229-229'')-bisdisulfure

burosumab

immunoglobulina G1-kappa, anti-[*Homo sapiens* FGF23 (factor de crecimiento de los fibroblastos 23)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-447) [*Homo sapiens* VH (IGHV1-46*01 (94.90%) -(IGHD) -IGHJ3*02) [8.8.10] (1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), bisagra (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-213')-disulfuro con la cadena ligera kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV1-13*02 (97.90%) -IGKJ3*01) [6.3.8] (1'-107') -IGKC*01, Km3 (107'-213')]; (226-226'':229-229'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT NHYMHWVRQA PGQGLEWMGI  50
INPISGSTSN AQKFQGRVTM TRDTSTSTVY MELSSLRSED TAVYYCARDI 100
VDAFDFWGQG TMVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK    447
```

Light chain / Chaîne légère / Cadena ligera

```
AIQLTQSPSS LSASVGDRVT ITCRASQGIS SALVWYQQKP GKAPKLLIYD  50
ASSLESGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ FNDYFTFGPG 100
TKVDIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                         213
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261'-321' 367"-425'
Intra-L (C23-C104) 23'-88' 133'-193'
23"'-88"' 133"'-193"'
Inter-H-L (h 5-CL 126) 220-213' 220"-213"'
Inter-H-H (h 11, h 14) 226-226" 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

camrelizumabum #

camrelizumab	immunoglobulin G4-kappa, anti-[*Homo sapiens* PDCD1 (programmed cell death 1, PD-1, PD1, CD279)], humanized monoclonal antibody; gamma4 heavy chain (1-443) [humanized VH (*Homo sapiens* IGHV3-7*01 (90.80%) -(IGHD) -IGHJ4*01) [8.8.9] (1-116) -IGHG4*01 (CH1 (117-214), hinge S10>P (224) (215-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (117-443)], (130-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (87.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (222-222":225-225")-bisdisulfide
camrélizumab	immunoglobuline G4-kappa, anti-[*Homo sapiens* PDCD1 (protéine 1 de mort cellulaire programmée, PD-1, PD1, CD279)], anticorps monoclonal humanisé; chaîne lourde gamma4 (1-443) [VH humanisé (*Homo sapiens* IGHV3-7*01 (90.80%) -(IGHD) -IGHJ4*01) [8.8.9] (1-116) -IGHG4*01 (CH1 (117-214), charnière S10>P (224) (215-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (117-443)], (130-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (87.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (222-222":225-225")-bisdisulfure
camrelizumab	inmunoglobulina G4-kappa, anti-[*Homo sapiens* PDCD1 (proteína 1 de muerte celular programada, PD-1, PD1, CD279)], anticuerpo monoclonal humanizado; cadena pesada gamma4 (1-443) [VH humanizado (*Homo sapiens* IGHV3-7*01 (90.80%) -(IGHD) -IGHJ4*01) [8.8.9] (1-116) -IGHG4*01 (CH1 (117-214), bisagra S10>P (224) (215-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (117-443)], (130-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (87.40%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (222-222":225-225")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYMMSWVRQA PGKGLEWVAT 50
ISGGGANTYY PDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARQL 100
YYFDYWGQGT TVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTKTYTCN 200
VDHKPSNTKV DKRVESKYGP PCPPCPAPEF LGGPSVFLFP PKPKDTLMIS 250
RTPEVTCVVV DVSQEDPEVQ FNWYVDGVEV HNAKTKPREE QFNSTYRVVS 300
VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR EPQVYTLPPS 350
QEEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF 400
FLYSRLTVDK SRWQEGNVFS CSVMHEALHN HYTQKSLSLS LGK        443
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCLASQTIG TWLTWYQQKP GKAPKLLIYT 50
ATSLADGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ VYSIPWTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                       214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	257-317	363-421
	22"-96"	143"-199"	257"-317"	363"-421"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (CH1 10-CL 126)	130-214'	130"-214'"		
Inter-H-H (h 8, h 11)	222-222"	225-225"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
293, 293"

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales

H CHS K2 C-terminal lysine clipping:
443, 443"

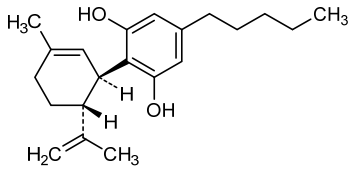
cannabidiolum

cannabidiol — 2-[(1*R*,6*R*)-3-methyl-6-(prop-1-en-2-yl)cyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol

cannabidiol — 2-[(1*R*,6*R*)-3-méthyl-6-(prop-1-én-2-yl)cyclohex-2-én-1-yl]-5-pentylbenzène-1,3-diol

cannabidiol — 2-[(1*R*,6*R*)-3-metil-6-(prop-1-en-2-il)ciclohex-2-en-1-il]-5-pentilbenceno-1,3-diol

$C_{21}H_{30}O_2$



casimersenum

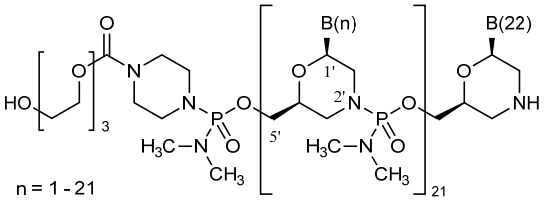
casimersen — *all-P-ambo*-[2',3'-azanediyl-*P*-(dimethylamino)-*P*,2',3'-trideoxy-2',3'-seco](2'-*N*→5')(C-A-A-T-G-C-C-A-T-C-C-T-G-G-A-G-T-T-C-C-T-G) 5'-{*P*-[4-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)piperazin-1-yl]-*N*,*N*-dimethylphosphonamidate}

casimersen — 5'-{*P*-[4-({2-[2-(2-hydroxyéthoxy)éthoxy]éthoxy}carbonyl)pipérazin-1-yl]-*N*,*N*-diméthylphosphonamidate} de *tout-P-ambo*-[2',3'-azanediyl-*P*-(diméthylamino)-*P*,2',3'-tridéoxy-2',3'-séco](2'-*N*→5')(C-A-A-T-G-C-C-A-T-C-C-T-G-G-A-G-T-T-C-C-T-G)

casimersén

5'-{*P*-[4-({2-[2-(2-hidroxietoxi)etoxi]etoxi}carbonil)piperazin-1-il]-*N*,*N*-dimetilfosfonamidato} de *todo*-*P*-*ambo*-[2',3'-azanediil-*P*-(dimetilamino)-*P*,2',3'-tridesoxi-2',3'-seco](2'-*N*→5')(C-A-A-T-G-C-C-A-T-C-C-T-G-G-A-G-T-T-C-C-T-G)

$C_{268}H_{424}N_{124}O_{95}P_{22}$



cenegerminum #

cenegermin

human beta-nerve growth factor (beta-NGF)-(1-118)-peptide (non-covalent dimer) produced in *Escherichia coli*

cénégermine

facteur de croissance bêta des cellules nerveuses (beta-NGF)-(1-118)-peptide, humain, produit par *Escherichia coli*

cenegermina

factor de crecimiento beta de las células nerviosas (beta-NGF)-(1-118)-péptido humano (dímero no covalente), producido por *Escherichia coli*

$C_{583}H_{902}N_{166}O_{173}S_8$

```
SSSHPIFHRG EFSVCDSVSV WVGDKTTATD IKGKEVMVLG EVNINNSVFK  50
QYFFETKCRD PNPVDSGCRG IDSKHWNSYC TTTHTFVKAL TMDGKQAAWR 100
FIRIDTACVC VLSRKAVR                                    118
```

Disulfide bridges position / Position des ponts disulfure / Posiciones de los puentes disulfuro
15-80 58-108 68-110

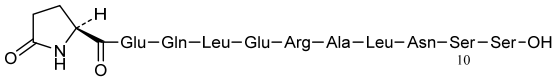
cenplacelum

cenplacel

Human placenta-derived adherent (PDA) cells that are culture-expanded, undifferentiated mesenchymal-like cells derived from full-term placental tissue of a human donor.
Cellular identity: Mesenchymal-like stromal cell: $CD34^-$, $CD10^+$, $CD105^+$, and $CD200^+$.
Cells lack the human leukocyte antigen (HLA) and costimulatory molecules on their membrane surface.

cenplacel

Cellules humaines adhérentes dérivées du placenta, en culture d'expansion, cellules semblables aux cellules mésenchymateuses non-différenciées dérivées de tissu placentaire à terme de donneur humain.
identité des cellules: cellules stromales semblables aux cellules mésenchymateuses: $CD34^-$, $CD10^+$, $CD105^+$, and $CD200^+$.
Les cellules sont dépourvues de l'antigène leucocytaire humain (HLA) et des molécules co-stimulantes à la surface de la membrane.

cenplacel	Células humanas adherentes derivadas de la placenta (PDA) expandidas por cultivo, células semejantes a las células mesenquimales no diferenciadas derivadas del tejido placentario a término. Identificación de las células: células estromales semejantes a las células mesenquimales: $CD34^-$, $CD10^+$, $CD105^+$, et $CD200^+$. Las células están desprovistas del antígeno leucocitario humano (HLA) y de las moléculas coestimulantes de la superficie de la membrana
cibinetidum	
cibinetide	5-oxo-L-prolyl-L-α-glutamyl-L-glutaminyl-L-leucyl-L-α-glutamyl-L-arginyl-L-alanyl-L-leucyl-L-asparaginyl-L-seryl-L-serine
cibinétide	5-oxo-L-prolyl-L-α-glutamyl-L-glutaminyl-L-leucyl-L-α-glutamyl-L-arginyl-L-alanyl-L-leucyl-L-asparaginyl-L-séryl-L-sérine
cibinetida	5-oxo-L-prolil-L-α-glutamil-L-glutaminil-L-leucil-L-α-glutamil-L-arginyl-L-alanil-L-leucil-L-asparaginil-L-seril-L-serina
	$C_{51}H_{84}N_{16}O_{21}$
	
crizanlizumabum #	
crizanlizumab	immunoglobulin G2-kappa, anti-[*Homo sapiens* SELP (selectin P, CD62)], humanized monoclonal antibody; gamma2 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV1-8*01 (81.60%) -(IGHD) -IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG2*02 (CH1 (123-220), hinge (221-232), CH2 K105>A (323) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.90%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimer (224-224":225-225":228-228":231-231")-tetrakisdisulfide
crizanlizumab	immunoglobuline G2-kappa, anti-[*Homo sapiens* SELP (sélectine P, CD62)], anticorps monoclonal humanisé; chaîne lourde gamma2 (1-448) [VH humanisé (*Homo sapiens* IGHV1-8*01 (81.60%) -(IGHD) -IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG2*02 (CH1 (123-220), charnière (221-232), CH2 K105>A (323) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (86.90%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimère (224-224":225-225":228-228":231-231")-tétrakisdisulfure

crizanlizumab

inmunoglobulina G2-kappa, anti-[*Homo sapiens* SELP (selectina P, CD62)], anticuerpo monoclonal humanizado; cadena pesada gamma2 (1-448) [VH humanizado (*Homo sapiens* IGHV1-8*01 (81.60%) -(IGHD) -IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG2*02 (CH1 (123-220), bisagra (221-232), CH2 K105>A (323) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-218')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (86.90%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dímero (224-224":225-225":228-228":231-231")-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKVSGYTFT SYDINWVRQA PGKGLEWMGW  50
IYPGDGSIKY NEKFKGRVTM TVDKSTDTAY MELSSLRSED TAVYYCARRG 100
EYGNYEGAMD YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVTSSNFGT 200
QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVQFNWYV DGMEVHNAKT KPREEQFNST 300
FRVVSVLTVV HQDWLNGKEY KCAVSNKGLP APIEKTISKT KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPMLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQSVD YDGHSYMNWY QQKPGKAPKL  50
LIYAASNLES GVPSRFSGSG SGTDFTLTIS SLQPEDFATY YCQQSDENPL 100
TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 149-205 262-322 368-426
22"-96" 149"-205" 262"-322" 368"-426"

Intra-L (C23-C104) 23'-92' 138'-198'
23'"-92'" 138'"-198'"

Inter-H-L (CH1 10-CL 126) 136-218' 136"-218'"

Inter-H-H (h 4, h 5, h 8, h 11) 224-224" 225-225" 228-228" 231-231"

*In addition to the isoform A, isoform A/B characterized by an inter-H-H (h 4 - CH1 10) 224-136' and an inter-H-L (h4-CL 126) 224'-218", instead of the inter-H-H (h 4 - h 4) 224-224" and of one of the two inter-H-L (CH1 10-CL 126) 136'-218".

*En plus del'isoforme A, isoforme A/B caractérisée par un inter-H-H (h 4 - CH1 10) 224-136' et un inter-H-L (h 4- CL 126) 224'-218", au lieu de l'inter-H-H (h4 - h 4) 224-224" et del'un des deux inter-H-L (CH1 10-CL 126) 136'-218".

*Además de la isoforma A, isoforma A/B caracterizado por un inter-H-H (h 4 - CH1 10) 224-116" y un inter-H-L (h 4- CL 126) 224'-218", en lugar del inter-H-H (h 4 - h 4) 224-224" y uno delos dos inter-H-L (CH1 10-CL 126) 136'-218".

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
HCH2N84.4:
298, 298"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

cupabimodum
cupabimod

all-P-ambo-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxycytidine duplex with *all-P-ambo*-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-

deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxyguanosine

cupabimod

duplex de *tout-P-ambo*-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxycytidine avec *tout-P-ambo*-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-désoxy-*P*-thioguanylyl-(3'→5')-2'-déoxyguanosine

cupabimod

duplex de *todo-P-ambo*-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxicitidina con *todo-P-ambo*-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxiguanosina

$C_{389}H_{491}N_{151}O_{198}P_{38}S_{38}$

(3'-5')d(*P*-thio) (C-C-T-T-G-A-A-G-G-G-A-T-T-T-C-C-C-T-C-C)

(5'-3')d(*P*-thio) (G-G-A-A-C-T-T-C-C-C-T-A-A-A-G-G-G-A-G-G)

daclizumabum beta #
daclizumab beta

immunoglobulin G1-kappa, anti-[*Homo sapiens* IL2RA (interleukin 2 receptor alpha subunit, IL-2RA, TAC, p55, CD25)], humanized monoclonal antibody;

	gamma1 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), hinge (215-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-213')-disulfide with kappa light chain (1'-213') [humanized V-KAPPA (*Homo sapiens* IGKV1-5*01 (84.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dimer (225-225":228-228")-bisdisulfide
daclizumab bêta	immunoglobuline G1-kappa, anti-[*Homo sapiens* IL2RA (sous-unité alpha du récepteur de l'interleukine 2, IL-2RA, TAC, p55, CD25)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-446) [VH humanisé (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), charnière (215-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-213')-disulfure avec la chaîne légère kappa (1'-213') [V-KAPPA humanisé (*Homo sapiens* IGKV1-5*01 (84.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dimère (225-225":228-228")-bisdisulfure
daclizumab beta	inmunoglobulina G1-kappa, anti-[*Homo sapiens* IL2RA (subunidad alfa del receptor de la interleukina 2, IL-2RA, TAC, p55, CD25)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-446) [VH humanizado (*Homo sapiens* IGHV1-46*01 (82.70%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), bisagra (215-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-213')-disulfuro con la cadena ligera kappa (1'-213') [V-KAPPA humanizado (*Homo sapiens* IGKV1-5*01 (84.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGYTFT SYRMHWVRQA PGQGLEWIGY  50
INPSTGYTEY NQKFKDKATI TADESTNTAY MELSSLRSED TAVYYCARGG 100
GVFDYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200
VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPST LSASVGDRVT ITCSASSSIS YMHWYQQKPG KAPKLLIYTT  50
SNLASGVPAR FSGSGSGTEF TLTISSLQPD DFATYYCHQR STYPLTFGQG 100
TKVEVKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                         213
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	260-320	366-424
	22"-96"	143"-199"	260"-320"	366"-424"
Intra-L (C23-C104)	23'-87'	133'-193'		
	23'"-87'"	133'"-193"		
Inter-H-L (h 5-CL 126)	219-213'	219"-213'"		
Inter-H-H (h 11, h 14)	225-225"	228-228"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary NS0-type glycans with low level of high mannose glycans (sum of Man5, Man6 and Man7 <1%) / glycanes de type NS0 bi-antennaires complexes fucosylés avec un taux bas de glycanes riches en mannose (total of Man5, Man6 et Man7 <1%) / glicanos de tipo NS0 biantenarios complejos fucosilados con una baja tasa de altas glicanos manosa (total de Man5, Man6 et Man7 <1%)

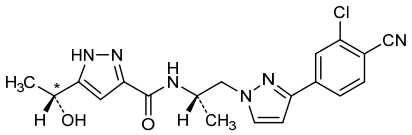
darolutamidum

darolutamide — *N*-{(2*S*)-1-[3-(3-chloro-4-cyanophenyl)-1*H*-pyrazol-1-yl]propan-2-yl}-5-[(1*RS*)-1-hydroxyethyl]-1*H*-pyrazole-3-carboxamide

darolutamide — *N*-{(2*S*)-1-[3-(3-chloro-4-cyanophényl)-1*H*-pyrazol-1-yl]propan-2-yl}-5-[(1*RS*)-1-hydroxyéthyl]-1*H*-pyrazole-3-carboxamide

darolutamida — *N*-{(2*S*)-1-[3-(4-ciano-3-clorofenil)-1*H*-pirazol-1-il]propan-2-il}-5-[(1*RS*)-1-hidroxietil]-1*H*-pirazol-3-carboxamida

$C_{19}H_{19}ClN_6O_2$



and epimer at C*
et l'épimère en C*
y el epímero al C*

depatuxizumabum #

depatuxizumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], humanized and chimeric monoclonal antibody;
gamma1 heavy chain humanized (1-446) [humanized VH (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), hinge (215-229),CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfide with kappa light chain chimeric (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (225-225":228-228")-bisdisulfide

dépatuxizumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (Récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB)], anticorps monoclonal humanisé et chimérique;
chaîne lourde gamma1 humanisée (1-446) [VH humanisé (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), charnière (215-229),CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfure avec la chaîne légère kappa chimérique (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (225-225":228-228")-bisdisulfure

depatuxizumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* EGFR (Receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB)], anticuerpo monoclonal humanizado y quimérico;

cadena pesada gamma1 humanizada (1-446) [VH humanizado (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), bisagra (215-229),CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfuro con la cadena ligera kappa quimérica (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (225-225":228-228")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSQTLSL TCTVSGYSIS SDFAWNWIRQ PPGKGLEWMG  50
YISYSGNTRY QPSLKSRITI SRDTSKNQFF LKLNSVTAAD TATYYCVTAG 100
RGFPYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200
VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS MSVSVGDRVT ITCHSSQDIN SNIGWLQQKP GKSFKGLIYH  50
GTNLDDGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCVQ YAQFPWTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	260-320	366-424
	22"-96"	143"-199"	260"-320"	366"-424"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)	219-214'	219"-214'"		
Inter-H-H (h 11, h 14)	225-225"	228-228"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

depatuxizumabum mafodotinum #

depatuxizumab mafodotin

immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], humanized and chimeric monoclonal antibody conjugated to auristatin F;
gamma1 heavy chain humanized (1-446) [humanized VH (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), hinge (215-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfide with kappa light chain chimeric (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (225-225":228-228")-bisdisulfide; conjugated, on an average of 4 cysteinyl, to monomethylauristatin F (MMAF), via a noncleavable maleimidocaproyl (mc) linker
For the *mafodotin* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

dépatuxizumab mafodotine

immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (Récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB)], anticorps monoclonal humanisé et chimérique conjugué à l'auristatine F;

chaîne lourde gamma1 humanisée (1-446) [VH humanisé (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), charnière (215-229),CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfure avec la chaîne légère kappa chimérique (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (225-225":228-228")-bisdisulfure; conjugué, sur 4 cystéinyl en moyenne, au monométhylauristatine F (MMAF), via un linker maléimidocaproyl (mc) non clivable

Pour la partie *mafodotine*, veuillez-vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

depatuxizumab mafodotina

inmunoglobulina G1-kappa, anti-[*Homo sapiens* EGFR (Receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB)], anticuerpo monoclonal humanizado y quimérico conjugado con la auristatina F;
cadena pesada gamma1 humanizada (1-446) [VH humanizado (*Homo sapiens* IGHV4-30-4*01 (84.50%) -(IGHD)-IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (117-214), bisagra (215-229),CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfuro con la cadena ligera kappa quimérica (1'-214') [*Mus musculus* V-KAPPA (*Mus musculus* IGKV14-100*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (225-225":228-228")-bisdisulfuro; conjugado, en 4 grupos cisteinil por término medio, con monometilauristatina F (MMAF), mediante un conector no escindible de tipo maleimidocaproil (mc)

Por la parte *mafodotina*, por favor vaya al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSQTLSL TCTVSGYSIS SDFAWNWIRQ PPGKGLEWMG  50
YISYSGNTRY QPSLKSRITI SRDTSKNQFF LKLNSVTAAD TATYYCVTAG 100
RGFPYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200
VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS MSVSVGDRVT ITCHSSQDIN SNIGWLQQKP GKSFKGLIYH  50
GTNLDDGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCVQ YAQFPWTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	260-320	366-424
	22"-96"	143"-199"	260"-320"	366"-424"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)*	219-214'	219"-214'"		
Inter-H-H (h 11, h 14)*	225-225"	228-228"		

*Two or three of the inter-chain disulfide bridges are not present, an average of 4 cysteinyl being conjugated each via a thioether bond to a drug linker.

*Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 4 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif.

*Faltan dos o tres puentes disulfuro inter-catenarios, una media de 4 cisteinil está conjugada a conectores de principio activo.

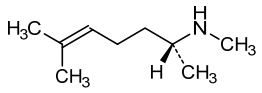
dexisometheptenum

dexisometheptene (2*R*)-*N*,6-dimethylhept-5-en-2-amine

dexisométhéptène (2*R*)-*N*,6-diméthylhept-5-én-2-amine

dexisometepteno (2*R*)-*N*,6-dimetilhept-5-en-2-amina

$C_9H_{19}N$



dezamizumabum #

dezamizumab immunoglobulin G1-kappa, anti-[*Homo sapiens* APCS (amyloid P component serum, serum amyloid P component, SAP, pentraxin-2, PTX2)], humanized monoclonal antibody;
gamma1 heavy chain (1-452) [humanized VH (*Homo sapiens* IGHV1-69*02 (85.70%) -(IGHD)-IGHJ5*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (123-220), hinge (221-235),CH2 (236-345), CH3 (346-450), CHS (451-452)) (123-452)], (225-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (231-231":234-234")-bisdisulfide

dézamizumab immunoglobuline G1-kappa, anti-[*Homo sapiens* APCS (composant amyloïde P du sérum, composant amyloïde P sérique, APS, pentraxine-2, PTX2)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-452) [VH humanisé (*Homo sapiens* IGHV1-69*02 (85.70%) -(IGHD)-IGHJ5*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (123-220), charnière (221-235),CH2 (236-345), CH3 (346-450), CHS (451-452)) (123-452)], (225-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (231-231":234-234")-bisdisulfure

dezamizumab inmunoglobulina G1-kappa, anti-[*Homo sapiens* APCS (componente amiloide P del suero, componente amiloide P serico, APS, pentraxina-2, PTX2)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-452) [VH humanizado (*Homo sapiens* IGHV1-69*02 (85.70%) -(IGHD)-IGHJ5*01) [8.8.15] (1-122) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 (123-220), bisagra (221-235),CH2 (236-345), CH3 (346-450), CHS (451-452)) (123-452)], (225-214')-disulfuro con la cadena lígera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (231-231":234-234")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGSSVKV SCKASGFTFA TYNMHWVRQA PGQGLEWMGY  50
IYPGDGNANY NQQFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARGD 100
FDYDGGYYFD SWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKKV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASENIY SYLAWYQQKP GKAPKLLIHN  50
AKTLAEGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQH HYGAPLTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 149-205 266-326 372-430
22"-96" 149"-205" 266"-326" 372"-430"
Intra-L (C23-C104) 23'-88' 134'-194'
23"'-88"' 134"'-194"'
Inter-H-L (h 5-CL 126) 225-214' 225"-214"'
Inter-H-H (h 11, h 14) 231-231" 234-234"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

dinutuximabum beta #

dinutuximab beta

immunoglobulin G1-kappa, anti-[*Homo sapiens* ganglioside GD2 (disialoganglioside GD2)], chimeric monoclonal antibody;
gamma1 heavy chain (1-443) [*Mus musculus* VH (IGHV1S135*01 -(IGHD)-IGHJ4*01) [8.8.6] (1-113) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (114-211), hinge (212-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (114-443)], (216-220')-disulfide with kappa light chain (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 -IGKJ5*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 (114'-220')]; dimer (222-222":225-225")-bisdisulfide

dinutuximab bêta

immunoglobuline G1-kappa, anti-[*Homo sapiens* ganglioside GD2 (disialoganglioside GD2)], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-443) [*Mus musculus* VH (IGHV1S135*01 -(IGHD)-IGHJ4*01) [8.8.6] (1-113) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (114-211), charnière (212-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (114-443)], (216-220')-disulfure avec la chaîne légère kappa (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 -IGKJ5*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 (114'-220')]; dimère (222-222":225-225")-bisdisulfure

dinutuximab beta

inmunoglobulina G1-kappa, anti-[*Homo sapiens* ganglió sido GD2 (disialoganglió sido GD2)], anticuerpo monoclonal quimérico;

	gamma1 heavy chain (1-443) [*Mus musculus* VH (IGHV1S135*01 -(IGHD)-IGHJ4*01) [8.8.6] (1-113) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (114-211), hinge (212-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (114-443)], (216-220')-disulfide with kappa light chain (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 -IGKJ5*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 (114'-220')]; dimer (222-222":225-225")-bisdisulfide
dinutuximab bêta	immunoglobuline G1-kappa, anti-[*Homo sapiens* ganglioside GD2 (disialoganglioside GD2)], anticorps monoclonal chimérique; chaîne lourde gamma1 (1-443) [*Mus musculus* VH (IGHV1S135*01 -(IGHD)-IGHJ4*01) [8.8.6] (1-113) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (114-211), charnière (212-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (114-443)], (216-220')-disulfure avec la chaîne légère kappa (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 -IGKJ5*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 (114'-220')]; dimère (222-222":225-225")-bisdisulfure
dinutuximab beta	inmunoglobulina G1-kappa, anti-[*Homo sapiens* gangliósido GD2 (disialogangliósido GD2)], anticuerpo monoclonal quimérico; cadena pesada gamma1 (1-443) [*Mus musculus* VH (IGHV1S135*01 -(IGHD)-IGHJ4*01) [8.8.6] (1-113) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (114-211), bisagra (212-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (114-443)], (216-220')-disulfuro con la cadena ligera kappa (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 -IGKJ5*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 (114'-220')]; dímero (222-222":225-225")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLQSGPE LEKPGASVMI SCKASGSSFT GYNMNWVRQN IGKSLEWIGA  50
IDPYYGGTSY NQKFKGRATL TVDKSSSTAY MHLKSLTSED SAVYYCVSGM 100
EYWGQGTSVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC LVKDYFPEPV 150
TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG TQTYICNVNH 200
KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP PKPKDTLMIS 250
RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE QYNSTYRVVS 300
VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR EPQVYTLPPS 350
REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF 400
FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS PGK        443
```

Light chain / Chaîne légère / Cadena ligera

```
EIVMTQSPAT LSVSPGERAT LSCRSSQSLV HRNGNTYLHW YLQKPGQSPK  50
LLIHKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDLGV YFCSQSTHVP 100
PLTFGAGTKL ELKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA 150
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC 200
EVTHQGLSSP VTKSFNRGEC                                  220
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H (C23-C104)  22-96    140-196     257-317   363-421
                    22"-96"  140"-196"   257"-317" 363"-421"
Intra-L (C23-C104)  23'-93'  140'-200'
                    23'"-93'" 140'"-200'"
Inter-H-L (h 5-CL 126)  216-220'  216"-220'"
Inter-H-H (h 11, h 14)  222-222"  225-225"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
293, 293"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

diroximeli fumaras diroximel fumarate	2-(2,5-dioxopyrrolidin-1-yl)ethyl methyl (2*E*)-but-2-enedioate

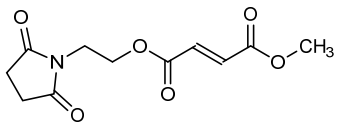
fumarate de diroximel

(2*E*)-but-2-ènedioate de 2-(2,5-dioxopyrrolidin-1-yl)éthyle et de méthyle

fumarato de diroximel

(2*E*)-but-2-enodioato de 2-(2,5-dioxopirrolidin-1-il)etilo y de metilo

$C_{11}H_{13}NO_6$



elacestrantum

elacestrant

(6*R*)-6-{2-[ethyl({4-[2-(ethylamino)ethyl]phenyl}methyl)amino]-4-methoxyphenyl}-5,6,7,8-tetrahydronaphthalen-2-ol

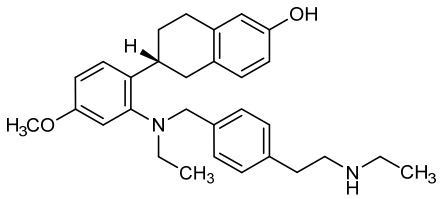
élacestrant

(6*R*)-6-{2-[éthyl({4-[2-(éthylamino)éthyl]phényl}méthyl)amino]-4-méthoxyphényl}-5,6,7,8-tétrahydronaphtalén-2-ol

elacestrant

(6*R*)-6-{2-[etil({4-[2-(etilamino)etil]fenil}metil)amino]-4-metoxifenil}-5,6,7,8-tetrahidronaftalen-2-ol

$C_{30}H_{38}N_2O_2$



elapegademasum #

elapegademase

[Cys^{74}>Ser,Ala^{245}>Thr]adenosine deaminase (*Bos taurus*, bovine)-(1-356)-peptide, produced in *Escherichia coli*, substituted on N^2 of the *N*-terminal alanyl residue (A^1) and on N^6 of lysyl residues (K) with an average of approximately 13 ω-methoxypoly(oxyethylene)-α-carbonyl groups (~5 kDa each)

élapégadémase

[Cys^{74}>Ser,Ala^{245}>Thr]adénosine déaminase (*Bos taurus*, bovine)-(1-356)-peptide, produit par *Escherichia coli*, substitué sur les N^2 du résidu alanyl *N*-terminal (A^1) et sur les N^6 des résidus lysyl (K) avec en en moyenne 13 groupes ω-métoxipoli(oxietileno)-α-carbonyle (~5 kDa chacun) approximativement

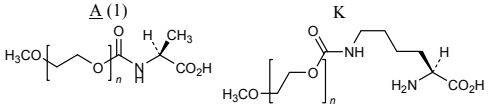
elapegademasa

[Cys^{74}>Ser,Ala^{245}>Thr]adenosina deaminasa (*Bos taurus*, bovino)-(1-356)-péptido, producido por *Escherichia coli*, sustituido en los N^2 del resto alanil*N*-terminal (A^1) y en los N^6 de los restos lisil (K) con una media de 13 grupos ω-metoxipoli(oxietileno)-α-carbonilo (~5 kDa cada uno de ellos) de forma aproximada

Sequence / Séquence / Secuencia

```
AQTPAFNKPK VELHVHLDGA IKPETILYYG RKRGIALPAD TPEELQNIIG  50
MDKPLSLPEF LAKFDYYMPA IAGSREAVKR IAYEFVEMKA KDGVVYVEVR 100
YSPHLLANSK VEPIPWNQAE GDLTPDEVVS LVNQGLQEGE RDFGVKVRSI 150
LCCMRHQPSW SSEVVELCKK YREQTVVAID LAGDETIEGS SLFPGHVKAY 200
AEAVKSGVHR TVHAGEVGSA NVVKEAVDTL KTERLGHGYH TLEDTTLYNR 250
LRQENMHFEV CPWSSYLTGA WKPDTEHPVV RFKNDQVNYS LNTDDPLIFK 300
STLDTDYQMT KNEMGFTEEE FKRLNINAAK SSFLPEDEKK ELLDLLYKAY 350
GMPSPA                                                 356
```

Potential pegylated residues / Résidus pégylés potentiels / Restos pegilados potenciales



elezanumabum #

elezanumab

immunoglobulin G1-lambda1, anti-[*Homo sapiens* RGMA (repulsive guidance molecule family member a, repulsive guidance molecule A, RGMa)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-450) [*Homo sapiens* VH (IGHV1-18*01 (92.90%) -(IGHD) -IGHJ6*03) [8.8.13](1-120) -IGHG1*01, Gm17,1 (CH1 (121-218), hinge (219-233), CH2 L1.2>A (238), L1.3>A (237), T14>Q (253) (234-343), CH3 M107>L (431) (344-448),CHS (449-450)) (121-450)], (223-214')-disulfide with lambda1 light chain (1'-215') [*Homo sapiens* V-LAMBDA (IGLV2-11*01 (89.90%) -IGLJ2*01) [9.3.9] (1'-109') -IGLC2*01 (110'-215')]; dimer (229-229'':232-232'')-bisdisulfide

élézanumab

immunoglobuline G1-lambda1, anti-[*Homo sapiens* RGMA (membre a de la famille de molécules d'orientation répulsive, molécule d'orientation répulsive A, RGMa)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-450) [*Homo sapiens* VH (IGHV1-18*01 (92.90%) -(IGHD) -IGHJ6*03) [8.8.13] (1-120) -IGHG1*01, Gm17,1 (CH1 (121-218), charnière (219-233),CH2 L1.2>A (238), L1.3>A (237), T14>Q (253) (234-343), CH3 M107>L (431) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfure avec la chaîne légère lambda1 (1'-215') [*Homo sapiens* V-LAMBDA (IGLV2-11*01 (89.90%) -IGLJ2*01) [9.3.9] (1'-109') -IGLC2*01 (110'-215')]; dimère (229-229'':232-232'')-bisdisulfure

elezanumab

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* RGMA (miembro de la familia de moléculas de orientación repulsiva, molécula de orientación repulsiva A, RGMa)], *Homo sapiens* anticuerpo monoclonal;

cadena pesada gamma1 (1-450) [*Homo sapiens* VH (IGHV1-18*01 (92.90%) -(IGHD) -IGHJ6*03) [8.8.13] (1-120) -IGHG1*01, Gm17,1 (CH1 (121-218), bisagra (219-233),CH2 L1.2>A (238), L1.3>A (237), T14>Q (253) (234-343), CH3 M107>L (431) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfuro con la cadena ligera lambda1 (1'-215') [*Homo sapiens* V-LAMBDA (IGLV2-11*01 (89.90%) -IGLJ2*01) [9.3.9] (1'-109') -IGLC2*01 (110'-215')]; dímero (229-229'':232-232'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGAE VKKPGASVKV SCKASGYTFT SHGISWVRQA PGQGLDWMGW  50
ISPYSGNTNY AQKLQGRVTM TTDTSTSTAY MELSSLRSED TAVYYCARVG 100
SGPYYYMDVW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPEAAGG PSVFLFPPKP 250
KDQLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV LHEALHNHYT QKSLSLSPGK 450
```

Light chain / Chaîne légère / Cadena ligera

```
QSALTQPRSV SGSPGQSVTI SCTGTSSSVG DSIYVSWYQQ HPGKAPKLML  50
YDVTKRPSGV PDRFSGSKSG NTASLTISGL QAEDEADYYC YSYAGTDTLF 100
GGGTKVTVLG QPKAAPSVTL FPPSSEELQA NKATLVCLIS DFYPGAVTVA 150
WKADSSPVKA GVETTTPSKQ SNNKYAASSY LSLTPEQWKS HRSYSCQVTH 200
EGSTVEKTVA PTECS                                       215
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	147-203	264-324	370-428
	22''-96''	147''-203''	264''-324''	370''-428''
Intra-L (C23-C104)	22'-90'	137'-196'		
	22'''-90'''	137'''-196'''		
Inter-H-L (h 5-CL 126)	223-214'	223''-214'''		
Inter-H-H (h 11, h 14)	229-229'	232-232''		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
300, 300''
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

elivaldogenum tavalentivecum #
elivaldogene tavalentivec

A VSV-G*-pseudotyped self-inactivating HIV-1-derived lentiviral vector (pLBP100 hALD) encoding human adrenoleukodystrophy (ALD) protein (ABCD1 gene) under the control of a modified myeloproliferative sarcoma virus promoter (MND**)
* VSV-G = vesicular stomatitis virus G envelope protein
** MND = myeloproliferative sarcoma virus enhancer with negative control region deleted, dl587rev primer-binding site substituted

élivaldogène tavalentivec

vecteur lentiviral dérivé du VIH-1 auto-inactivant (pLBP100 hALD) pseudotypé VSV-G*, codant pour la protéine humaine (gène ABCD1) de l'adrénoleucodystrophie (ALD), sous le contrôle d'un promoteur du virus du sarcome myéloprolifératif modifié (MND**)
* VSV-G = glycoprotéine G de l'enveloppe du virus de la stomatite vésiculaire
** MND = promoteur du virus du sarcome myéloprolifératif dont la région de contrôle négatif a été supprimée, le site de liaison de l'amorce substitué par dl587rev

elivaldogén tavalentivec	vector lentiviral derivado del VIH-1 auto-inactivante (pLBP100 hALD) pseudotipo VSV-G*, que codifica para la proteína humana (gen ABCD1) de la adrenoleucodistrofia (ALD), bajo el control de un promotor del virus del sarcoma mieloproliferativo modificado (MND**) * VSV-G = glicoproteína G del virus de la estomatitis vesicular ** MND = promotor del virus del sarcoma mieloproliferativo bajo la región de control negativo ha sido suprimido, el sitio de enlace del inicio substituido por dl587rev
eltrapuldencelum	
eltrapuldencel	Autologous dendritic cells loaded with antigen from self-renewing, proliferating autologous irradiated tumour cells, in a solution of granulocyte-macrophage colony stimulating factor (GM-CSF). Patient's monocytes are collected from peripheral blood by leukocyte apheresis, led to differentiate into dendritic cells in culture and incubated with expanded irradiated autologous self-renewing, cancer-initiating cells (CICs).
eltrapuldencel	cellules dendritiques autologues chargées avec un antigène de cellules tumorales autologues, auto-renouvellantes, proliférantes et irradiées, dans une solution de facteur de stimulation des colonies de granulocytes et de macrophages (GM-CSF). Les monocytes des patients sont recueillis par leucaphérèse à partir de sang périphérique, conduits à se différencier en cellules dendritiques par culture et incubés avec des cellules initiatrices de cancer (CICs) autologues ayant des propriétés d'auto-renouvellement.
eltrapuldencel	células dendríticas autólogas cargadas con un antígeno de células tumorales autólogas, autorenovables, proliferantes e irradiadas, en una solución de factor de estimulación de colonias de granulocitos y de macrófagos (GM-CSF). Los monocitos de los pacientes se recogen por leucoféresis a partir de sangre periférica, conducidos a diferenciarse en células dendríticas para el cultivo e incubados con las células iniciadoras de cáncer (CICs) autólogas con las propiedades de autorenovación.
emapalumabum #	
emapalumab	immunoglobulin G1-lambda1, anti-[*Homo sapiens* IFNG (interferon gamma, IFN gamma)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-453) [*Homo sapiens* VH (IGHV3-23*01 -(IGHD) -IGHJ5*02) [8.8.16] (1-123) -IGHG1*03, Gm17,1 (CH1 (124-221), hinge (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453)) (124-453)], (226-216')-disulfide with lambda1 light chain (1'-217') [*Homo sapiens* V-LAMBDA (IGLV6-57*01 (99.00%) -IGLJ3*02) [8.3.10] (1'-111') -IGLC2*01 (112'-217')]; dimer (232-232":235-235")-bisdisulfide

émapalumab

immunoglobuline G1-lambda1, anti-[*Homo sapiens* IFNG (interféron gamma, IFN gamma)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-453) [*Homo sapiens* VH (IGHV3-23*01 -(IGHD) -IGHJ5*02) [8.8.16] (1-123) - IGHG1*03, Gm17,1 (CH1 (124-221), charnière (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453)) (124-453)],(226-216')-disulfure avec la chaîne légère lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV6-57*01 (99.00%) -IGLJ3*02) [8.3.10] (1'-111') -IGLC2*01 (112'-217')]; dimère (232-232":235-235")-bisdisulfure

emapalumab

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* IFNG (interferón gamma, IFN gamma)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-453) [*Homo sapiens* VH (IGHV3-23*01 -(IGHD) -IGHJ5*02) [8.8.16] (1-123) - IGHG1*03, Gm17,1 (CH1 (124-221), bisagra (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453)) (124-453)], (226-216')-disulfuro con la cadena ligera lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV6-57*01 (99.00%) -IGLJ3*02) [8.3.10] (1'-111') -IGLC2*01 (112'-217')]; dímero (232-232":235-235")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA  50
ISGSGGSTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKDG 100
SSGWYVPHWF DPWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TQTYICNVNH KPSNTKVDKR VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP 250
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 350
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 400
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
NFMLTQPHSV SESPGKTVTI SCTRSSGSIA SNYVQWYQQR PGSSPTTVIY  50
EDNQRPSGVP DRFSGSIDSS SNSASLTISG LKTEDEADYY CQSYDGSNRW 100
MFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT 150
VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV 200
THEGSTVEKT VAPTECS                                      217
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	150-206	267-327	373-431
	22"-96"	150"-206"	267-327"	373"-431"
Intra-L (C23-C104)	22'-91'	139'-198'		
	22'"-91'"	139'"-198'"		
Inter-H-L (h 5-CL 126)	226-216'	226"-216'"		
Inter-H-H (h 11, h 14)	232-232'	235-235"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
303, 303"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

ensartinibum

ensartinib

6-amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-*N*-{4-[(3*R*,5*S*)-3,5-dimethylpiperazine-1-carbonyl]phenyl}pyridazine-3-carboxamide

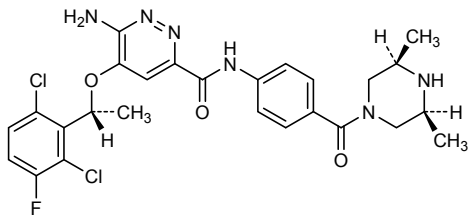
ensartinib

6-amino-5-[(1*R*)-1-(2,6-dichloro-3-fluorophényl)éthoxy]-*N*-{4-[(3*R*,5*S*)-3,5-diméthylpiperazine-1-carbonyl]phényl}pyridazine-3-carboxamide

ensartinib

6-amino-5-[(1*R*)-1-(2,6-dicloro-3-fluorofenil)etoxi]-*N*-{4-[(3*R*,5*S*)-3,5-dimetilpiperazina-1-carbonil]fenil}piridazina-3-carboxamida

$C_{26}H_{27}Cl_2FN_6O_3$



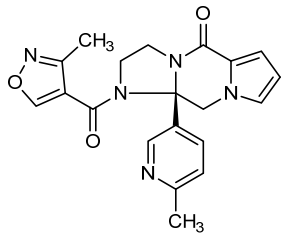
enzaplatovirum

enzaplatovir — (10a*R*)-1-(3-methyl-1,2-oxazole-4-carbonyl)-10a-(6-methylpyridin-3-yl)-2,3,10,10a-tetrahydro-1*H*,5*H*-imidazo[1,2-*a*]pyrrolo[1,2-*d*]pyrazin-5-one

enzaplatovir — (10a*R*)-1-(3-méthyl-1,2-oxazole-4-carbonyl)-10a-(6-méthylpyridin-3-yl)-2,3,10,10a-tétrahydro-1*H*,5*H*-imidazo[1,2-*a*]pyrrolo[1,2-*d*]pyrazin-5-one

enzaplatovir — (10a*R*)-1-(3-metil-1,2-oxazol-4-carbonil)-10a-(6-metilpiridin-3-il)-2,3,10,10a-tetrahidro-1*H*,5*H*-imidazo[1,2-*a*]pirrolo[1,2-*d*]pirazin-5-ona

$C_{20}H_{19}N_5O_3$



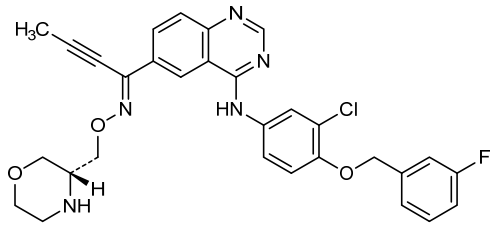
epertinibum

epertinib — *N*-{3-chloro-4-[(3-fluorophenyl)methoxy]phenyl}-6-[(1*Z*)-*N*-{[(3*R*)-morpholin-3-yl]methoxy}but-2-ynimidoyl]quinazolin-4-amine

épertinib — *N*-{3-chloro-4-[(3-fluorophényl)méthoxy]phényl}-6-[(1*Z*)-*N*-{[(3*R*)-morpholin-3-yl]méthoxy}but-2-ynimidoyl]quinazolin-4-amine

epertinib — *N*-{3-cloro-4-[(3-fluorofenil)metoxi]fenil}-6-[(1*Z*)-*N*-{[(3*R*)-morfolin-3-il]metoxi}but-2-inimidoil]quinazolin-4-amina

$C_{30}H_{27}ClFN_5O_3$



eptinezumabum #

eptinezumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* CALCA (calcitonin related polypeptide alpha) calcitonin gene-related peptide 1, CGRP1, 83-119 and *Homo sapiens* CALCB (calcitonin related polypeptide beta) calcitonin gene-related peptide 2, CGRP2, 82-118], humanized monoclonal antibody; gamma1 heavy chain (1-441) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ3*02) [8.7.5] (1-111) -*Homo sapiens* IGHG1*03 (CH1 K119>A (156) (112-209), hinge (210-224), CH2 N84.4>A (291) (225-334), CH3 (335-439), CHS (440-441)) (112-441)], (214-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV1-27*01 (86.20%) -IGKJ4*01) [8.3.13] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dimer (220-220":223-223")-bisdisulfide
eptinezumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* CALCA (polypeptide alpha apparenté à la calcitonine) peptide 1 apparenté au gène de la calcitonine, CGRP1, 83-119 et *Homo sapiens* CALCB (polypeptide bêta apparenté à la calcitonine) peptide 2 apparenté au gène de la calcitonine, CGRP2, 82-118], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-441) [VH humanisé (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ3*02) [8.7.5] (1-111) -*Homo sapiens* IGHG1*03 (CH1 K119>A (156) (112-209), charnière (210-224), CH2 N84.4>A (291) (225-334), CH3 (335-439), CHS (440-441)) (112-441)], (214-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV1-27*01 (86.20%) -IGKJ4*01) [8.3.13] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dimère (220-220":223-223")-bisdisulfure
eptinezumab	inmunoglobulina G1-kappa, anti-[*Homo sapiens* CALCA (polipéptido alfa relacionado con la calcitonina) péptido 1 relacionado con el gen de la calcitonina, CGRP1, 83-119 y *Homo sapiens* CALCB (polipéptido beta relacionado con la calcitonina) péptido 2 relacionado con el gen de la calcitonina, CGRP2, 82-118], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-441) [VH humanizado (*Homo sapiens* IGHV3-66*01 (81.40%) -(IGHD)-IGHJ3*02) [8.7.5] (1-111) -*Homo sapiens* IGHG1*03 (CH1 K119>A (156) (112-209), bisagra (210-224), CH2 N84.4>A (291) (225-334), CH3 (335-439), CHS (440-441)) (112-441)], (214-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizado (*Homo sapiens* IGKV1-27*01 (86.20%) -IGKJ4*01) [8.3.13] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dímero (220-220":223-223")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAVSGIDLS GYYMNWVRQA PGKGLEWVGV  50
IGINGATYYA SWAKGRFTIS RDNSKTTVYL QMNSLRAEDT AVYFCARGDI 100
WGQGTLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV KDYFPEPVTV 150
SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ TYICNVNHKP 200
SNTKVDARVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK PKDTLMISRT 250
PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY ASTYRVVSVL 300
TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP QVYTLPPSRE 350
EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP VLDSDGSFFL 400
YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG K          441
```

Light chain / Chaîne légère / Cadena ligera

```
QVLTQSPSSL SASVGDRVTI NCQASQSVYH NTYLAWYQQK PGKVPKQLIY  50
DASTLASGVP SRFSGSGSGT DFTLTISSLQ PEDVATYYCL GSYDCTNGDC 100
FVFGGGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-95	138-194	255-315	361-419
	22"-95"	138"-194"	255"-315"	361"-419"
Intra-L (C23-C104)	22'-89'	139'-199'	Intra-L	95'-100'
	22'''-89'''	139'''-199'''	(C110-C115)	95'''-100'''
Inter-H-L (h 5-CL 126)	214-219'	214"-219'''		
Inter-H-H (h 11, h 14)	220-220"	223-223"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4>A (291, 291"):
No N-glycosylation sites / pas de sites de N-glycosylation /ningún posición de N-glicosilación

erenumabum #

erenumab	immunoglobulin G2-lambda, anti-[*Homo sapiens* CALCRL (calcitonin receptor like receptor, calcitonin gene-related peptide receptor, CGRPR, CGRP-R, CRLR)], *Homo sapiens* monoclonal antibody; gamma2 heavy chain (1-456) [*Homo sapiens* VH (IGHV3-30*03 (93.90%) -(IGHD) -IGHJ6*01) [8.8.23] (1-130) -IGHG2*01, G2m.. (CH1 (131-228), hinge (229-240), CH2 (241-349), CH3 (350-454), CHS (455-456)) (131-456)], (144-215')-disulfide with lambda light chain (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-51*01 (98.00%) -IGLJ2*01) [8.3.11] (1'-110') -IGLC1*01 (111'-216')]; dimer (232-232":233-233":236-236":239-239")-tetrakisdisulfide
érénumab	immunoglobuline G2-lambda, anti-[*Homo sapiens* CALCRL (récepteur analogue au récepteur de la calcitonine, récepteur du peptide apparenté au gène de la calcitonine, CGRPR, CGRP-R, CRLR)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma2 (1-456) [*Homo sapiens* VH (IGHV3-30*03 (93.90%) -(IGHD) -IGHJ6*01) [8.8.23] (1-130) -IGHG2*01, G2m.. (CH1 (131-228), charnière (229-240), CH2 (241-349), CH3 (350-454), CHS (455-456)) (131-456)], (144-215')-disulfure avec la chaîne légère lambda (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-51*01 (98.00%) -IGLJ2*01) [8.3.11] (1'-110') -IGLC1*01 (111'-216')]; dimère (232-232":233-233":236-236":239-239")-tétrakisdisulfure
erenumab	inmunoglobulina G2-lambda, anti-[*Homo sapiens* CALCRL (receptor análogo del receptor de la calcitonina, receptor del péptido relacionado con el gen de la calcitonina, CGRPR, CGRP-R, CRLR)], *Homo sapiens* anticuerpo monoclonal;

cadena pesada gamma2 (1-456) [*Homo sapiens* VH (IGHV3-30*03 (93.90%) -(IGHD) -IGHJ6*01) [8.8.23] (1-130) -IGHG2*01, G2m.. (CH1 (131-228), bisagra (229-240), CH2 (241-349), CH3 (350-454), CHS (455-456)) (131-456)], (144-215')-disulfuro con la cadena ligera lambda (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-51*01 (98.00%) -IGLJ2*01) [8.3.11] (1'-110') -IGLC1*01 (111'-216')]; dímero (232-232'':233-233'':236-236'':239-239'')-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGGG VVQPGRSLRL SCAASGFTFS SFGMHWVRQA PGKGLEWVAV  50
ISFDGSIKYS VDSVKGRFTI SRDNSKNTLF LQMNSLRAED TAVYYCARDR 100
LNYYDSSGYY HYKYYGMAVW GQGTTVTVSS ASTKGPSVFP LAPCSRSTSE 150
STAALGCLVK DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT 200
VPSSNFGTQT YTCNVDHKPS NTKVDKTVER KCCVECPPCP APPVAGPSVF 250
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVQFNWYVDG VEVHNAKTKP 300
REEQFNSTFR VVSVLTVVHQ DWLNGKEYKC KVSNKGLPAP IEKTISKTKG 350
QPREPQVYTL PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY 400
KTTPPMLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL 450
SLSPGK                                                  456
```

Light chain / Chaîne légère / Cadena ligera

```
QSVLTQPPSV SAAPGQKVTI SCSGSSSNIG NNYVSWYQQL PGTAPKLLIY  50
DNNKRPSGIP DRFSGSKSGT STTLGITGLQ TGDEADYYCG TWDSRLSAVV 100
FGGGTKLTVL GQPKANPTVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV 150
AWKADGSPVK AGVETTKPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT 200
HEGSTVEKTV APTECS                                       216
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 157-213 270-330 376-434
22"-96" 157"-213" 270"-330" 376"-434"
Intra-L (C23-C104) 22'-89' 138'-197'
22'"-89'" 138'"-197"
Inter-H-L (CH1 10-CL 126) 144-215' 144"-215'"
Inter-H-H (h 4, h 5, h 8, h 11) 232-232" 233-233" 236-236" 239-239"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
306, 306"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

eretidigenum velentivecum #
eretidigene velentivec

Recombinant, non-replicating, lentiviral vector w1.6_hWAS_WPREmut6 (VSV-G*) encoding the human Wiskott-Aldrich syndrome (WAS) gene under the control of its native promoter, post-transcriptionally-regulated by a modified WPRE (mut6 WPRE**)
* VSV-G = vesicular stomatitis virus G envelope protein
** WPRE m6 = WPRE mut6 = mut6 = mut6 WPRE: mutated woodchuck hepatitis virus posttranscriptional regulatory element

érétidigène vélentivec

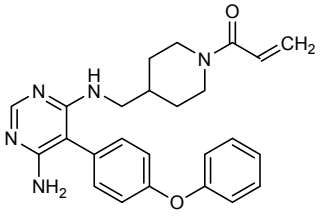
vecteur lentiviral recombinant sans capacité de réplication w1.6_hWAS_WPREmut6 (VSV-G*) contenant le gène humain du syndrome de Wiskott-Aldrich sous le contrôle de son promoteur natif, régulé en post-transcription par WPRE** modifié (mut6 WPRE**)
* VSV-G = glycoprotéine G du virus de la stomatite vésiculaire
**WPRE m6 = WPRE mut6 = mut6 = mut6 WPRE: élément muté de régulation post-transcriptionnelle du virus de l'hépatite de la marmotte d'Amérique

eretidigén velentivec	vector lentiviral recombinante no replicativo w1.6_hWAS_WPREmut6 (VSV-G*) que contiene el gen humano del síndrome de Wiskott-Aldrich bajo el control de su promotor nativo, regulado post-transcripcionalmente por WPRE** modificado (mut6 WPRE**) * VSV-G = glicoproteína G del virus de la estomatitis vesicular **WPRE m6 = WPRE mut6 = mut6 = mut6 WPRE: elemento mutado de regulación post-transcriptionnal del virus de la hepatitis de la marmota de América

evobrutinibum

evobrutinib	1-[4-({[6-amino-5-(4-phenoxyphenyl)pyrimidin-4-yl]amino}methyl)piperidin-1-yl]prop-2-en-1-one
évobrutinib	1-[4-({[6-amino-5-(4-phénoxyphényl)pyrimidin-4-yl]amino}méthyl)pipéridin-1-yl]prop-2-én-1-one
evobrutinib	1-[4-({[6-amino-5-(4-fenoxifenil)pirimidin-4-il]amino}metil)piperidin-1-il]prop-2-en-1-ona

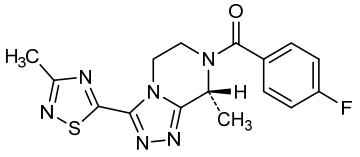
$C_{25}H_{27}N_5O_2$



fezolinetantum

fezolinetant	(4-fluorophenyl)[(8*R*)-8-methyl-3-(3-methyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]methanone
fézolinétant	(4-fluorophényl)[(8*R*)-8-méthyl-3-(3-méthyl-1,2,4-thiadiazol-5-yl)-5,6-dihydro-1,2,4-triazolo[4,3-*a*]pyrazin-7(8*H*)-yl]méthanone
fezolinetant	(4-fluorofenil)[(8*R*)-8-metil-3-(3-metil-1,2,4-tiadiazol-5-il)-5,6-dihidro-1,2,4-triazolo[4,3-*a*]pirazin-7(8*H*)-il]metanona

$C_{16}H_{15}FN_6OS$



flurdihydroergotaminum

flurdihydroergotamine	5'α-benzyl-12'-hydroxy-2'-methyl-2-(trifluoromethyl)-(10α)-9,10-dihydroergotaman-3',6',18-trione

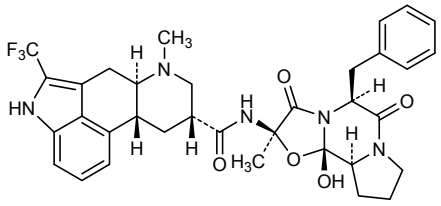
flurdihydroergotamine

5'α-benzyl-12'-hydroxy-2'-méthyl-2-(trifluorométhyl)-(10α)-9,10-dihydroergotamane-3',6',18-trione

flurdihidroergotamina

5'α-bencil-12'-hidroxi-2'-metil-2-(trifluorometil)-(10α)-9,10-dihidroergotaman-3',6',18-triona

$C_{34}H_{36}F_3N_5O_5$



follitropinum epsilon #

follitropin epsilon

heterodimer of human glycoprotein hormones alpha chain and follitropin subunit beta (FSH-beta), follicle-stimulating hormone, produced in human chronic myelogenous leukaemia cells, glycoform epsilon

follitropine epsilon

hétérodimère constitué de la chaîne alpha des hormones glycoprotéiques et de la sous-unité bêta de la follitropine (HFS-bêta) humaines, hormone folliculostimulante, produite dans des cellules humaines de leucémie myéloïde chronique, forme glycosylée epsilon

folitropina épsilon

heterodímero constituido por la cadena alfa de las hormonas glicoproteícas y la subunidad beta de la folitropina (HFS-beta) humanas, hormona estimulante del folículo, producida en células humanas de la leucemia mieloide crónica, forma glicosilada épsilon

alpha chain / chaîne alpha / cadena alfa

```
APDVQDCPEC TLQENPFFSQ PGAPILQCMG CCFSRAYPTP LRSKKTMLVQ 50
KNVTSESTCC VAKSYNRVTV MGGFKVENHT ACHCSTCYYH KS         92
```

beta chain / chaîne bêta / cadena beta

```
NSCELTNITI AIEKEECRFC ISINTTWCAG YCYTRDLVYK DPARPKIQKT 50'
CTFKELVYET VRVPGCAHHA DSLYTYPVAT QCHCGKCDSD STDCTVRGLG 100'
PSYCSFGEMK E                                           111'
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

7-31 10-60 28-82 32-84 59-87
3'-51' 17'-66' 20'-104' 28'-82' 32'-84' 87'-94'

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)

Asn-52 Asn-78 Asn-7' Asn-24'

fostemsavirum

fostemsavir

{3-[(4-benzoylpiperazin-1-yl)-oxoacetyl]-4-methoxy-7-(3-methyl-1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-1-yl}methyl dihydrogen phosphate

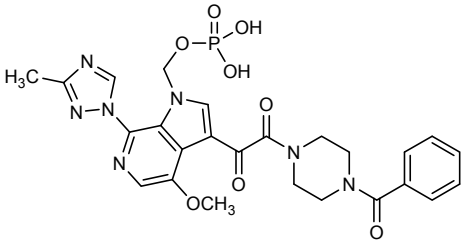
fostemsavir

dihydrogénophosphate de {3-[(4-benzoylpipérazin-1-yl)-oxoacétyl]-4-méthoxy-7-(3-méthyl-1*H*-1,2,4-triazol-1-yl)-1*H*-pyrrolo[2,3-*c*]pyridin-1-yl}méthyle

fostemsavir

dihidrogenofosfato de {3-[(4-benzoilpiperazin-1-il)-oxoacetil]-4-metoxi-7-(3-metil-1*H*-1,2,4-triazol-1-il)-1*H*-pirrolo[2,3-*c*]piridin-1-il}metilo

$C_{25}H_{26}N_7O_8P$



fremanezumabum #

fremanezumab

immunoglobulin G2-kappa, anti-[*Homo sapiens* CALCA (calcitonin related polypeptide alpha) calcitonin gene-related peptide 1, CGRP1, 83-119 and *Homo sapiens* CALCB (calcitonin related polypeptide beta) calcitonin gene-related peptide 2, CGRP2, 82-118], humanized monoclonal antibody;
gamma2 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV3-7*01 (85.70%) -(IGHD) -IGHJ4*01) [8.10.13] (1-122) -*Homo sapiens* IGHG2*01, G2m..(CH1 (123-220), hinge (221-232), CH2 A115>S (331), P116>S (332) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV3-11*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (224-224":225-225":228-228":231-231")-tetrakisdisulfide

frémanezumab

immunoglobuline G2-kappa, anti-[*Homo sapiens* CALCA (polypeptide alpha apparenté à la calcitonine) peptide 1 apparenté au gène de la calcitonine, CGRP1, 83-119 et *Homo sapiens* CALCB (polypeptide bêta apparenté à la calcitonine) peptide 2 apparenté au gène de la calcitonine, CGRP2, 82-118], anticorps monoclonal humanisé;
chaîne lourde gamma2 (1-448) [VH humanisé (*Homo sapiens* IGHV3-7*01 (85.70%) -(IGHD) -IGHJ4*01) [8.10.13] (1-122) -*Homo sapiens* IGHG2*01, G2m..(CH1 (123-220), charnière (221-232), CH2 A115>S (331), P116>S (332) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV3-11*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (224-224":225-225":228-228":231-231")-tétrakisdisulfure

fremanezumab

inmunoglobulina G2-kappa, anti-[*Homo sapiens* CALCA (polipéptido alfa relacionado con la calcitonina) péptido 1 relacionado con el gen de la calcitonina, CGRP1, 83-119 y *Homo sapiens* CALCB (polipéptido beta relacionado con la calcitonina) péptido 2 relacionado con el gen de la calcitonina, CGRP2, 82-118], anticuerpo monoclonal humanizado;

cadena pesada gamma2 (1-448) [VH humanizado (*Homo sapiens* IGHV3-7*01 (85.70%) -(IGHD) -IGHJ4*01) [8.10.13] (1-122) -*Homo sapiens* IGHG2*01, G2m.. (CH1 (123-220), bisagra (221-232), CH2 A115>S (331), P116>S (332) (233-341), CH3 (342-446), CHS (447-448)) (123-448)], (136-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV3-11*01 (85.30%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (224-224":225-225":228-228":231-231")-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS NYWISWVRQA PGKGLEWVAE  50
IRSESDASAT HYAEAVKGRF TISRDNAKNS LYLQMNSLRA EDTAVYYCLA 100
YFDYGLAIQN YWGQGTLVTV SSASTKGPSV FPLAPCSRST SESTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSNFGT 200
QTYTCNVDHK PSNTKVDKTV ERKCCVECPP CPAPPVAGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVQFNWYV DGVEVHNAKT KPREEQFNST 300
FRVVSVLTVV HQDWLNGKEY KCKVSNKGLP SSIEKTISKT KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPMLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSLSPGERAT LSCKASKRVT TYVSWYQQKP GQAPRLLIYG  50
ASNRYLGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCSQ SYNYPYTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-98	149-205	262-322	368-426
	22"-98"	149"-205"	262"-322"	368"-426"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23"'-88"'	134"'-194"'		
Inter-H-L (CH1 10-CL 126)	136-214'	136"-214"'		
Inter-H-H (h 4, h 5, h 8, h 11)	224-224"	225-225"	228-228"	231-231"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
298, 298"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

gemtuzumabum ozogamicinum #
gemtuzumab ozogamicin

immunoglobulin G4-kappa, anti-[*Homo sapiens* CD33 (sialic acid binding Ig-like lectin 3, SIGLEC3, SIGLEC-3, gp67, p67)], humanized monoclonal antibody conjugated to *N*-acetyl-gamma calicheamicin;
gamma4 heavy chain (1-443) [humanized VH (*Homo sapiens* IGHV1-3*01 (72.90%) -(IGHD) -IGHJ5*01) [8.8.9] (1-116)), IGHG4*01 (CH1 (117-214), hinge S10>P (224) (215-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (117-443)], (130-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV1-5*01 (81.90%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimer (232-232":235-235")-bisdisulfide; conjugated, on an average of 2 or 3 lysyl (0-6), to *N*-acetyl-*S*'-des(methylsulfanyl)-*S*'-(4-hydrazinyl-2-methyl-4-oxobutan-2-yl)calicheamicin γ_1 via a bifunctional 4-(4-acetylphenoxy)butanoyle (AcBut) linker

gemtuzumab ozogamicine

immunoglobuline G4-kappa, anti-[*Homo sapiens* CD33 (lectine 3 de type Ig-like liant l'acide sialique, SIGLEC3, SIGLEC-3, gp67, p67)], anticorps monoclonal humanisé conjugué à la *N*-acétyl-gamma calichéamicine;
chaîne lourde gamma4 chain (1-443) [VH humanisé (*Homo sapiens* IGHV1-3*01 (72.90%) -(IGHD) -IGHJ5*01) [8.8.9] (1-116)), IGHG4*01 (CH1 (117-214), charnière S10>P (224) (215-226), CH2 (227-336), CH3 (337-441),

CHS (442-443)) (117-443)], (130-218')-disulfure avec la chaîne légère (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV1-5*01 (81.90%) - IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimère (232-232":235-235")-bisdisulfure; conjugué, sur 2 ou 3 lysyl en moyenne (0-6), à la *N*-acétyl-*S*'-dés(méthylsulfanyl)-*S*'-(4-hydrazinyl-2-méthyl-4-oxobutan-2-yl)calichéamicine γ_1 via un linker bifunctionnel 4-(4-acétylphénoxy)butanoyle (AcBut)

gemtuzumab ozogamicina

inmunoglobulina G4-kappa, anti-[*Homo sapiens* CD33 (lectina de tipo inmunoglobulina 3 que se une al ácido siálico, SIGLEC3, SIGLEC-3, gp67, p67)], anticuerpo monoclonal humanizado conjugado con la *N*-acetil-gamma calicheamicina;
cadena pesada gamma4 cadena (1-443) [VH humanizado (*Homo sapiens* IGHV1-3*01 (72.90%) -(IGHD) -IGHJ5*01) [8.8.9] (1-116)), IGHG4*01 (CH1 (117-214), bisagra S10>P (224) (215-226), CH2 (227-336), CH3 (337-441), CHS (442-443)) (117-443)], (130-218')-disulfuro con la cadena ligera (1'-218') [V-KAPPA humanizada (*Homo sapiens* IGKV1-5*01 (81.90%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dímero (232-232":235-235")-bisdisulfuro; conjugado, sobre 2 o 3 lisil por término medio (0-6), a la *N*-acetil-*S*'-des(metilsulfanil)-*S*'-(4-hidrazinil-2-metil-4-oxobutan-2-il)calicheamicina γ_1 mediante un enlace bifuncional 4-(4-acetilfenoxi)butanoil (AcBut)

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGAE VKKPGSSVKV SCKASGYTIT DSNIHWVRQA PGQSLEWIGY  50
IYPYNGGTDY NQKFKNRATL TVDNPTNTAY MELSSLRSED TAFYYCVNGN 100
PWLAYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTKTYTCN 200
VDHKPSNTKV DKRVESKYGP PCPPCPAPEF LGGPSVFLFP PKPKDTLMIS 250
RTPEVTCVVV DVSQEDPEVQ FNWYVDGVEV HNAKTKPREE QFNSTYRVVS 300
VLTVLHQDWL NGKEYKCKVS NKGLPSSIEK TISKAKGQPR EPQVYTLPPS 350
QEEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT PPVLDSDGSF 400
FLYSRLTVDK SRWQEGNVFS CSVMHEALHN HYTQKSLSLS LGK        443
```

Light chain / Chaîne légère / Cadena ligera

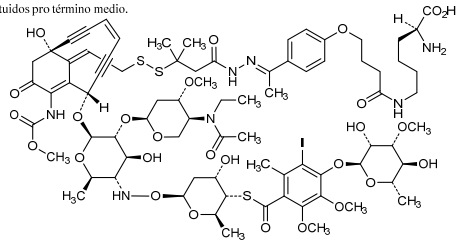
```
DIQLTQSPST LSASVGDRVT ITCRASESLD NYGIRFLTWF QQKPGKAPKL  50
LMYAASNQGS GVPSRFSGSG SGTEFTLTIS SLQPDDFATY YCQQTKEVPW 100
SFGQGTKVEV KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 143-199 257-317 363-421
22"-96" 143"-199" 257"-317" 363"-421"
Intra-L (C23-C104) 23'-92' 138'-198'
23'"-92'" 138'"-198'"
Inter-H-L (CH1 10-CL 126) 130-218' 130"-218'"
Inter-H-H (h 8, h 11) 222-222" 225-225"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
293, 293"
Fucosylated complex bi-antennary NS0-type glycans / glycanes de type NS0 bi-antennaires complexes fucosylés / glicanos de tipo NS0 biantenarios complejos fucosilados
Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
443, 443"

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales
An average of 2 or 3 lysyl are substituted. 2 ou 3 lysyl sont substitués en moyenne. 2 o 3 lisil estan sustituidos pro término medio.



golodirsenum

golodirsen

all-P-ambo-[2',3'-azanediyl-*P*-(dimethylamino)-*P*,2',3'-trideoxy-2',3'-seco](2'-*N*→5')(G-T-T-G-C-C-T-C-C-G-G-T-T-C-T-G-A-A-G-G-T-G-T-T-C) 5'-{*P*-[4-({2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}carbonyl)piperazin-1-yl]-*N*,*N*-dimethylphosphonamidate}

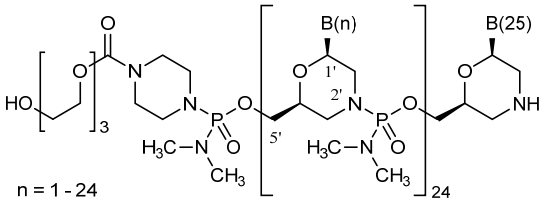
golodirsen

tout-P-ambo-5'-{*P*-[4-({2-[2-(2-hydroxy-éthoxy)éthoxy]éthoxy}carbonyl)pipérazin-1-yl]-*N*,*N*-diméthylphosphonamidate} de [2',3'-azanediyl-*P*-(diméthylamino)-*P*,2',3'-tridéoxy-2',3'-séco](2'-*N*→5')(G-T-T-G-C-C-T-C-C-G-G-T-T-C-T-G-A-A-G-G-T-G-T-T-C)

golodirsén

todo-P-ambo-5'-{*P*-[4-({2-[2-(2-hidroxietoxi)etoxi]etoxi}carbonil)piperazin-1-il]-*N*,*N*-dimetilfosfonamidato} de [2',3'-azanediil-*P*-(dimetilamino)-*P*,2',3'-tridesoxi-2',3'-seco](2'-*N*→5')(G-T-T-G-C-C-T-C-C-G-G-T-T-C-T-G-A-A-G-G-T-G-T-T-C)

$C_{305}H_{481}N_{138}O_{112}P_{25}$



B(1-25):
G-T-T-G-C-C-T-C-C-G-G-T-T-C-T-G-A-A-G-G-T-G-T-T-C

hemoglobinum betafumarilum (bovinum) #

hemoglobin betafumaril (bovine)

$S^{3.\beta92}$,$S^{3.\beta'92}$-bis(2-amino-2-oxoethyl)-$N^{6.\beta81}$,$N^{6.\beta'81}$-[(2*E*)-(but-2-enedioyl)]bovine hemoglobin ($\alpha_2\beta_2$ tetramer)

hémoglobine bêtafumaril (bovine)

$S^{3.\beta92}$,$S^{3.\beta'92}$-bis(2-amino-2-oxoéthyl)-$N^{6.\beta81}$,$N^{6.\beta'81}$-[(2*E*)-(but-2-ènedioyl)]hémoglobine bovine (tétramère $\alpha_2\beta_2$)

hemoglobina betafumarilo (bovina)

$S^{3.\beta92}$,$S^{3.\beta'92}$-bis(2-amino-2-oxoetil)-$N^{6.\beta81}$,$N^{6.\beta'81}$-[(2*E*)-(but-2-enedioil)]hemoglobina bovina (tetrámero $\alpha_2\beta_2$)

Alpha chain / Chaîne alpha / Cadena alfa

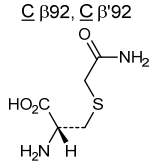
```
VLSAADKGNV KAAWGKVGGH AAEYGAEALE RMFLSFPTTK TYFPHFDLSH  50
GSAQVKGHGA KVAAALTKAV EHLDDLPGAL SELSDLHAHK LRVDPVNFKL 100
LSHSLLVTLA SHLPSDFTPA VHASLDKFLA NVSTVLTSKY R          141
```

Beta chain / Chaîne bêta / Cadena beta

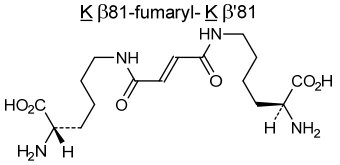
```
MLTAEEKAAV TAFWGKVKVD EVGGEALGRL LVVYPWTQRF FESFGDLSTA  50
DAVMNNPKVK AHGKKVLDSF SNGMKHLDDL KGTFAALSEL HCDKLHVDPE 100
NFKLLGNVLV VVLARNFGKE FTPVLQADFQ KVVAGVANAL AHRYH       145
```

Modified residues / Résidus modifiés / Restos modificados

C β92, C β'92



K β81-fumaryl- K β'81



ifabotuzumabum #

ifabotuzumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* EPHA3 (ephrin receptor A3, EPH receptor A3, ephrin type-A receptor 3, tyrosine protein kinase TYR04, tyrosine-protein kinase receptor REK4, ETK, ETK1, HEK, HEK4)], humanized monoclonal antibody; gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV1-2*02 (91.80%) -(IGHD)-IGHJ6*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, Gm3 (CH1 (119-216), hinge (217-231), CH2 (232-341), CH3 (342-447), CHS (448-449)) (119-448)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1D-16*01 (91.60%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimer (227-227":230-230")-bisdisulfide
ifabotuzumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* EPHA3 (récepteur A3 d'éphrine, récepteur A3 d'EPH, récepteur 3 type-A d'éphrine, protéine tyrosine kinase TYR04, récepteur tyrosine-protéine kinase REK4, ETK, ETK1, HEK, HEK4)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* IGHV1-2*02 (91.80%) -(IGHD)-IGHJ6*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, Gm3 (CH1 (119-216), charnière (217-231), CH2 (232-341), CH3 (342-447), CHS (448-449)) (119-448)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1D-16*01 (91.60%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimère (227-227":230-230")-bisdisulfure
ifabotuzumab	inmunoglobulina G1-kappa, anti-[*Homo sapiens* EPHA3 (receptor A3 de efrina, receptor A3 d'EPH, receptor 3 tipo-A de efrina, tirosina protein kinasa TYR04, receptor tirosina-protein kinasa REK4, ETK, ETK1, HEK, HEK4)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-449) [VH humanizado (*Homo sapiens* IGHV1-2*02 (91.80%) -(IGHD)-IGHJ6*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, Gm3 (CH1 (119-216), bisagra (217-231), CH2 (232-341), CH3 (342-447), CHS (448-449)) (119-448)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1D-16*01 (91.60%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dímero (227-227":230-230")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT GYWMNWVRQA PGQGLEWMGD  50
IYPGSGNTNY DEKFQGRVTM TRDTSISTAY MELSRLRSDD TAVYYCARGG 100
YYEDFDSWGQ GTTVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSF LSASVGDRVT ITCRASQGII SYLAWYQQKP EKAPKRLIYA  50
ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCGQ YANYPYTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 145-201 262-322 368-426
22"-96" 145"-201" 262"-322" 368"-426"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 221-214' 221"-214'"
Inter-H-H (h 11, h 14) 227-227" 230-230"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
298, 298"
Afucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes afucosylés / glicanos de tipo CHO biantenarios complejos no fucosilados

ilmetropii iodidum

ilmetropium iodide

(1*R*,3*r*,5*S*)-3-{[(2*RS*)-2-(hydroxymethyl)-2-phenylbutanoyl]oxy}-8,8-dimethyl-8-azabicyclo[3.2.1]octanium iodide

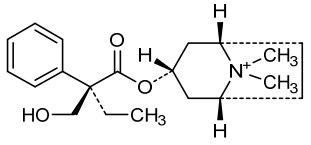
iodure d'ilmétropium

iodure de (1*R*,3*r*,5*S*)-3-{[(2*RS*)-2-(hydroxyméthyl)-2-phénylbutanoyl]oxy}-8,8-diméthyl-8-azabicyclo[3.2.1]octanium

ioduro de ilmetropio

ioduro de (1*R*,3*r*,5*S*)-3-{[(2*RS*)-2-fenil-2-(hidroximetil)butanoil]oxi}-8,8-dimetil-8-azabiciclo[3.2.1]octanio

$C_{20}H_{30}INO_3$



and enantiomer
et énantiomère
y enantiómero

imlatoclaxum

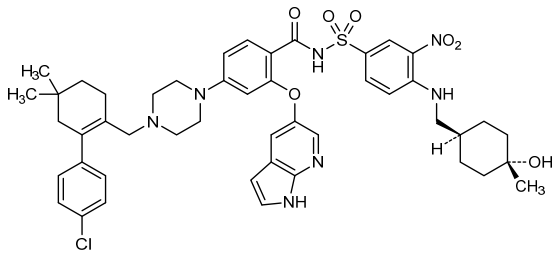
imlatoclax

4-(4-{[2-(4-chlorophenyl)-4,4-dimethylcyclohex-1-en-1-yl]methyl}piperazin-1-yl)-*N*-(4-{[(*trans*-4-hydroxy-4-methylcyclohexyl)methyl]amino}-3-nitrobenzenesulfonyl)-2-[(1*H*-pyrrolo[2,3-*b*]pyridin-5-yl)oxy]benzamide

imlatoclax

4-(4-{[2-(4-clorofenil)-4,4-dimetilciclohex-1-en-1-il]metil}piperazin-1-il)-*N*-(4-{[(*trans*-4-hidroxi-4-metilciclohexil)metil]amino}-3-nitrobencenosulfonil)-2-[(1*H*-pirrolo[2,3-*b*]piridin-5-il)oxi]benzamida

$C_{47}H_{54}ClN_7O_7S$



inotersenum

inotersen

all-P-ambo-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine

inotersen

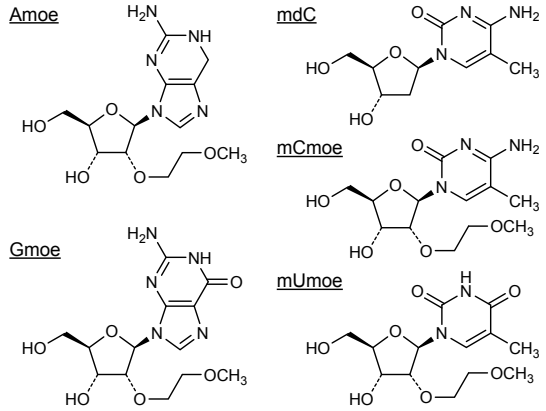
tout-P-ambo-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-déoxy-*P*-thioguanylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-déoxy-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthylcytidine

inotersén

todo-P-ambo-5-metil-2'-*O*-(2-metoxietil)-*P*-tiouridilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiocitidilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiouridilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioadenilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiouridilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiocitidilil-(3'→5')-5-metil-2'-*O*-(2-metoxietil)-*P*-tiocitidilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metilcitidina

$C_{230}H_{318}N_{69}O_{121}P_{19}S_{19}$

(3'-5')(*P*-thio)(mUmoe-mCmoe-mUmoe-mUmoe-Gmoe-dG-dT-dT-dA-mdC--dA-dT-dG-dA-dA-Amoe-mUmoe-mCmoe-mCmoe-mCmoe)



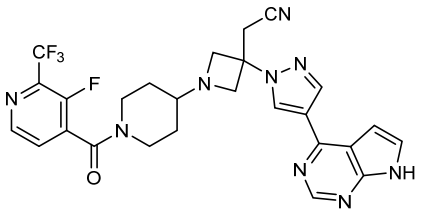
itacitinibum

itacitinib — (1-{1-[3-fluoro-2-(trifluoromethyl)pyridine-4-carbonyl]piperidin-4-yl}-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azetidin-3-yl)acetonitrile

itacitinib — (1-{1-[3-fluoro-2-(trifluorométhyl)pyridine-4-carbonyl]pipéridin-4-yl}-3-[4-(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)-1*H*-pyrazol-1-yl]azétidin-3-yl)acetonitrile

itacitinib — (1-{1-[3-fluoro-2-(trifluorometil)piridina-4-carbonil]piperidin-4-il}-3-[4-(7*H*-pirrolo[2,3-*d*]pirimidin-4-il)-1*H*-pirazol-1-il]azetidin-3-il)acetonitrile

$C_{26}H_{23}F_4N_9O$



larotrectinibum

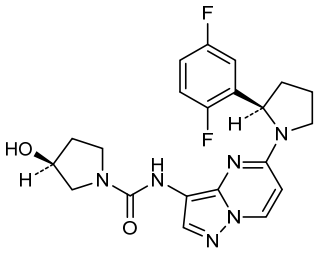
larotrectinib — (3*S*)-*N*-{5-[(2*R*)-2-(2,5-difluorophenyl)pyrrolidin-1-yl]pyrazolo[1,5-*a*]pyrimidin-3-yl}-3-hydroxypyrrolidine-1-carboxamide

larotrectinib — (3*S*)-*N*-{5-[(2*R*)-2-(2,5-difluorophényl)pyrrolidin-1-yl]pyrazolo[1,5-*a*]pyrimidin-3-yl}-3-hydroxypyrrolidine-1-carboxamide

larotrectinib

(3*S*)-*N*-{5-[(2*R*)-2-(2,5-difluorofenil)pirrolidin-1-il]pirazolo[1,5-*a*]pirimidin-3-il}-3-hidroxipirrolidina-1-carboxamida

$C_{21}H_{22}F_2N_6O_2$



lisavanbulinum

lisavanbulin

(2*S*)-2,6-diamino-*N*-[4-[2-(2-{4-[(2-cyanoethyl)amino]-1,2,5-oxadiazol-3-yl}-1*H*-benzimidazol-1-yl)acetyl]phenyl}hexanamide

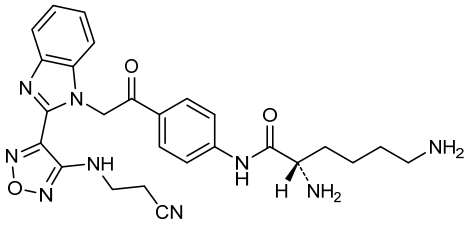
lisavanbuline

(2*S*)-2,6-diamino-*N*-[4-[2-(2-{4-[(2-cyanoéthyl)amino]-1,2,5-oxadiazol-3-yl}-1*H*-benzimidazol-1-yl)acétyl]phényl}hexanamide

lisavanbulina

(2*S*)-2,6-diamino-*N*-[4-[2-(2-{4-[(2-cianoetil)amino]-1,2,5-oxadiazol-3-il}-1*H*-benzimidazol-1-il)acetil]fenil}hexanamida

$C_{26}H_{29}N_9O_3$



lumicitabinum

lumicitabine

4'-*C*-(chloromethyl)-2'-deoxy-2'-fluorocytidine 3',5'-bis(2-methylpropanoate)

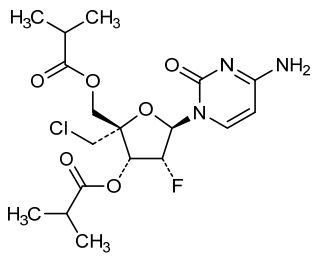
lumicitabine

3',5'-bis(2-méthylpropanoate) de 4'-*C*-(chlorométhyl)-2'-déoxy-2'-fluorocytidine

lumicitabina

3',5'-bis(2-metilpropanoato) de 4'-*C*-(clorometil)-2'-desoxi-2'-fluorocitidina

$C_{18}H_{25}ClFN_3O_6$



lupartumabum #

lupartumab	immunoglobulin G1-lambda1, anti-[*Homo sapiens* LYPD3 (Ly6/PLAUR domain containing 3, GPI-anchored cell-surface protein C4.4a, C4.4A)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfide with lambda1 light chain (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimer (226-226":229-229")-bisdisulfide
lupartumab	immunoglobuline G1-lambda1, anti-[*Homo sapiens* LYPD3 (protéine 3 contenant un domaine Ly6/PLAUR, protéine C4.4a GPI-ancrée à la surface cellulaire, C4.4A)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), charnière (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfure avec la chaîne légère lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimère (226-226":229-229")-bisdisulfure
lupartumab	inmunoglobulina G1-lambda1, anti-[*Homo sapiens* LYPD3 (proteína 3 que contiene un dominio Ly6/PLAUR, proteína C4.4a GPI-anclada en la superficie celular, C4.4A)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), bisagra (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfuro con la cadena ligera lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dímero (226-226":229-229")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMSWVRQA PGKGLEWVSY  50
ISSSGSTIYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREG 100
LWAFDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG     446
```

Light chain / Chaîne légère / Cadena ligera

```
ESVLTQPPSV SGAPGQRVTI SCTGSSSNIG AGYVVHWYQQ LPGTAPKLLI  50
YDNNKRPSGV PDRFSGSKSG TSASLAISGL RSEDEADYYC AAWDDRLNGP 100
VFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT 150
VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV 200
THEGSTVEKT VAPTECS                                     217
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261"-321" 367"-425"
Intra-L (C23-C104) 22'-90' 139'-198'
22'"-90'" 139'"-198'"
Inter-H-L (h 5-CL 126) 220-216' 220"-216'"
Inter-H-H (h 11, h 14) 226-226' 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

lupartumabum amadotinum #

lupartumab amadotin

immunoglobulin G1-lambda1, anti-[*Homo sapiens* LYPD3 (Ly6/PLAUR domain containing 3, GPI-anchored cell-surface protein C4.4a, C4.4A)], *Homo sapiens* monoclonal antibody conjugated to an auristatin W derivative; gamma1 heavy chain (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfide with lambda1 light chain (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimer (226-226":229-229")-bisdisulfide; *S*-substituted on an average of 4 reduced cysteinyl by reaction with *N*-demethyl-*N*-[4-(6-maleimidohexanohydrazido)-4-oxobutyl]auristatin W amide

lupartumab amadotine

immunoglobuline G1-lambda1, anti-[*Homo sapiens* LYPD3 (protéine 3 contenant un domaine Ly6/PLAUR, protéine C4.4a GPI-ancrée à la surface cellulaire, C4.4A)], *Homo sapiens* anticorps monoclonal conjugué à un dérivé de l'auristatine W;
chaîne lourde gamma1 (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), charnière (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfure avec la chaîne légère lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dimère (226-226":229-229")-bisdisulfure; *S*-substitué, sur 4 cystéines réduits en moyenne, par reaction avec *N*-desméthyl-*N*-[4-(6-maléimidohexanohydrazido)-4-oxobutyl]auristatine W amide

lupartumab amadotina

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* LYPD3 (proteína 3 que contiene un dominio Ly6/PLAUR, proteína C4.4a GPI-anclada a la superficie celular, C4.4A)], *Homo sapiens* anticuerpo monoclonal conjugado con un derivado de la auristatina W;
cadena pesada gamma1 (1-446) [*Homo sapiens* VH (IGHV3-48*03 (92.90%) -(IGHD) -IGHJ4*01) [8.8.10](1-117) -IGHG1*01, Gm17,1 (CH1 (118-215), bisagra (216-230), CH2 (231-340), CH3 (341-445), CHS K>del (446)) (118-446)], (220-216')-disulfuro con la cadena ligera lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV1-47*01 (87.90%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 (112'-217')]; dímero (226-226":229-229")-bisdisulfuro;
S-sustituido, en 4 grupos cisteinil reducidos por término medio, por reacción con *N*-desmetil-*N*-[4-(6-maleimidohexanohidrazido)-4-oxobutil]auristatina W amida

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS NAWMSWVRQA PGKGLEWVSY  50
ISSSGSTIYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAREG 100
LWAFDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPG     446
```

Light chain / Chaîne légère / Cadena ligera

```
ESVLTQPPSV SGAPGQRVTI SCTGSSSNIG AGYVVHWYQQ LPGTAPKLLI  50
YDNNKRPSGV PDRFSGSKSG TSASLAISGL RSEDEADYYC AAWDDRLNGP 100
VFGGGTKLTV LGQPKAAPSV TLFPPSSEEL QANKATLVCL ISDFYPGAVT 150
VAWKADSSPV KAGVETTTPS KQSNNKYAAS SYLSLTPEQW KSHRSYSCQV 200
THEGSTVEKT VAPTECS                                     217
```

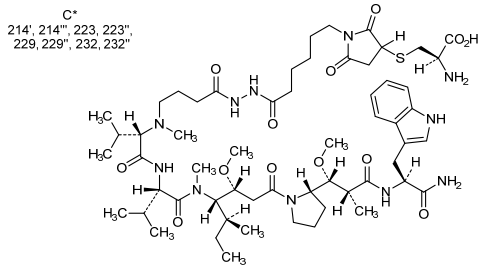
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261"-321" 367"-425"
Intra-L (C23-C104) 22'-90' 139'-198'
22'"-90'" 139'"-198'"
Inter-H-L (h 5-CL 126)* 220-216' 220"-216'"
Inter-H-H (h 11, h 14)* 226-226' 229-229"

*Two or three of the inter-chain disulfide bridges are not present, an average of 4 cysteinyl being conjugated each via a thioether bond to a drug linker.
*Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 4 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif.
*Faltan dos o tres puentes disulfuro inter-catenarios, una media de 4 cisteinil está conjugada a conectores de principio activo.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales



lutikizumabum #

lutikizumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* IL1A (interleukin 1 alpha) and *Homo sapiens* IL1B (interleukin 1 beta, IL-1B, 1L1F2)], humanized monoclonal antibody, tetravalent bispecific; gamma1 heavy chain (1-577) [humanized VH anti-IL1B (*Homo sapiens* IGHV3-23*04 (80.60%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -6-mer linker (120-125) -*Homo sapiens* VH anti-IL1A (IGHV3-30*03 (88.80%) -(IGHD)-IGHJ1*01) [8.8.15] (126-247) -*Homo sapiens* IGHG1*01 (CH1 (248-345), hinge (346-360), CH2 L1.3>A (364), L1.2>A (365), (361-470), CH3 (471-575), CHS (576-577)) (248-577)], (350-327')-disulfide with kappa light chain (1'-327') [humanized V-KAPPA anti-IL1B (*Homo sapiens* IGKV1-27*01 (82.10%) -IGKJ2*01) [6.3.9] (1'-106') -7-mer linker -*Homo sapiens* V-KAPPA anti-IL1A (IGKV1-12*01 (92.60%) -IGKJ4*01) [6.3.9] (114'-220') -*Homo sapiens* IGKC*01, Km3 (221'-327')]; dimer (356-356":359-359")-bisdisulfide
lutikizumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* IL1A (interleukine 1 alpha) et *Homo sapiens* IL1B (interleukine 1 bêta, IL-1B, 1L1F2)], anticorps monoclonal humanisé, tétravalent bispécifique; chaîne lourde gamma1 chaîne (1-577) [VH humanisé anti-IL1B (*Homo sapiens* IGHV3-23*04 (80.60%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -6-mer linker (120-125) -*Homo sapiens* VH anti-IL1A (IGHV3-30*03 (88.80%) -(IGHD)-IGHJ1*01) [8.8.15] (126-247)-*Homo sapiens* IGHG1*01 (CH1 (248-345), charnière (346-360), CH2 L1.3>A (364), L1.2>A (365), (361-470), CH3 (471-575), CHS (576-577)) (248-577)], (350-327')-disulfure avec la chaîne légère (1'-327') [V-KAPPA humanisé anti-IL1B (*Homo sapiens* IGKV1-27*01 (82.10%) -IGKJ2*01) [6.3.9] (1'-106') -7-mer linker -*Homo sapiens* V-KAPPA anti-IL1A (IGKV1-12*01 (92.60%) -IGKJ4*01) [6.3.9] (114'-220') -*Homo sapiens* IGKC*01, Km3 (221'-327')]; dimère (356-356":359-359")-bisdisulfure
lutikizumab	immunoglobulina G1-kappa, anti-[*Homo sapiens* IL1A (interleukina 1 alfa) y *Homo sapiens* IL1B (interleukina 1 beta, IL-1B, 1L1F2)], anticuerpo monoclonal humanizado, tetravalente biespecífico; cadena pesada gamma1 cadena (1-577) [VH humanizado anti-IL1B (*Homo sapiens* IGHV3-23*04 (80.60%) -(IGHD)-IGHJ4*01) [8.8.12] (1-119) -linker 6-mer (120-125) -*Homo sapiens* VH anti-IL1A (IGHV3-30*03 (88.80%) -(IGHD)-IGHJ1*01) [8.8.15] (126-247)-*Homo sapiens* IGHG1*01 (CH1 (248-345), bisagra (346-360), CH2 L1.3>A (364), L1.2>A (365), (361-470), CH3 (471-575), CHS (576-577)) (248-577)], (350-327')-disulfuro con la cadena ligera (1'-327') [V-KAPPA humanizado anti-IL1B (*Homo sapiens* IGKV1-27*01 (82.10%) -IGKJ2*01) [6.3.9] (1'-106') linker 7-mer -*Homo sapiens* V-KAPPA anti-IL1A (IGKV1-12*01 (92.60%) -IGKJ4*01) [6.3.9] (114'-220') -*Homo sapiens* IGKC*01, Km3 (221'-327')]; dímero (356-356":359-359")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG VVQPGRSLRL SCSASGFIFS RYDMSWVRQA PGKGLEWVAY  50
ISHGGAGTYY PDSVKGRFTI SRDNSKNTLF LQMDSLRPED TGVYFCARGG 100
VTKGYFDVWG QGTPVTVSSA STKGPQVQLV ESGGGVVQPG RSLRLSCTAS 150
GFTFSMFGVH WVRQAPGKGL EWVAAVSYDG SNKYYAESVK GRFTISRDNS 200
KNILFLQMDS LRLEDTAVYY CARGRPKVVI PAPLAHWGQG TLVTFSSAST 250
KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF 300
PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC 350
DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED 400
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 450
CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK 500
GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG 550
NVFSCSVMHE ALHNHYTQKS LSLSPGK                         577
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASGNIH NYLTWYQQTP GKAPKLLIYN  50
AKTLADGVPS RFSGSGSGTD YTFTISSLQP EDIATYYCQH FWSIPYTFGQ 100
GTKLQITRTV AAPDIQMTQS PSSVSASVGD RVTITCRASQ GISSWLAWYQ 150
QKPGKAPKLL IYEASNLETG VPSRFSGSGS GSDFTLTISS LQPEDFATYY 200
CQQTSSFLLS FGGGTKVEHK RTVAAPSVFI FPPSDEQLKS GTASVVCLLN 250
NFYPREAKVQ WKVDNALQSG NSQESVTEQD SKDSTYSLSS TLTLSKADYE 300
KHKVYACEVT HQGLSSPVTK SFNRGEC                         327
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	147-221	274-330	391-451	497-555
	22"-96"	147"-221"	274"-330"	391"-451"	497"-555"
Intra-L (C23-C104)	23'-88'	136'-201'	247'-307'		
	23'"-88'"	136'"-201'"	247'"-307'"		
Inter-H-L (h 5-CL 126)	350-327'	350"-327'"			
Inter-H-H (h 11, h 14)	356-356"	359-359"			

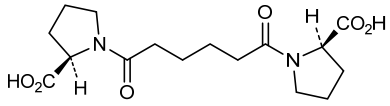
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
427, 427"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

miridesapum
miridesap — 1,1'-hexanedioyldi-D-proline

miridésap — 1,1'-hexanedioyldi-D-proline

miridesap — 1,1'-hexanodioildi-D-prolina

$C_{16}H_{24}N_2O_6$

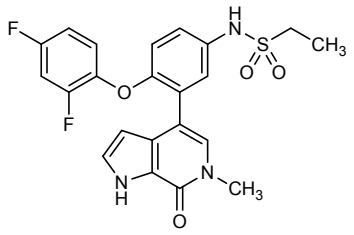


mivebresibum
mivebresib — *N*-[4-(2,4-difluorophenoxy)-3-(6-methyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)phenyl]ethanesulfonamide

mivébrésib — *N*-[4-(2,4-difluorophénoxy)-3-(6-méthyl-7-oxo-6,7-dihydro-1*H*-pyrrolo[2,3-*c*]pyridin-4-yl)phényl]éthanesulfonamide

mivebresib — *N*-[4-(2,4-difluorofenoxi)-3-(6-metil-7-oxo-6,7-dihidro-1*H*-pirrolo[2,3-*c*]piridin-4-il)fenil]etanosulfonamida

$C_{22}H_{19}F_2N_3O_4S$



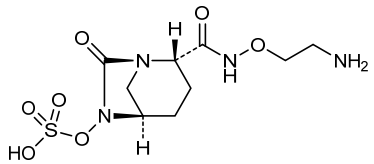
nacubactamum

nacubactam — (1*R*,2*S*,5*R*)-2-[(2-aminoethoxy)carbamoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yl hydrogen sulfate

nacubactam — hydrogénosulfate de (1*R*,2*S*,5*R*)-2-[(2-aminoéthoxy)carbamoyl]-7-oxo-1,6-diazabicyclo[3.2.1]octan-6-yle

nacubactam — hidrogenosulfato de (1*R*,2*S*,5*R*)-2-[(2-aminoetoxi)carbamoil]-7-oxo-1,6-diazabiciclo[3.2.1]octan-6-ilo

$C_9H_{16}N_4O_7S$



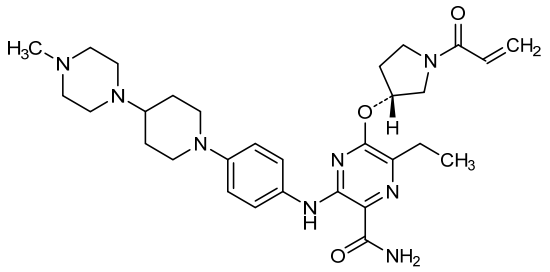
naquotinibum

naquotinib — 6-ethyl-3-{4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]anilino}-5-{[(3*R*)-1-(prop-2-enoyl)pyrrolidin-3-yl]oxy}pyrazine-2-carboxamide

naquotinib — 6-éthyl-3-{4-[4-(4-méthylpipérazin-1-yl)pipéridin-1-yl]anilino}-5-{[(3*R*)-1-(prop-2-énoyl)pyrrolidin-3-yl]oxy}pyrazine-2-carboxamide

naquotinib — 6-etil-3-{4-[4-(4-metilpiperazin-1-il)piperidin-1-il]anilino}-5-{[(3*R*)-1-(prop-2-enoil)pirrolidin-3-il]oxi}pirazina-2-carboxamida

$C_{30}H_{42}N_8O_3$



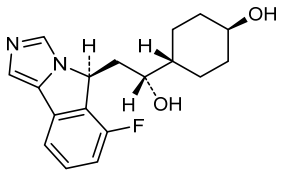
navoximodum

navoximod — *trans*-4-{(1*R*)-2-[(5*S*)-6-fluoro-5*H*-imidazo[5,1-*a*]isoindol-5-yl]-1-hydroxyethyl}cyclohexan-1-ol

navoximod — *trans*-4-{(1*R*)-2-[(5*S*)-6-fluoro-5*H*-imidazo[5,1-*a*]isoindol-5-yl]-1-hydroxyéthyl}cyclohexan-1-ol

navoximod — *trans*-4-{(1*R*)-2-[(5*S*)-6-fluoro-5*H*-imidazo[5,1-*a*]isoindol-5-il]-1-hidroxietil}ciclohexan-1-ol

$C_{18}H_{21}FN_2O_2$



nelatimotidum

nelatimotide — L-cysteinyl[human Wilms tumor protein (WT33)-(126-134)-peptide] (1-10) and [236-L-tyrosine(M>Y)]human Wilms tumor protein (WT33)-(235-243)-peptide (1'-9'), (1-1')-disulfide

nélatimotide — (1-1')-disulfure entre le L-cystéinyl-[protéine tumorale de Wilms humaine (WT33)-(126-133)-peptide] (1-10) et le [236-L-tyrosine(M>Y)]protéine tumorale de Wilms humaine (WT33)-(235-243)-peptide (1'-9')

nelatimotida — (1-1')-disulfuro entre la L-cisteinil[proteína tumoral de Wilms humana (WT33)-(126-134)-péptido] (1-10) y la [236-L-tirosina(M>Y)]proteína tumoral de Wilms humana (WT33)-(235-243)-péptido (1'-9')

$C_{106}H_{153}N_{27}O_{28}S_4$

H−Cys−Arg−Met−Phe−Pro−Asn−Ala−Pro−Tyr−Leu−OH
1 10
H−Cys−Tyr−Thr−Trp−Asn−Gln−Met−Asn−Leu−OH
1' 9'

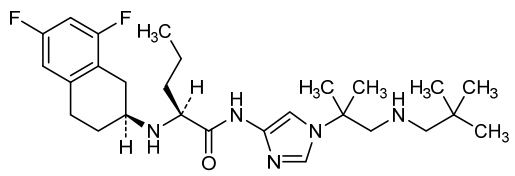
nirogacestatum

nirogacestat — (2*S*)-2-{[(2*S*)-6,8-difluoro-1,2,3,4-tetrahydronaphthalen-2-yl]amino}-*N*-(1-{1-[(2,2-dimethylpropyl)amino]-2-methylpropan-2-yl}-1*H*-imidazol-4-yl)pentanamide

nirogacéstat — (2*S*)-2-{[(2*S*)-6,8-difluoro-1,2,3,4-tétrahydronaphtalén-2-yl]amino}-*N*-(1-{1-[(2,2-diméthylpropyl)amino]-2-méthylpropan-2-yl}-1*H*-imidazol-4-yl)pentanamide

nirogacestat — (2*S*)-2-{[(2*S*)-6,8-difluoro-1,2,3,4-tetrahidronaftalen-2-il]amino}-*N*-(1-{1-[(2,2-dimetilpropil)amino]-2-metilpropan-2-il}-1*H*-imidazol-4-il)pentanamida

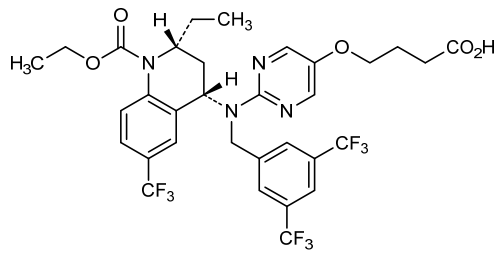
$C_{27}H_{41}F_2N_5O$



obicetrapibum

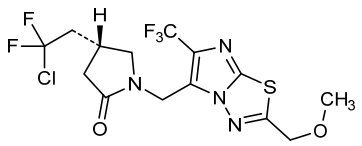
obicetrapib	4-{[2-({[3,5-bis(trifluoromethyl)phenyl]methyl}[(2*R*,4*S*)-1-(ethoxycarbonyl)-2-ethyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinolin-4-yl]amino)pyrimidin-5-yl]oxy}butanoic acid
obicétrapib	acide 4-{[2-({[3,5-bis(trifluorométhyl)phényl]méthyl}[(2*R*,4*S*)-1-(éthoxycarbonyl)-2-éthyl-6-(trifluorométhyl)-1,2,3,4-tétrahydroquinoléin-4-yl]amino)pyrimidin-5-yl]oxy}butanoïque
obicetrapib	ácido 4-{[2-({[3,5-bis(trifluorometil)fenil]metil}[(2*R*,4*S*)-2-etil-1-(etoxicarbonil)-6-(trifluorometil)-1,2,3,4-tetrahidroquinolein-4-il]amino)pirimidin-5-il]oxi}butanoico

$C_{32}H_{31}F_9N_4O_5$



ofranergenum obadenovecum #

ofranergene obadenovec	A recombinant non-replicating adenovirus type 5 vector carrying a fas-chimera transgene consisting of fas and human tumour necrosis factor receptor 1 (TNFR1), under transcriptional control of a murine pre-proendothelin promoter (PPE-1-3X*) *PPE-1-3X = modified PPE-1 promoter that contains three copies of the endothelial cells (EC)-positive regulatory elements.
ofranergéne obadénovec	vecteur adenoviral 5 recombinant sans capacité de réplication, contenant un transgène chimérique-fas constitué du fas et du récepteur 1 du facteur de nécrose tumorale humain (TNFR1), sous le contrôle transcriptionnel d'un promoteur pré-pro-endothéline murin (PPE-1-3X*) *PPE-1-3X = promoteur pré-pro-endothéline modifié contenant trois copies d'éléments de régulation positive provenant des cellules endothéliales

ofranergén obadenovec	vector adenoviral 5 recombinante no replicante, que contiene un transgec quimérico-fas constituido del fas y del receptor 1 del factor de necrosis tumoral humano (TNFR1), bajo el control transcripcional de un promotor pre-pro-endotelina murino (PPE-1-3X*) *PPE-1-3X = promotor pre-pro-endotelina modificado que contiene tres copias de elementos de regulación positiva que proviene de las células endoteliales
padsevonilum	
padsevonil	(4*R*)-4-(2-chloro-2,2-difluoroethyl)-1-{[2-(methoxymethyl)-6-(trifluoromethyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]methyl}pyrrolidin-2-one
padsévonil	(4*R*)-4-(2-chloro-2,2-difluoroéthyl)-1-{[2-(méthoxyméthyl)-6-(trifluorométhyl)imidazo[2,1-*b*][1,3,4]thiadiazol-5-yl]méthyl}pyrrolidin-2-one
padsevonil	(4*R*)-4-(2-cloro-2,2-difluoroetil)-1-{[2-(metoximetil)-6-(trifluorometil)imidazo[2,1-*b*][1,3,4]tiadiazol-5-il]metil}pirrolidin-2-ona
	$C_{14}H_{14}ClF_5N_4O_2S$
	
palucorcelum	
palucorcel	allogeneic human umbilical tissue derived cells (hUTC) obtained by enzymatic digestion of post-partum blood-free umbilical cord tissue and *ex vivo* expansion. Cells secrete trophic factors and do not express markers of endothelial cells (CD31), cord blood cells (CD45), epithelial cells (E-cadherin) and fibroblasts (FSP-1).
palucorcel	cellules humaines allogéniques dérivées de tissu ombilical (hUTC) obtenues par réactions enzymatiques de tissu de cordon ombilical post-partum exsangue et par expansion *ex vivo*. Les cellules secrètent des facteurs trophiques et n'expriment pas les marqueurs des cellules endothéliales (CD31), des cellules sanguines du cordon (CD45), des célulles épithéliales (cadhérine E) ni des fibroblastes (FSP-1).
palucorcel	células humanas alogénicas derivadas de tejido umbilical (hUTC) obtenidas por reacciones enzimáticas de tejido de cordón umbilical posparto libre de sangre y por expansión *ex vivo*. Las células secretan los factores tróficos y no expresan los marcadores de las células endoteliales (CD31), las células sanguíneas del cordón (CD45), las células epiteliales (cadherina E) y los fibroblastos (FSP-1).

pegunigalsidasum alfa #

pegunigalsidase alfa

glycyl-human α-galactosidasyl-L-seryl-L-α-glutamyl-L-lysyl-L-α-aspartyl-L-α-glutamyl-L-leucine, non-covalent dimer, glycosylated with plant glycans, produced in *Nicotiana tabacum* cells, substituted with an average of eight 4-({α-[2-(3-carboxypropanamido)ethyl]poly(oxyethylene)-ω-yl}amino)-4-oxobutanoyl groups (2 kDa each) and cross-linking (polyethylene glycol-*O*,*O*'-diyl)bis[ethane-2,1-diylazanediyl(1,4-dioxobutane-4,1-diyl)] bridges (2 kDa each) per dimeric protein on Gly^{1}-*N* and Lys-*N*^{6} sites

pégunigalsidase alfa

glycyl-α-galactosidasyl humain-L-séryl-L-α-glutamyl-L-lysyl-L-α-aspartyl-L-α-glutamyl-L-leucine, dimère non covalent, glycosylé avec des glycanes de plantes, produit par des cellules de *Nicotiana tabacum*, substitué avec une moyenne de 8 groupes 4-({α-[2-(3-carboxypropanamido)éthyl]poly(oxyéthylène)-ω-yl}amino)-4-oxobutanoyle (2 kDa chacun) et lié par des ponts (polyéthylène glycol-*O*,*O*'-diyl)bis[éthane-2,1-diylazanediyl(1,4-dioxobutane-4,1-diyl)] (2 kDa chacun) par deux monomères sur les sites Gly^{1}-*N* et Lys-*N*^{6}

pegunigalsidasa alfa

glicil-α-galactosidasil humano-L-seril-L-α-glutamil-L-lisil-L-α-aspartil-L-α-glutamil-L-leucina, dímero no covalente, glicosilado con los glicanos de plantas, producido por las células de *Nicotiana tabacum*, sustituido con una media de 8 grupos 4-({α-[2-(3-carboxipropanamido)etil]poli(oxietileno)-ω-il}amino)-4-oxobutanoilo (2 kDa cada uno de ellos) y unido por los puentes (polietileno glicol-*O*,*O*'-diil)bis[etano-2,1-diilazanediil(1,4-dioxobutano-4,1-diil)] (2 kDa cada uno de ellos) por ambos monómeros sobre los lugares Gly^{1}-*N* y Lys-*N*^{6}

Monomer / Monomère / Monómero

```
GLDNGLARTP TMGWLHWERF MCNLDCQEEP DSCISEKLFM EMAELMVSEG 50
WKDAGYEYLC IDDCWMAPQR DSEGRLQADP QRFPHGIRQL ANYVHSKGLK 100
LGIYADVGNK TCAGFPGSFG YYDIDAQTFA DWGVDLLKFD GCYCDSLENL 150
ADGYKHMSLA LNRTGRSIVY SCEWPLYMWP FQKPNYTEIR QYCNHWRNFA 200
DIDDSWKSIK SILDWTSFNQ ERIVDVAGPG GWNDPDMLVI GNFGLSWNQQ 250
VTQMALWAIM AAPLFMSNDL RHISPQAKAL LQDKDVIAIN QDPLGKQGYQ 300
LRQGDNFEVW ERPLSGLAWA VAMINRQEIG GPRSYTIAVA SLGKGVACNP 350
ACFITQLLPV KRKLGFYEWT SRLRSHINPT GTVLLQLENT MQMSLKDLLS 400
EKDEL                                                  405
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

22-64 26-33 112-142 172-193 348-352

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)

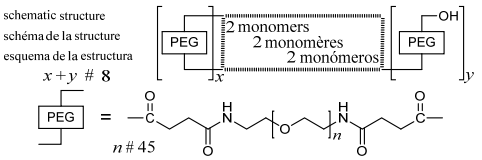
Asn-109 Asn-162 Asn-185 Asn-378

Potential *N*-substituted residues with pegylated radical Gly-1 and *N*-6 of lysines

Résidus potentiellement *N*-substitués par le radical pegylé Gly-1 et *N*-6 des lysines

Restos potencialmente *N*-sustituidos por el radical pegilado Gly-1 y *N*-6 de las lisinas

schematic structure
schéma de la structure
esquema de la estructura



pegvorhyaluronidasum alfa #

pegvorhyaluronidase alfa

human hyaluronidase PH-20 (hyaluronoglucosaminidase PH-20, sperm adhesion molecule 1, EC 3.2.1.35) precursor-(36-482)-peptide (mature (1-447)-peptide), produced in Chinese hamster ovary (CHO) cells, glycoform alfa, substituted on N^6 of an average of 4 to 5 lysyl residues with 4-[ω-methoxypoly(oxyethylene)-α-yl]butanoyl groups (~30 kDa each)

pègvorhyaluronidase alfa

hyaluronidase PH-20 humaine (hyaluronoglucosaminidase PH-20, molécule adhésive 1 du sperme, EC 3.2.1.35) précurseur-(36-482)-peptide (à maturité-(1-447)-peptide), produite par des cellules ovariennes de hamster chinois (CHO), forme glycosylée alfa, substituée sur les N^6 de 4 à 5 résidus lysyl en moyenne par des groupes 4-[ω-méthoxypoly(oxyéthylène)-α-yl]butanoyle (~30 kDa chacun)

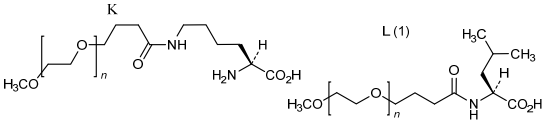
pegvorhialuronidasa alfa

hialuronidasa PH-20 humana (hialuronoglucosaminidasa PH-20, molécula de adhesión 1 de esperma, EC 3.2.1.35) precursor-(36-482)-péptido (maduro-(1-447)-péptido), producida por células ováricas de hamster chino (CHO), forma glicosilada alfa, sustituída en N^6 de 4 a 5 restos lysyl pro termino medio por grupos 4-[ω-metoxipoli(oxietileno)-α-il]butanoilo (~ 30 kDa cada uno)

```
LNFRAPPVIP NVPFLWAWNA PSEFCLGKFD EPLDMSLFSF IGSPRINATG 50
QGVTIFYVDR LGYYPYIDSI TGVTVNGGIP QKISLQDHLD KAKKDITFYM 100
PVDNLGMAVI DWEEWRPTWA RNWKPKDVYK NRSIELVQQQ NVQLSLTEAT 150
EKAKQEFEKA GKDFLVETIK LGKLLRPNHL WGYYLFPDCY NHHYKKPGYN 200
GSCFNVEIKR NDDLSWLWNE STALYPSIYL NTQQSPVAAT LYVRNRVREA 250
IRVSKIPDAK SPLPVFAYTR IVFTDQVLKF LSQDELVYTF GETVALGASG 300
IVIWGTLSIM RSMKSCLLLD NYMETILNPY IINVTLAAKM CSQVLCQEQG 350
VCIRKNWNSS DYLHLNPDNF AIQLEKGGKF TVRGKPTLED LEQFSEKFYC 400
SCYSTLSCKE KADVKDTDAV DVCIADGVCI DAFLKPPMET EEPQIFY 457
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
25-316 189-203 341-352 346-400 402-408 423-429

Pegylated residues / Résidus pégylés / Restos pegilados



Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-47 Asn-131 Asn-200 Asn-219 Asn-333 Asn-358

pimodivirum

pimodivir

(2*S*,3*S*)-3-{[5-fluoro-2-(5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-4-yl]amino}bicyclo[2.2.2]octane-2-carboxylic acid

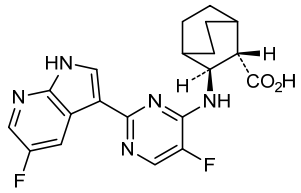
pimodivir

acide (2*S*,3*S*)-3-{[5-fluoro-2-(5-fluoro-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)pyrimidin-4-yl]amino}bicyclo[2.2.2]octane-2-carboxylique

pimodivir

ácido (2*S*,3*S*)-3-{[5-fluoro-2-(5-fluoro-1*H*-pirrolo[2,3-*b*]piridin-3-il)pirimidin-4-il]amino}biciclo[2.2.2]octano-2-carboxílico

$C_{20}H_{19}F_2N_5O_2$



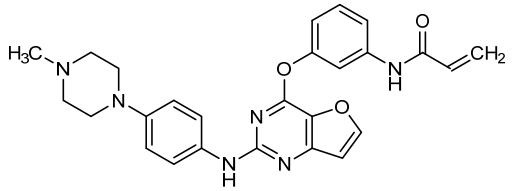
poseltinibum

poseltinib — *N*-[3-({2-[4-(4-methylpiperazin-1-yl)anilino]furo[3,2-*d*]pyrimidin-4-yl}oxy)phenyl]prop-2-enamide

poseltinib — *N*-[3-({2-[4-(4-méthylpipérazin-1-yl)anilino]furo[3,2-*d*]pyrimidin-4-yl}oxy)phényl]prop-2-énamide

poseltinib — *N*-[3-({2-[4-(4-metilpiperazin-1-il)anilino]furo[3,2-*d*]pirimidin-4-il}oxi)fenil]prop-2-enamida

$C_{26}H_{26}N_6O_3$



ranevetmabum #

ranevetmab — immunoglobulin G1-kappa, anti-[*Mus musculus* NGF (nerve growth factor, nerve growth factor beta polypeptide, NGFB, beta-NGF)], caninized monoclonal antibody; gamma1 heavy chain (1-453) [caninizedVH (*Rattus norvegicus* IGHV5S13*01 (71.40%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) -*Canis lupus familiaris* IGHG1*01 (CH1 (123-219), hinge (220-233), CH2 (234-343), CH3 (344-451), CHS (452-453)) (123-453)], (137-213')-disulfide with kappa light chain (1'-217') [caninizedV-KAPPA (*Rattus norvegicus* IGKV12S34*01 (76.80%) -IGKJ2-3*01) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-213') -4-mer (214'-217')]; dimer (224-224'':226-226'':232-232'')-trisdisulfide

ranévetmab — immunoglobuline G2-kappa, anti-[*Mus musculus* NGF (facteur de croissance du nerf, facteur de croissance du nerf polypeptide bêta, NGFB, bêta-NGF)], anticorps monoclonal caninisé;
chaîne lourde gamma2 (1-453) [VH caninisé (*Rattus norvegicus* IGHV5S13*01 (71.40%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) -*Canis lupus familiaris* IGHG1*01 (CH1 (123-219), charnière (220-233), CH2 (234-343), CH3 (344-451), CHS (452-453)) (123-453)], (137-213')-disulfure avec la chaîne légèrekappa (1'-217') [V-KAPPA caninisé (*Rattus norvegicus* IGKV12S34*01 (76.80%) -IGKJ2-3*01) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-213') -4-mer (214'-217')]; dimère (224-224'':226-226'':232-232'')-trisdisulfure

ranevetmab

inmunoglobulina G2-kappa, anti-[*Mus musculus* NGF (factor de crecimiento de los nervios, factor de crecimiento de nervios polipéptido beta, NGFB, beta-NGF)], anticuerpo monoclonal caninizado;
cadena pesada gamma2 (1-453) [VH caninizado (*Rattus norvegicus* IGHV5S13*01 (71.40%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) -*Canis lupus familiaris* IGHG1*01 (CH1 (123-219), bisagra (220-233), CH2 (234-343), CH3 (344-451), CHS (452-453)) (123-453)], (137-213')-disulfuro con la cadena ligerakappa (1'-217') [V-KAPPA caninizado (*Rattus norvegicus* IGKV12S34*01 (76.80%) -IGKJ2-3*01) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-213') -4-mer (214'-217')]; dímero (224-224'':226-226'':232-232'')-trisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCVASGFSLT NNNVNWVRQA PGKGLEWVGG  50
VWAGGATDYN SALKSRFTIS RDNAKNTVFL QMHSLRSEDT AVYYCARDGG 100
YSSSTLYAMD AWGQGTSVTV SSASTTAPSV FPLAPSCGST SGSTVALACL 150
VSGYFPEPVT VSWNSGSLTS GVHTFPSVLQ SSGLHSLSSM VTVPSSRWPS 200
ETFTCNVVHP ASNTKVDKPV FNECRCTDTP PCPVPEPLGG PSVLIFPPKP 250
KDILRITRTP EVTCVVLDLG REDPEVQISW FVDGKEVHTA KTQSREQQFN 300
GTYRVVSVLP IEHQDWLTGK EFKCRVNHID LPSPIERTIS KARGRAHKPS 350
VYVLPPSPKE LSSSDTVSIT CLIKDFYPPD IDVEWQSNGQ QEPERKHRMT 400
PPQLDEDGSY FLYSKLSVDK SRWQQGDPFT CAVMHETLQN HYTDLSLSHS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPAS LSLSQGETVT ITCRASEDIY NALAWYQQKP GQAPKLLIYN  50
TDTLHTGVPS RFSGSGSGTD FSLTISSLEP EDVAVYYCQH YFHYPRTFGQ 100
GTKVELKRND AQPAVYLFQP SPDQLHTGSA SVVCLLNSFY PKDINVKWKV 150
DGVIQDTGIQ ESVTEQDKDS TYSLSSTLTM SSTEYLSHEL YSCEITHKSL 200
PSTLIKSFQR SECQRVD                                     217
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-95	149-205	264-324	371-431
	22''-95''	149''-205''	264''-324''	371''-431''
Intra-L (C23-C104)	23'-88'	134'-193'		
	23'''-88'''	134'''-193'''		
Inter-H-L (CH1 11-CL 126)	137-213'	137''-213'''		
Inter-H-H (h 14, h 17)	224-224''	226-226''	232-232''	

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
300, 300''
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

ravoxertinibum

ravoxertinib

1-[(1*S*)-1-(4-chloro-3-fluorophenyl)-2-hydroxyethyl]-4-{2-[(1-methyl-1*H*-pyrazol-5-yl)amino]pyrimidin-4-yl}pyridin-2(1*H*)-one

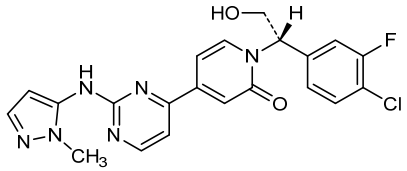
ravoxertinib

1-[(1*S*)-1-(4-chloro-3-fluorophényl)-2-hydroxyéthyl]-4-{2-[(1-méthyl-1*H*-pyrazol-5-yl)amino]pyrimidin-4-yl}pyridin-2(1*H*)-one

ravoxertinib

1-[(1*S*)-1-(4-cloro-3-fluorofenil)-2-hidroxietil]-4-{2-[(1-metil-1*H*-pirazol-5-il)amino]pirimidin-4-il}piridin-2(1*H*)-ona

$C_{21}H_{18}ClFN_6O_2$



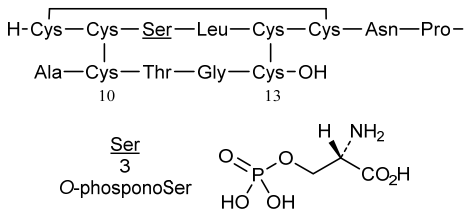
recanaclotidum

recanaclotide — *S*^{1},*S*^{6}:*S*^{2},*S*^{10}:*S*^{5},*S*^{13}-tricyclo(L-cysteinyl-L-cysteinyl-*O*-phosphono-L-seryl-L-leucyl-L-cysteinyl-L-cysteinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cysteinyl-L-threonylglycyl-L-cysteine)

récanaclotide — *S*^{1},*S*^{6}:*S*^{2},*S*^{10}:*S*^{5},*S*^{13}-tricyclo(L-cystéinyl-L-cystéinyl-*O*-phosphono-L-séryl-L-leucyl-L-cystéinyl-L-cystéinyl-L-asparaginyl-L-prolyl-L-alanyl-L-cystéinyl-L-thréonylglycyl-L-cystéine)

recanaclotida — *S*^{1},*S*^{6}:*S*^{2},*S*^{10}:*S*^{5},*S*^{13}-triciclo(L-cisteinil-L-cisteinil-*O*-fosfono-L-seril-L-leucil-L-cisteinil-L-cisteinil-L-asparaginil-L-prolil-L-alanil-L-cisteinil-L-treonilglicil-L-cisteína)

$C_{45}H_{71}N_{14}O_{20}PS_6$



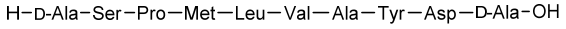
reltecimodum

reltecimod — D-alanyl-[T-cell-specific surface glycoprotein CD28-(8-15)-peptide]-D-alanine:
D-alanyl-L-seryl-L-prolyl-L-methionyl-L-leucyl-L-valyl-L-alanyl-L-tyrosyl-L-α-aspartyl-D-alanine

reltécimod — D-alanyl-[(8-15)-peptide de glycoprotéine de surface CD28 spécifique des cellules T]-D-alanine:
D-alanyl-L-séryl-L-prolyl-L-méthionyl-L-leucyl-L-valyl-L-alanyl-L-tyrosyl-L-α-aspartyl-D-alanine

reltecimod — D-alanil-[(8-15)-péptido de glicoproteína de superfice CD28 específica de las células T]-D-alanina:
D-alanil-L-seril-L-prolil-L-metionil-L-leucil-L-valil-L-alanil-L-tirosil-L-α-aspartil-D-alanina

$C_{46}H_{72}N_{10}O_{15}S$



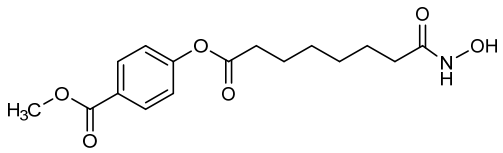
remetinostatum

remetinostat — methyl 4-{[8-(hydroxyamino)-8-oxooctanoyl]oxy}benzoate

rémétinostat — 4-{[8-(hydroxyamino)-8-oxooctanoyl]oxy}benzoate de méthyle

remetinostat — 4-{[8-(hidroxiamino)-8-oxooctanoil]oxi}benzoato de metilo

$C_{16}H_{21}NO_6$



remtolumabum #

remtolumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* IL17A (interleukin 17A, IL-17A) and *Homo sapiens* TNF (tumor necrosis factor (TNF) superfamily member 2, TNFSF2, TNF-alpha, TNFA)], *Homo sapiens* monoclonal antibody, tetravalent bispecific;
gamma1 heavy chain (1-587) [*Homo sapiens* VH anti-TNF (IGHV3-9*01 (93.90%) -(IGHD) -IGHJ4*01) [8.8.14] (1-121) -10-mer bis(tetraglycyl-seryl) linker (122-132) -*Homo sapiens* VH' anti-IL17A (IGHV1-69*01 (85.70%) -(IGHD) -IGHJ6*01) [8.8.19] (132-257) -IGHG1*01, G1m17,1 (CH1 (258-355), hinge (356-370), CH2 (371-480), CH3 (481-585), CHS (586-587)) (258-587)], (360-331')-disulfide with kappa light chain (1'-331') [*Homo sapiens* V-KAPPA anti-TNF (IGKV1-27*01 (95.80%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* V-KAPPA anti-IL17A (IGKV6-21*01 (90.50%) -IGKJ3*01) [6.3.9] (118'-224') -IGKC*01, Km3 (225'-213')]; dimer (366-366'':369-369'')-bisdisulfide

remtolumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* IL17A (interleukine 17A, IL-17A) et *Homo sapiens* TNF (facteur de nécrose tumorale membre 2 de la superfamille du TNF, TNFSF2, TNF-alpha, TNFA)], *Homo sapiens* anticorps monoclonal, tétravalent bispécifique;
chaîne lourde gamma1 (1-587) [*Homo sapiens* VH anti-TNF (IGHV3-9*01 (93.90%) -(IGHD) -IGHJ4*01) [8.8.14] (1-121) -10-mer bis(tétraglycyl-séryl) linker (122-132) -*Homo sapiens* VH' anti-IL17A (IGHV1-69*01 (85.70%) -(IGHD) -IGHJ6*01) [8.8.19] (132-257) -IGHG1*01, G1m17,1 (CH1 (258-355), charnière (356-370), CH2 (371-480), CH3 (481-585), CHS (586-587)) (258-587)], (360-331')-disulfure avec la chaîne légère kappa (1'-331') [*Homo sapiens* V-KAPPA anti-TNF (IGKV1-27*01 (95.80%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* V-KAPPA anti-IL17A (IGKV6-21*01 (90.50%) -IGKJ3*01) [6.3.9] (118'-224') -IGKC*01, Km3 (225'-213')]; dimère (366-366'':369-369'')-bisdisulfure

remtolumab — inmunoglobulina G1-kappa, anti-[*Homo sapiens* IL17A (interleukina 17A, IL-17A) y *Homo sapiens* TNF (factor de necrosis tumoral miembro 2 de la superfamilia del TNF, TNFSF2, TNF-alfa, TNFA)], *Homo sapiens* anticuerpo monoclonal, tetravalente biespecífico;

cadena pesada gamma1 (1-587) [*Homo sapiens* VH anti-TNF (IGHV3-9*01 (93.90%) -(IGHD) -IGHJ4*01) [8.8.14] (1-121) -10-mer bis(tetraglicil-seril) linker (122-132) -*Homo sapiens* VH' anti-IL17A (IGHV1-69*01 (85.70%) -(IGHD) -IGHJ6*01) [8.8.19] (132-257) -IGHG1*01, G1m17,1 (CH1 (258-355), bisagra (356-370), CH2 (371-480), CH3 (481-585), CHS (586-587)) (258-587)], (360-331')-disulfuro con la cadena ligera kappa (1'-331') [*Homo sapiens* V-KAPPA anti-TNF (IGKV1-27*01 (95.80%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* V-KAPPA anti-IL17A (IGKV6-21*01 (90.50%) -IGKJ3*01) [6.3.9] (118'-224') -IGKC*01, Km3 (225'-213')]; dímero (366-366'':369-369'')-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGRSLRL SCAASGFTFD DYAMHWVRQA PGKGLEWVSA  50
ITWNSGHIDY ADSVEGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCAKVS 100
YLSTASSLDY WGQGTLVTVS SGGGGSGGGG SEVQLVQSGA EVKKPGSSVK 150
VSCKASGGSF GGYGIGWVRQ APGQGLEWMG GITPFFGFAD YAQKFQGRVT 200
ITADESTTTA YMELSGLTSD DTAVYYCARD PNEFWNGYYS THDFDSWGQG 250
TTVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS 300
GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK 350
VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT LMISRTPEVT 400
CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH 450
QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK 500
NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL 550
TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK               587
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQGIR NYLAWYQQKP GKAPKLLIYA  50
ASTLQSGVPS RFSGSGSGTD FTLTISSLQP EDVATYYCQR YNRAPYTFGQ 100
GTKVEIKRGG SGGGGSGEIV LTQSPDFQSV TPKEKVTITC RASQDIGSEL 150
HWYQQKPDQP PKLLIKYASH STSGVPSRFS GSGSGTDFTL TINGLEAEDA 200
GTYYCHQTDS LPYTFGPGTK VDIKRTVAAP SVFIFPPSDE QLKSGTASVV 250
CLLNNFYPRE AKVQWKVDNA LQSGNSQESV TEQDSKDSTY SLSSTLTLSK 300
ADYEKHKVYA CEVTHQGLSS PVTKSFNRGE C                     331
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

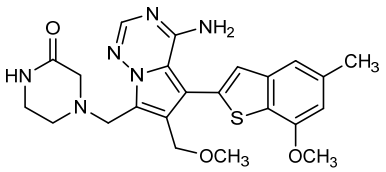
Intra-H (C23-C104) 22-96 153-227 284-340 401-461 507-565
22''-96'' 153''-227'' 284''-340'' 401''-461'' 507''-565''
Intra-L (C23-C104) 23'-88' 140'-205' 251'-311'
23'''-88''' 140'''-205''' 251'''-311'''
Inter-H-L (h 5-CL 126) 360-331' 360''-331'''
Inter-H-H (h 11, h 14) 366-366'' 369-369''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
437, 437''
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

rogaratinibum

rogaratinib	4-{[4-amino-6-(methoxymethyl)-5-(7-methoxy-5-methyl-1-benzothiophen-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl]methyl}piperazin-2-one
rogaratinib	4-{[4-amino-6-(méthoxyméthyl)-5-(7-méthoxy-5-méthyl-1-benzothiophén-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-7-yl]méthyl}pipérazin-2-one
rogaratinib	4-{[4-amino-5-(5-metil-7-metoxi-1-benzotiofen-2-il)-6-(metoximetil)pirrolo[2,1-*f*][1,2,4]triazin-7-il]metil}piperazin-2-ona

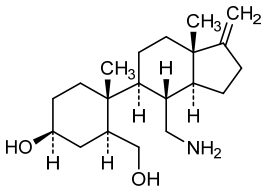
$C_{23}H_{26}N_6O_3S$



rosiptorum

rosiptor	7-amino-17-methylidene-6,7-seco-5α-androstane-3β,6-diol
rosiptor	7-amino-17-méthylidène-6,7-séco-5α-androstane-3β,6-diol
rosiptor	7-amino-17-metilideno-6,7-seco-5α-androstano-3β,6-diol

$C_{20}H_{35}NO_2$



rosmantuzumabum #

rosmantuzumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* RSPO3 (R-spondin 3, thrombospondin type I (TSP1) domain containing protein 2, THSD2)], humanized monoclonal antibody; gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV1-46*01 (84.50%) -(IGHD)-IGHJ4*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (83.80%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimer (226-226":229-229")-bisdisulfide
rosmantuzumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* RSPO3 (R-spondine 3, protéine 2 contenant un domaine thrombospondine de type I (TSP1), THSD2)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV1-46*01 (84.50%) -(IGHD)-IGHJ4*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, (CH1 (118-215), charnière (216-230),), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-218')-disulfure avec la chaîne légère (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (83.80%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimère (226-226":229-229")-bisdisulfure

rosmantuzumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* RSPO3 (R-espondina 3, proteína 2 que contiene un dominio tromboespondina de tipo I (TSP1), THSD2)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-447) [VH humanizado (*Homo sapiens* IGHV1-46*01 (84.50%) -(IGHD)-IGHJ4*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, (CH1 (118-215), bisagra (216-230),), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-218')-disulfuro con la cadena ligera (1'-218') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (83.80%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dímero (226-226":229-229")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT DYSIHWVRQA PGQGLEWIGY  50
IYPSNGDSGY NQKFKNRVTM TRDTSTSTAY MELSRLRSED TAVYYCATYF 100
ANNFDYWGQG TTLTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK    447
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKASQSVD YDGDSYMNWY QQKPGKAPKL  50
LIYAASNLES GVPSRFSGSG SGTDFTLTIS PVQAEDFATY YCQQSNEDPL 100
TFGAGTKLEL KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	144-200	261-321	367-425
	22"-96"	144"-200"	261"-321"	367"-425"
Intra-L (C23-C104)	23'-92'	138'-198'		
	23'"-92'"	138'"-198'"		
Inter-H-L (h 5-CL 126)	220-218'	220"-218'"		
Inter-H-H (h 11, h 14)	226-226"	229-229"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
447, 447"

rosomidnarum
rosomidnar

DNA oligonucleotide sequence that is complementary to a region upstream of the B-cell lymphoma (BCL-2) gene: 2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-deoxyguanosine

rosomidnar	séquence oligonucléotide d'ADN complémentaire d'une région en amont du gène (BCL-2) lymphome formé de lymphocytes B: 2'-déoxycytidylyl-(3'→5')-2'-déoxyadénylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyadénylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyadénylyl-(3'→5')-thymidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxycytidylyl-(3'→5')-2'-déoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-déoxyguanosine
rosomidnar	secuencia de oligonucleótidos de ADN complementaria de una región ascendente del gen (BCL-2) de linfomas de células B: 2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicytidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-timidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-timidilil-(3'→5')-2'-desoxiguanosina $C_{227}H_{291}N_{88}O_{141}P_{23}$ (3'-5')d(C-A-C-G-C-A-C-G-C-G-C-A-T-C-C-C-C-G-C-C-C-G-T-G)

rozanolixizumabum #

rozanolixizumab	immunoglobulin G4-kappa, anti-[*Homo sapiens* FCGRT (Fc fragment of IgG receptor and transporter, neonatal Fc receptor, FcRn, transmembrane alpha chain of the neonatal receptor)], humanized and chimeric monoclonal antibody; gamma4 heavy chain (1-444) humanized [humanized VH (*Homo sapiens* IGHV3-7*01 (86.50%) -(IGHD) -IGHJ4*01) [8.8.10] (1-117)), *Homo sapiens* IGHG4*01 (CH1 (118-215), hinge S10>P (225) (216-227),CH2 (228-337), CH3 (338-442), CHS (443-444)) (118-444)], (131-219')-disulfide with kappa light chain chimeric (1'-219') [synthetic V-KAPPA (*Homo sapiens* IGKV1-9*01 (76.00%) -*Homo sapiens* IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dimer (223-223":226-226")-bisdisulfide

rozanolixizumab

immunoglobuline G4-kappa, anti-[*Homo sapiens* FCGRT (récepteur du fragment Fc des IgG et transporteur, récepteur Fc néonatal, FcRn, chaîne alpha transmembranaire du récepteur néonatal)], anticorps monoclonal humanisé et chimérique;
chaîne lourde gamma4 humanisée (1-444) [VH humanisé (*Homo sapiens* IGHV3-7*01 (86.50%) -(IGHD) -IGHJ4*01) [8.8.10] (1-117)), *Homo sapiens* IGHG4*01 (CH1 (118-215), charnière S10>P (225) (216-227), CH2 (228-337), CH3 (338-442), CHS (443-444)) (118-444)], (131-219')-disulfure avec la chaîne légère kappa chimérique (1'-219') [V-KAPPA synthétique (*Homo sapiens*IGKV1-9*01 (76.00%) -*Homo sapiens* IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dimère (223-223":226-226")-bisdisulfure

rozanolixizumab

inmunoglobulina G4-kappa, anti-[*Homo sapiens* FCGRT (receptor del fragmento Fc de las IgG y transportador, receptor Fc neonatal, FcRn, cadena alfa transmembranaria del receptor neonatal)], anticuerpo monoclonal humanizado y quimérico;
cadena pesada gamma4 humanizada (1-444) [VH humanizado (*Homo sapiens* IGHV3-7*01 (86.50%) -(IGHD) -IGHJ4*01) [8.8.10] (1-117)), *Homo sapiens* IGHG4*01 (CH1 (118-215), bisagra S10>P (225) (216-227), CH2 (228-337), CH3 (338-442), CHS (443-444)) (118-444)], (131-219')-disulfuro con la cadena ligera kappa quimérica (1'-219') [V-KAPPA sintético (*Homo sapiens*IGKV1-9*01 (76.00%) -*Homo sapiens* IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 (113'-219')]; dímero (223-223":226-226")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY  50
IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI 100
VRPFLYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC 200
NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI 250
SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV 300
SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP 350
SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS 400
FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK       444
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCKSSQSLV GASGKTYLYW LFQKPGKAPK  50
RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI SSLQPEDFAT YYCLQGTHFP 100
HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	144-200	258-318	364-422
	22"-96"	144"-200"	258"-318"	364"-422"
Intra-L (C23-C104)	23'-93'	139'-199'		
	23'"-93'"	139'"-199'"		
Inter-H-L (CH1 10-CL 126)	131-219'	131"-219'"		
Inter-H-H (h 8, h 11)	223-223"	226-226"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
294, 294"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

sacituzumabum #	
sacituzumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* TACSTD2 (tumor-associated calcium signal transducer 2, membrane component chromosome 1 surface marker 1, M1S1, gastrointestinal tumor-associated antigen GA7331, pancreatic carcinoma marker protein GA733-1, epithelial glycoprotein-1, EGP-1, trophoblast antigen-2, cell surface glycoprotein Trop-2, TROP2)], humanized monoclonal antibody; gamma1 heavy chain (1-451) [humanized VH (*Homo sapiens* IGHV7-4-1*02 (85.70%) -(IGHD)-IGHJ2*01) [8.8.14] (1-121) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (122-219), hinge (220-234), CH2 (235-344), CH3 (345-449), CHS (450-451)) (122-451)], (224-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-9*01 (82.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (230-230":233-233")-bisdisulfide
sacituzumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* TACSTD2 (transducteur 2 de signaux calciques associé aux tumeurs, composant membranaire du chromosome 1 marqueur de surface 1, M1S1, antigène GA7331 associé aux tumeurs gastrointestinales, protéine GA733-1 marqueur de carcinomes pancréatiques, glycoprotéine épithéliale 1, EGP-1, antigène 2 du trophoblaste, glycoprotéine Trop-2 à la surface des cellules, TROP2)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-451) [VH humanisé (*Homo sapiens* IGHV7-4-1*02 (85.70%) -(IGHD)-IGHJ2*01) [8.8.14] (1-121) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (122-219), charnière (220-234), CH2 (235-344), CH3 (345-449), CHS (450-451)) (122-451)], (224-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-9*01 (82.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (230-230":233-233")-bisdisulfure
sacituzumab	inmunoglobulina G1-kappa, anti-[*Homo sapiens* TACSTD2 (transductor 2 de señales cálcicas asociado a los tumores, componente membranario del cromosoma 1 marcador de superficie 1, M1S1, antígeno GA7331 asociado a todos los tumores gastrointestinales, proteína GA733-1 marcador de carcinomas pancreáticos, glicoproteína epitelial 1, EGP-1, antígeno 2 de trofoblasto, glicoproteína Trop-2 de la superficie de las células, TROP2)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-451) [VH humanizado (*Homo sapiens* IGHV7-4-1*02 (85.70%) -(IGHD)-IGHJ2*01) [8.8.14] (1-121) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (122-219), bisagra (220-234), CH2 (235-344), CH3 (345-449), CHS (450-451)) (122-451)], (224-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-9*01 (82.20%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (230-230":233-233")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQQSGSE LKKPGASVKV SCKASGYTFT NYGMNWVKQA PGQGLKWMGW  50
INTYTGEPTY TDDFKGRFAF SLDTSVSTAY LQISSLKADD TAVYFCARGG 100
FGSSYWYFDV WGQGSLVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV 150
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ 200
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 250
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY 300
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP 350
QVYTLPPSRE EMTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP 400
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG 450
K                                                       451
```

Light chain / Chaîne légère / Cadena ligera

```
DIQLTQSPSS LSASVGDRVS ITCKASQDVS IAVAWYQQKP GKAPKLLIYS  50
ASYRYTGVPD RFSGSGSGTD FTLTISSLQP EDFAVYYCQQ HYITPLTFGA 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 148-204 265-325 371-429
22"-96" 148"-204" 265"-325" 371'-429"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 224-214' 224"-214'"
Inter-H-H (h 11, h 14) 230-230" 233-233"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
301, 301"
Fucosylated complex bi-antennary Sp2/0-type glycans / glycanes de type Sp2/0 bi-antennaires complexes fucosylés / glicanos de tipo Sp2/0 biantenarios complejos fucosilados

satoreotidum

satoreotide

S^2,S^7-cyclo{4-chloro-L-phenylalanyl-D-cysteinyl-4-[(4*S*)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phenylalanyl-4-(carbamoylamino)-D-phenylalanyl-L-lysyl-L-threonyl-L-cysteinyl-D-tyrosinamide}

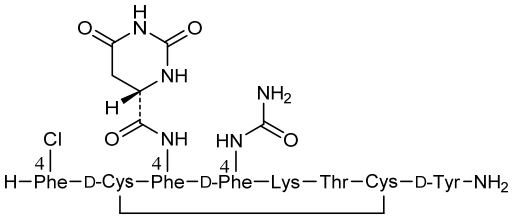
satoréotide

S^2,S^7-cyclo{4-chloro-L-phénylalanyl-D-cystéinyl-4-[(4*S*)-2,6-dioxo-1,3-diazinane-4-carboxamido]-L-phénylalanyl-4-(carbamoylamino)-D-phénylalanyl-L-lysyl-L-thréonyl-L-cystéinyl-D-tyrosinamide}

satoreotida

S^2,S^7-ciclo{4-cloro-L-fenilalanil-D-cisteinil-4-[(4*S*)-2,6-dioxo-1,3-diazinano-4-carboxamido]-L-fenilalanil-4-(carbamoilamino)-D-fenilalanil-L-lisil-L-treonil-L-cisteinil-D-tirosinamida}

$C_{58}H_{72}ClN_{15}O_{14}S_2$



seladelparum

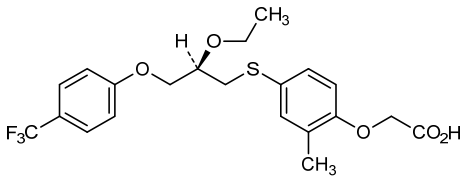
seladelpar

[4-({(2*R*)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl}sulfanyl)-2-methylphenoxy]acetic acid

séladelpar — acide [4-({(2*R*)-2-éthoxy-3-[4-(trifluorométhyl)phénoxy]propyl}sulfanyl)-2-méthylphénoxy]acétique

seladelpar — ácido [4-({(2*R*)-2-etoxi-3-[4-(trifluorometil)fenoxi]propil}sulfanil)-2-metilfenoxi]acético

$C_{21}H_{23}F_3O_5S$



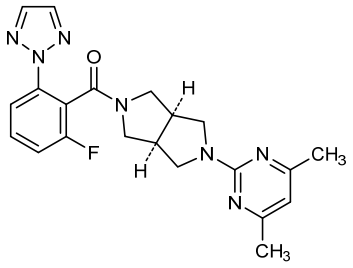
seltorexantum

seltorexant — [(3a*R*,6a*S*)-5-(4,6-dimethylpyrimidin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl][2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phenyl]methanone

seltorexant — [(3a*R*,6a*S*)-5-(4,6-diméthylpyrimidin-2-yl)hexahydropyrrolo[3,4-*c*]pyrrol-2(1*H*)-yl][2-fluoro-6-(2*H*-1,2,3-triazol-2-yl)phényl]méthanone

seltorexant — [(3a*R*,6a*S*)-5-(4,6-dimetilpirimidin-2-il)hexahidropirrolo[3,4-*c*]pirrol-2(1*H*)-il][2-fluoro-6-(2*H*-1,2,3-triazol-2-il)fenil]metanona

$C_{21}H_{22}FN_7O$



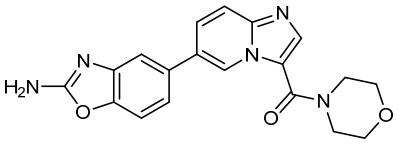
serabelisibum

serabelisib — [6-(2-amino-1,3-benzoxazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl](morpholin-4-yl)methanone

sérabélisib — [6-(2-amino-1,3-benzoxazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl](morpholin-4-yl)méthanone

serabelisib — [6-(2-amino-1,3-benzoxazol-5-il)imidazo[1,2-*a*]piridin-3-il](morfolin-4-il)metanona

$C_{19}H_{17}N_5O_3$



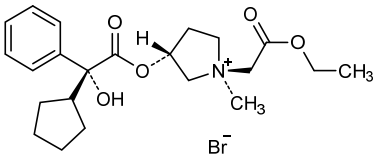
sofpironii bromidum

sofpironium bromide — 1-*ambo*-(3*R*)-3-{[(*R*)-(cyclopentyl)hydroxy(phenyl) acetyl]oxy}-1-(2-ethoxy-2-oxoethyl)-1-methylpyrrolidinium bromide

bromure de sofpironium — bromure de 1-*ambo*-(3*R*)-3-{[(*R*)-(cyclopentyl)hydroxyl (phényl)acétyl]oxy}-1-(2-éthoxy-2-oxoéthyl)-1-méthylpyrrolidinium

bromuro de sofpironio — bromuro de 1-*ambo*-(3*R*)-3-{[(*R*)-(ciclopentil)hidroxi (fenil)acetil]oxi}-1-(2-etoxi-2-oxoetil)-1-metilpirrolidinio

$C_{22}H_{32}BrNO_5$



and epimer at N^+
et l'épimère en N^+
y el epímero al N^+

somatrogonum #

somatrogon — fusion protein of human choriogonadotropin subunit β (CG-β)-(118-145)-peptide (1-28) with human somatotropin (growth hormone, GH) (29-219) and two tandem copies of human choriogonadotropin subunit β (CG-β)-(118-145)-peptide (220-247, 248-275), *O*-glycosylated on 12-18 serines, produced in Chinese hamster ovary (CHO) cells

somatrogon — sous-unité bêta de la choriogonadotrophine humaine (CG-β)-(118-145)-peptide (1-28) protéine de fusion avec la somatropine humaine (hormone de croissance, GH) (29-219) protéine de fusion avec deux copies de la sous-unité bêta de la choriogonadotrophine humaine (CG-β)-(118-145)-peptide (1-28), 12-18 sérines sont *O*-glycosylées, produite par des cellules ovariennes de hamster chinois (CHO)

somatrogón — subunidad beta de la coriogonadotropina humana (CG-β)-(118-145)-péptido (1-28) proteína de fusión con la somatropina humana (hormona de crecimiento, GH) (29-219) proteína de fusión con ambas copias de la subunidad beta de la coriogonadotropina humana (CG-β)-(118-145)-péptido (1-28), 12-18 serinas *O*-glicosiladas, producidas por las células de ovario de hamster chino (CHO)

Sequence / Séquence / Secuencia

```
SSSSKAPPPS LPSPSRLPGP SDTPILPQFP TIPLSRLFDN AMLRAHRLHQ 50
LAFDTYQEFE EAYIPKEQKY SFLQNPQTSL CFSESIPTPS NREETQQKSN 100
LELLRISLLL IQSWLEPVQF LRSVFANSLV YGASDSNVYD LLKDLEEGIQ 150
TLMGRLEDGS PRTGQIFKQT YSKFDTNSHN DDALLKNYGL LYCFRKDMDK 200
VETFLRIVQC RSVEGSCGFS SSSKAPPPSL PSPSRLPGPS DTPILPQSSS 250
SKAPPPSLPS PSRLPGPSDT PILPQ                            275
```

Disulfide bridges location / Position des ponts disulfures / Posiciones de los puentes disulfuro
81-193 210-217

Potential glycosylation sites / Sites potentiels de glycosylation / Sitios potenciales de glicosilación

Ser-1*	Ser-2*	Ser-3*	Ser-4*	**Ser-10**	**Ser-13**	**Ser-15**	**Ser-21**
Ser-220*	Ser-221*	Ser-222*	Ser-223*	**Ser-229**	**Ser-232**	**Ser-234**	**Ser-240**
Ser-248*	Ser-249*	Ser-250*	Ser-251*	**Ser-257**	**Ser-260**	**Ser-262**	**Ser-268**

* when two serines are linked together, only one can be glycosylated.
quand deux sérines sont liées l'une à l'autre, une seule peut être glycosylée.
cuando dos serinas están ligadas una al otra, una sola puede ser glicosilada .

suptavumabum #

suptavumab	immunoglobulin G1-kappa, anti-[human respiratory syncytial virus (RSV) fusion glycoprotein F], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-453) [*Homo sapiens* VH (IGHV3-9*01 (87.90%) -(IGHD) -IGHJ6*01) [8.8.16](1-123) -IGHG1*01, G1m17,1 (CH1 (124-221), hinge (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453))(124-453)], (226-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107')-IGKC*01, Km3 (108'-214')]; dimer (232-232":235-235")-bisdisulfide
suptavumab	immunoglobuline G1-kappa, anti-[glycoprotéine de fusion F du virus respiratoire syncytial (VRS) humain], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-453) [*Homo sapiens* VH (IGHV3-9*01 (87.90%) -(IGHD) -IGHJ6*01) [8.8.16] (1-123) -IGHG1*01, G1m17,1 (CH1 (124-221), charnière (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453))(124-453)], (226-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01, Km3 (108'-214')]; dimère (232-232":235-235")-bisdisulfure
suptavumab	inmunoglobulina G1-kappa, anti-[glicoproteína de fusión F del virus respiratorio sincitial (VRS) humano], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-453) [*Homo sapiens* VH (IGHV3-9*01 (87.90%) -(IGHD) -IGHJ6*01) [8.8.16] (1-123) -IGHG1*01, G1m17,1 (CH1 (124-221), bisagra (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453))(124-453)], (226-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01, Km3 (108'-214')]; dímero (232-232":235-235")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGD LVQPGRSLRL SCVASGFTFD DYAMHWVRQA PGKGLEWVSG  50
VSWSGSTVGY ADSVKGRFTV SRDNAQKSLY LQMNSLRAED TALYYCVKDA 100
YKFNYYYYGL DVWGQGTTVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP 250
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 350
EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 400
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
EIVMTQSPAT LSVSPGERAT LSCRASQTIL SNLAWYLQKP GQAPRLLIYG  50
ASTRATGLPA RFSGSGSGTE FTLTISSLQS EDFAVYYCQQ YNNWPLTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                         214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 150-206 267-327 373-431
22"-96" 150"-206" 267"-327" 373"-431"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 226-214' 226"-214"
Inter-H-H (h 11, h 14) 232-232" 235-235"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
303, 303"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

telisotuzumabum #

telisotuzumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* MET (met proto-oncogene, hepatocyte growth factor (HGF) receptor, HGFR, scatter factor (SF) receptor, HGF/SF receptor, receptor tyrosine-protein kinase c-met, papillary renal cell carcinoma 2, RCCP2)], humanized monoclonal antibody; gamma1 heavy chain (1-445) [humanized VH (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216), hinge K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimer (223-223":225-225":228:228")-trisdisulfide

télisotuzumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* MET (proto-oncogène met, récepteur du facteur de croissance hépatocytaire, HGFR, récepteur du facteur de dispersion, récepteur de l'HGF/SF, récepteur protéine-tyrosine kinase c-Met, carcinome papillaire à cellules rénales 2, RCCP2)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-445) [VH humanisé (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216),charnière K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimère (223-223":225-225":228:228")-trisdisulfure

telisotuzumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* MET (proto-oncogen met, receptor del factor de crecimiento de hepatocitos, HGFR, receptor del factor de dispersión, receptor del HGF/SF, receptor proteína-tirosina kinasa c-Met, carcinoma papilar de células renales 2, RCCP2)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-445) [VH humanizado (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216),bisagra K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA humanizado (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dímero (223-223":225-225":228:228")-trisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYIFT AYTMHWVRQA PGQGLEWMGW  50
IKPNNGLANY AQKFQGRVTM TRDTSISTAY MELSRLRSDD TAVYYCARSE 100
ITTEFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDCHCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG      445
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPDS LAVSLGERAT INCKSSESVD SYANSFLHWY QQKPGQPPKL  50
LIYRASTRES GVPDRFSGSG SGTDFTLTIS SLQAEDVAVY YCQQSKEDPL 100
TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	145-201	260-320	366-424
	22"-96"	145"-201"	260"-320"	366"-424"
Intra-L (C23-C104)	23'-92'	138'-198'		
	23'"-92'"	138'"-198'"		
Inter-H-L (h 5-CL 126)	221-218'	221"-218'"		
Inter-H-H (h 11, h 14)	225-225"	228-228"	(h 8>C)	223-223"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

telisotuzumabum vedotinum #
telisotuzumab vedotin

immunoglobulin G1-kappa, anti-[*Homo sapiens* MET (met proto-oncogene, hepatocyte growth factor (HGF) receptor, HGFR, scatter factor (SF) receptor, HGF/SF receptor, receptor tyrosine-protein kinase c-met, papillary renal cell carcinoma 2, RCCP2)], humanized monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-445) [humanized VH (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216), hinge K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimer (223-223":225-225":228:228")-trisdisulfide; conjugated, on an average of 3 cysteinyl, to

	monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker For the *vedotin* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*
télisotuzumab védotine	immunoglobuline G1-kappa, anti-[*Homo sapiens* MET (proto-oncogène met, récepteur du facteur de croissance hépatocytaire, HGFR, récepteur du facteur de dispersion, récepteur de l'HGF/SF, récepteur protéine-tyrosine kinase c-Met, carcinome papillaire à cellules rénales 2, RCCP2)], anticorps monoclonal humanisé conjugué à l'auristatine E; chaîne lourde gamma1 (1-445) [VH humanisé (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216),charnière K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA humanisé (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dimère (223-223":225-225":228:228")-trisdisulfure; conjugué, sur 3 cystéinyl en moyenne, au monométhylauristatine E (MMAE), via un linker clivable de type maléimidocaproyl-valyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) Pour la partie *védotine*, veuillez-vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*
telisotuzumab vedotina	inmunoglobulina G1-kappa, anti-[*Homo sapiens* MET (protooncogén met, receptor del factor de crecimiento de los hepatocitos, HGFR, receptor del factor de dispersión, receptor del HGF/SF, receptor proteína-tirosina kinasa c-Met, carcinoma papilar de las células renales 2, RCCP2)], anticuerpo monoclonal humanizado conjugado con la auristatina E; cadena pesada gamma1 (1-445) [VH humanizado (*Homo sapiens* IGHV1-2*02 (92.90%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3 (CH1 (119-216),bisagra K7>del, T8>C (223), T10>del (217-229), CH2 (230-339), CH3 (340-444), CHS K>del (445)) (119-445)], (221-218')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA humanizado (*Homo sapiens* IGKV4-1*01 (85.10%) -IGKJ4*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01, Km3 (112'-218')]; dímero (223-223":225-225":228:228")-trisdisulfuro; conjugado, sobre una media de 3 cisteinil, a la monometilauristatina E (MMAE), mediante un enlace escindible de tipo maleimidocaproil-valil-citrulinil-*p*-aminobenciloxicarbonil (mc-val-cit-PABC) Para la fracción *vedotina* se pueden referir al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYIFT AYTMHWVRQA PGQGLEWMGW  50
IKPNNGLANY AQKFQGRVTM TRDTSISTAY MELSRLRSDD TAVYYCARSE 100
ITTEFDYWGQ GTLVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDCHCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPG      445
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPDS LAVSLGERAT INCKSSESVD SYANSFLHWY QQKPGQPPKL  50
LIYRASTRES GVPDRFSGSG SGTDFTLTIS SLQAEDVAVY YCQQSKEDPL 100
TFGGGTKVEI KRTVAAPSVF IFPPSDEQLK SGTASVVCLL NNFYPREAKV 150
QWKVDNALQS GNSQESVTEQ DSKDSTYSLS STLTLSKADY EKHKVYACEV 200
THQGLSSPVT KSFNRGEC                                    218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 145-201 260-320 366-424
22"-96" 145"-201" 260"-320" 366"-424"
Intra-L (C23-C104) 23'-92' 138'-198'
23'"-92'" 138'"-198'"
Inter-H-L (h 5-CL 126)* 221-218' 221"-218"
Inter-H-H (h 11, h 14)* 225-225" 228-228" (h 8>C) 223-223"

*Two or three of the inter-chain disulfide bridges are not present, an average of 3 cysteinyl being conjugated each via a thioether bond to a drug linker.

*Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 3 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif.

*Faltan dos o tres puentes disulfuro inter-catenarios, una media de 3 cisteinil está conjugada a conectores de principio activo.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

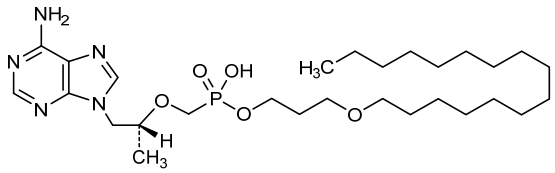
tenofovirum exalidexum

tenofovir exalidex — 3-(hexadecyloxy)propyl hydrogen ({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]oxy}methyl)phosphonate

ténofovir exalidex — ({[(2*R*)-1-(6-amino-9*H*-purin-9-yl)propan-2-yl]oxy}méthyl)hydrogénophosphonate de 3-(hexadécyloxy)propyle

tenofovir exalidex — ({[(2*R*)-1-(6-amino-9*H*-purin-9-il)propan-2-il]oxi}metil)hidrogenofosfonato de 3-(hexadeciloxi)propilo

$C_{28}H_{52}N_5O_5P$

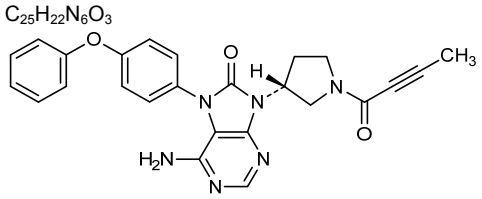


tirabrutinibum

tirabrutinib — 6-amino-9-[(3*R*)-1-(but-2-ynoyl)pyrrolidin-3-yl]-7-(4-phenoxyphenyl)-7,9-dihydro-8*H*-purin-8-one

tirabrutinib — 6-amino-9-[(3*R*)-1-(but-2-ynoyl)pyrrolidin-3-yl]-7-(4-phénoxyphényl)-7,9-dihydro-8*H*-purin-8-one

tirabrutinib — 6-amino-9-[(3*R*)-1-(but-2-inoil)pirrolidin-3-il]-7-(4-fenoxifenil)-7,9-dihidro-8*H*-purin-8-ona



tonabacasum #

tonabacase — *Staphylococcus aureus* phage 1 (SAP-1)-derived soluble endolysin (*Staphylococcus aureus* phage lysin-1, bacteriolysin SAL-1), produced in *Escherichia coli*

tonabacase — endolysine soluble dérivée du phage 1 de *Staphylococcus aureus* (lysine du phage 1 de *Staphylococcus aureus*, bactériolysine SAL-1), produite par *Escherichia coli*

tonabacasa — endolisina soluble derivada del fago 1 de *Staphylococcus aureus* (lisina del fago 1 de *Staphylococcus aureus*, bacteriolisina SAL-1), producida por *Escherichia coli*

Sequence / Séquence / Secuencia

```
AKTQAEINKR LDAYAKGTVD SPYRIKKATS YDPSFGVMEA GAIDADGYYH 50
AQCQDLITDY VLWLTDNKVR TWGNAKDQIK QSYGTGFKIH ENKPSTVPKK 100
GWIAVFTSGS YQQWGHIGIV YDGGNTSTFT ILEQNWNGYA NKKPTKRVDN 150
YYGLTHFIEI PVKAGTTVKK ETAKKSASKT PAPKKKATLK VSKNHINYTM 200
DKRGKKPEGM VIHNDAGRSS GQQYENSLAN AGYARYANGI AHYYGSEGYV 250
WEAIDAKNQI AWHTGDGTGA NSGNFRFAGI EVCQSMSASD AQFLKNEQAV 300
FQFTAEKFKE WGLTPNRKTV RLHMEFVPTA CPHRSMVLHT GFNPVTQGRP 350
SQAIMNKLKD YFIKQIKNYM DKGTSSSTVV KDGKTSSAST PATRPVTGSW 400
KKNQYGTWYK PENATFVNGN QPIVTRIGSP FLNAPVGGNL PAGATIVYDE 450
VCIQAGHIWI GYNAYNGNRV YCPVRTCQGV PPNHIPGVAW GVFK       494
```

tonogenconcelum #

tonogenconcel — Allogeneic primary human chondrocytes transduced with a retroviral vector expressing human transforming growth factor-beta1 (TGF-β1). A master cell bank of primary human chondrocytes, grown from cartilage tissue obtained from the surgical excision of a polydactyly finger from a three-year-old female donor, was prepared. After transduction of cells from the master cell bank, a single clonal population was selected using limiting dilution and submitted to irradiation.
Cells express TGF-β1, Type I and Type II collagen as well as Type I and Type II TGF-β1 receptors; they lack expression of gag and pol genes.

tonogenconcel — Chondrocytes humains primaires allogéniques transduits par un vecteur rétroviral exprimant le facteur de croissance transformant-bêta1 (TGF-β1). Une banque de cellules primaires a été préparée à partir de tissu cartilagineux obtenu par excision chirurgicale d'un doigt surnuméraire d'un donneur âgé de 3 ans et de sexe féminin. Après transduction des cellules de la banque de cellules primaires, un seul clone a été sélectionné en utilisant une dilution limitative et en le soumettant à une irradiation.
Les cellules expriment le TGF- β1, du collagène de type I et II ainsi que les récepteurs de type I et II du TGF- β1; elles sont dépourvues d'expression de gènes gag et pol.

tonogenconcel

Condrocitos humanos primarios alogénicos transducidos por un vector retroviral que expresa el factor de crecimiento transformador-bêta1 (TGF-β1). Un banco de células primarias preparado a partir de tejido cartilaginoso obtenido por escisión quirúrgica de un dedo adicional de un donante de 3 años de edad y de sexo femenino. Después de la transducción de las células del banco de células primarias, se selecciona un único clon utilizando una dilución limitante y se somete a radiación.
Las células que expresan el TGF- β1, del colágeno de tipo I y II así como los receptes de tipo I y II del TGF- β1; ellas carecen de la expresión de los genes gag y pol.

tozuleristidum
tozuleristide

$N^{6.27}$-[6-(2-{(1*E*,2*E*,4*E*,6*E*)-7-[1,1-dimethyl-3-(4-sulfonatobutyl)-1*H*-benzo[*e*]indol-3-ium-2-yl]hepta-2,4,6-trien-1-ylidene}-1,1-dimethyl-1,2-dihydro-3*H*-benzo[*e*]indol-3-yl)hexanoyl]-[Lys^{15}>Arg,Lys^{23}>Arg]chlorotoxin (*Leiurus quinquestriatus quinquestriatus*) (Egyptian scorpion)

tozuléristide

$N^{6.27}$-[6-(2-{(1*E*,2*E*,4*E*,6*E*)-7-[1,1-diméthyl-3-(4-sulfonatobutyl)-1*H*-benzo[*e*]indol-3-ium-2-yl]hepta-2,4,6-trién-1-ylidène}-1,1-diméthyl-1,2-dihydro-3*H*-benzo[*e*]indol-3-yl)hexanoyl]-[Lys^{15}>Arg,Lys^{23}>Arg]chlorotoxine de *Leiurus quinquestriatus quinquestriatus* (scorpion égyptien)

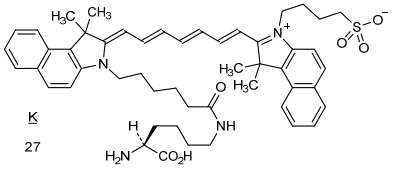
tozuleristida

$N^{6.27}$-[6-(2-{(1*E*,2*E*,4*E*,6*E*)-7-[1,1-dimetil-3-(4-sulfonatobutil)-1*H*-benzo[*e*]indol-3-ium-2-il]hepta-2,4,6-trien-1-ilideno}-1,1-dimetil-1,2-dihidro-3*H*-benzo[*e*]indol-3-il)hexanoil]-[Lys^{15}>Arg,Lys^{23}>Arg]clorotoxina de *Leiurus quinquestriatus quinquestriatus* (escorpión egipcio)
$C_{203}H_{296}N_{58}O_{52}S_{12}$

Sequence / Sequence / Secuencia
MCMPCFTTDH QMARRCDDCC GGRGRGKCYG PQCLCR 36

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
2-19 5-28 16-33 20-35

Modified residue / Résidu modifié / Resto modificado



trastuzumabum duocarmazinum #
trastuzumab duocarmazine

immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB2 (epidermal growth factor receptor 2, receptor tyrosine-protein kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], humanized monoclonal antibody conjugated to the pro-drug *seco*-duocarmycin-hydroxybenzamide-azaindole (*seco*-DUBA);

	gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* (IGHV3-66-*01 (81.60%) -(IGHD)-IGHJ6*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (121-218), hinge (219-233),CH2 (234-343), CH3 D12>E (359), L14>M (361) (344-448), CHS K>del (449)) (121-449)], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimer (229-229":232-232")-bisdisulfide, conjugated on an average of 2 or 4 cysteines, to *seco*-DUBA via the cleavable linker *N*-[2-(2-maleimidoethoxy)ethoxycarbonyl]-L-valyl-L-citrullinyl-*p*-aminobenzyloxycarbonyl-*N*-[2-(2-hydroxyethoxy)ethyl]-*N*-[2-(methylamino)ethyl]carbamoyl
trastuzumab duocarmazine	immunoglobuline G1-kappa, anti-[*Homo sapiens* ERBB2 (récepteur 2 du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticorps monoclonal humanisé conjugué à la pro-drogue *seco*-duocarmycine-hydroxybenzamide-azaindole (*seco*-DUBA); chaîne lourde gamma1 (1-449) [VH humanisé (*Homo sapiens* (IGHV3-66-*01 (81.60%) -(IGHD)-IGHJ6*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (121-218), charnière (219-233),CH2 (234-343), CH3 D12>E (359), L14>M (361) (344-448), CHS K>del (449)) (121-449)], (223-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dimère (229-229":232-232")-bisdisulfure, conjugué sur une moyenne de 2 ou 4 cystéines au *séco*-DUBA via le linker clivable *N*-[2-(2-maléimidoéthoxy)éthoxycarbonyl]-L-valyl-L-citrullinyl-*p*-aminobenzyloxycarbonyl-*N*-[2-(2-hydroxyéthoxy)éthyl]-*N*-[2-(méthylamino)éthyl]carbamoyle
trastuzumab duocarmazina	inmunoglobulina G1-kappa, anti-[*Homo sapiens* ERBB2 (receptor 2 del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticuerpo monoclonal humanizado conjugado con el profármaco *seco*-duocarmicina-hidroxibenzamida-azaindol (*seco*-DUBA); cadena pesada gamma1 (1-449) [VH humanizado (*Homo sapiens* (IGHV3-66-*01 (81.60%) -(IGHD)-IGHJ6*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (121-218), bisagra (219-233),CH2 (234-343), CH3 D12>E (359), L14>M (361) (344-448), CHS K>del (449)) (121-449)], (223-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 (108'-214')]; dímero (229-229":232-232")-bisdisulfuro; conjugado en 2 o 4 cisteínas, por término medio con *seco*-DUBA mediante el enlace escin-dible *N*-[2-(2-maleimidoetoxi)etoxicarbonil]-L-valil-L-citrulinil-*p*-aminobenciloxicarbonil-*N*-[2-(2-hidroxietoxi)etil]-*N*-[2-(metilamino)etil]carbamoilo

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR  50
IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG 100
GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPG  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS  50
ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	147-203	264-324	370-428
	22"-96"	147"-203"	264"-324"	370"-428"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)*	223-214'	223"-214'"		
Inter-H-H (h 11, h 14)*	229-229"	232-232"		

*Two or three of the inter-chain disulfide bridges are not present, on average 2 or 4 cysteinyl being conjugated each via a thioether bond to a drug linker.

*Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 2 or 4 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif.

*Faltan dos o tres puentes disulfuro inter-catenarios, una media de 2 o 4 cisteinil está conjugada a conectores de principio activo.

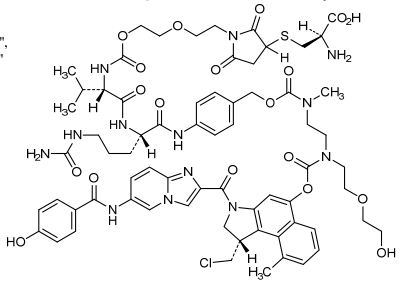
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4:
300, 300"

Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales

C*
214', 214'", 223, 223",
229, 229", 232, 232"



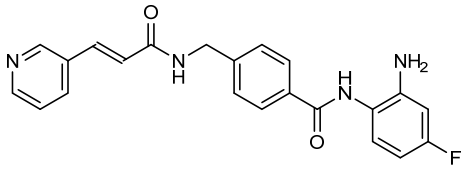
tucidinostatum

tucidinostat — *N*-(2-amino-4-fluorophenyl)-4-{[(2*E*)-3-(pyridin-3-yl)prop-2-enamido]methyl}benzamide

tucidinostat — *N*-(2-amino-4-fluorophényl)-4-{[(2*E*)-3-(pyridin-3-yl)prop-2-énamido]méthyl}benzamide

tucidinostat — *N*-(2-amino-4-fluorofenil)-4-{[(2*E*)-3-(piridin-3-il)prop-2-enamido]metil}benzamida

$C_{22}H_{19}FN_4O_2$



upadacitinibum

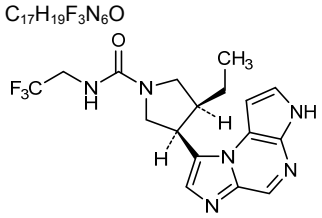
upadacitinib — (3*S*,4*R*)-3-ethyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroethyl)pyrrolidine-1-carboxamide

upadacitinib

(3*S*,4*R*)-3-éthyl-4-(3*H*-imidazo[1,2-*a*]pyrrolo[2,3-*e*]pyrazin-8-yl)-*N*-(2,2,2-trifluoroéthyl)pyrrolidine-1-carboxamide

upadacitinib

(3*S*,4*R*)-3-etil-4-(3*H*-imidazo[1,2-*a*]pirrolo[2,3-*e*]pirazin-8-il)-*N*-(2,2,2-trifluoroetil)pirrolidina-1-carboxamida



uprifosbuvirum

uprifosbuvir

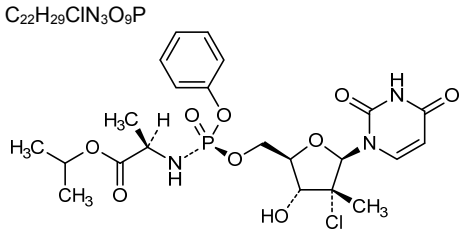
propan-2-yl *N*-[(*R*)-{[(2*R*,3*R*,4*R*,5*R*)-4-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-methyloxolan-2-yl]methoxy}phenoxyphosphoryl]-D-alaninate

uprifosbuvir

N-[(*R*)-{[(2*R*,3*R*,4*R*,5*R*)-4-chloro-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-3-hydroxy-4-méthyloxolan-2-yl]méthoxy}phénoxyphosphoryl]-D-alaninate de propan-2-yle

uprifosbuvir

N-[(*R*)-{[(2*R*,3*R*,4*R*,5*R*)-4-cloro-5-(2,4-dioxo-3,4-dihidropirimidin-1(2*H*)-il)-3-hidroxi-4-metiloxolan-2-il]metoxi}fenoxifosforil]-D-alaninato de propan-2-ilo



utomilumabum #

utomilumab

immunoglobulin G2-lambda, anti-[*Homo sapiens* TNFRSF9 (tumor necrosis factor receptor (TNFR) superfamily member 9, 4-1BB, T cell antigen ILA, CD137)], *Homo sapiens* monoclonal antibody;
gamma2 heavy chain (1-442) [*Homo sapiens* VH (IGHV5-10-1*04 (94.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -IGHG2*01, G2m.. (CH1 (117-214), hinge (215-226), CH2 (227-335), CH3 (336-440), CHS (441-442)) (117-442)], (130-213')-disulfide with lambda light chain (1'-214') [*Homo sapiens* V-LAMBDA (IGLV3-1*01 (90.00%) -IGLJ7*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dimer (218-218":219-219":222-222":225-225")-tetrakisdisulfide

utomilumab

immunoglobuline G2-lambda, anti-[*Homo sapiens* TNFRSF9 (membre 9 de la superfamille des récepteurs du facteur de nécrose tumorale, 4-1BB, antigène ILA de lymphocyte T, CD137)], *Homo sapiens* anticorps monoclonal;

	chaîne lourde gamma2 (1-442) [*Homo sapiens* VH (IGHV5-10-1*04 (94.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -IGHG2*01, G2m.. (CH1 (117-214), charnière (215-226), CH2 (227-335), CH3 (336-440), CHS (441-442)) (117-442)], (130-213')-disulfure avec la chaîne légère lambda (1'-214') [*Homo sapiens* V-LAMBDA (IGLV3-1*01 (90.00%) -IGLJ7*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dimère (218-218'':219-219'':222-222'':225-225'')-tétrakisdisulfure
utomilumab	inmunoglobulina G2-lambda, anti-[*Homo sapiens* TNFRSF9 (miembro 9 de la superfamilia de los receptores del factor de necrosis tumoral, 4-1BB, antígeno ILA de linfocito T, CD137)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma2 (1-442) [*Homo sapiens* VH (IGHV5-10-1*04 (94.90%) -(IGHD)-IGHJ4*01) [8.8.9] (1-116) -IGHG2*01, G2m.. (CH1 (117-214), bisagra (215-226), CH2 (227-335), CH3 (336-440), CHS (441-442)) (117-442)], (130-213')-disulfuro con la cadena ligera lambda (1'-214') [*Homo sapiens* V-LAMBDA (IGLV3-1*01 (90.00%) -IGLJ7*01) [6.3.11] (1'-108') -IGLC2*01 (109'-214')]; dímero (218-218'':219-219'':222-222'':225-225'')-tetrakisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGAE VKKPGESLRI SCKGSGYSFS TYWISWVRQM PGKGLEWMGK  50
IYPGDSYTNY SPSFQGQVTI SADKSISTAY LQWSSLKASD TAMYYCARGY 100
GIFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS NFGTQTYTCN 200
VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP KPKDTLMISR 250
TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTFRVVSV 300
LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE PQVYTLPPSR 350
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PMLDSDGSFF 400
LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP GK         442
```

Light chain / Chaîne légère / Cadena ligera

```
SYELTQPPSV SVSPGQTASI TCSGDNIGDQ YAHWYQQKPG QSPVLVIYQD  50
KNRPSGIPER FSGSNSGNTA TLTISGTQAM DEADYYCATY TGFGSLAVFG 100
GGTKLTVLGQ PKAAPSVTLF PPSSEELQAN KATLVCLISD FYPGAVTVAW 150
KADSSPVKAG VETTTPSKQS NNKYAASSYL SLTPEQWKSH RSYSCQVTHE 200
GSTVEKTVAP TECS                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	256-316	362-420
	22''-96''	143''-199''	256''-316''	362''-420''
Intra-L (C23-C104)	22'-87'	136'-195'		
	22'''-87'''	136'''-195'''		
Inter-H-L (CH1 10-CL 126)	130-213'	130''-213'''		
Inter-H-H (h 4, h 5, h 8, h 11)	218-218''	219-219''	222-222''	225-225''

*In addition to the isoform A, isoform A/B characterized by an inter-H-H (h 4 - CH1 10) 218-130'' and an inter-H-L (h 4-CL 126) 218''-213'', instead of the inter-H-H (h 4 - h 4) 218-218'' and of one of the two inter-H-L (CH1 10-CL 126) 130''-213'', isoform B characterized by an inter-H-H (h 5 - CH1 10) 219-130 and an inter-H-L (h 5- CL 126) 219''-213', instead of the inter-H-H (h 5 - h 5) 219-219'' and of the inter-H-L (CH1 10-CL 126) 130-213'.

*En plus de l'isoforme A, isoforme A/B caractérisée par un inter-H-H (h 4 - CH1 10) 218-130'' et un inter-H-L (h 4- CL 126) 218''-213'', au lieu de l'inter-H-H (h 4 - h 4) 218-218'' et de l'un des deux inter-H-L (CH1 10-CL 126) 130''-213'', isoforme B caractérisée par un inter-H-H (h 5 - CH1 10) 219-130 et un inter-H-L (h 5- CL 126) 219''-213', au lieu de l'inter-H-H (h 5 - h 5) 219-219'' et de l'inter-H-L (CH1 10-CL 126) 130-213'.

*Además de la isoforma A, isoforma A/B caracterizado por un inter-H-H (h4 - CH1 10) 218-130'' y un inter-H-L (h 4- CL 126) 218''-213'', en lugar del inter-H-H (h 4 - h 4) 218-218'' y uno de los dos inter-H-L (CH1 10-CL 126) 130''-213'', isoforma B caracterizado por un inter-H-H (h 5 - CH1 10) 219-130 y un inter-H-L (h 5- CL 126) 219''-213', en lugar del inter-H-H (h 5 - h 5) 219-219'' y del inter-H-L (CH1 10-CL 126) 130-213'.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H VH N66:
59, 59'' (partially occupied, with up to two sialic acids)
H CH2 N84.4:
292, 292'' (fully occupied)
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados.

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
442, 442''

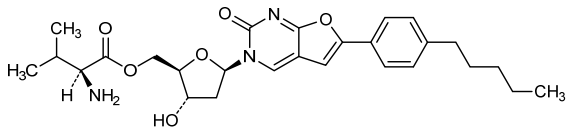
valnivudinum

valnivudine — {(2*R*,3*S*,5*R*)-3-hydroxy-5-[2-oxo-6-(4-pentylphenyl)furo[2,3-*d*]pyrimidin-3(2*H*)-yl]oxolan-2-yl}methyl L-valinate

valnivudine — L-valinate de {(2*R*,3*S*,5*R*)-3-hydroxy-5-[2-oxo-6-(4-pentylphényl)furo[2,3-*d*]pyrimidin-3(2*H*)-yl]oxolan-2-yl}methyl

valnivudina — L-valinato de {(2*R*,3*S*,5*R*)-3-hidroxi-5-[2-oxo-6-(4-pentilfenil)furo[2,3-*d*]pirimidin-3(2*H*)-il]oxolan-2-il}metilo

$C_{27}H_{35}N_3O_6$



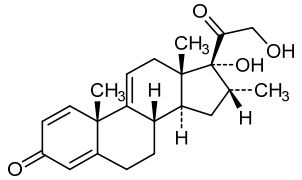
vamorolonum

vamorolone — 17,21-dihydroxy-16α-methylpregna-1,4,9(11)-triene-3,20-dione

vamorolone — 17,21-dihydroxy-16α-méthylprègna-1,4,9(11)-triène-3,20-dione

vamorolona — 17,21-dihidroxi-16α-metilpregna-1,4,9(11)-trieno-3,20-diona

$C_{22}H_{28}O_4$



vandefitemcelum

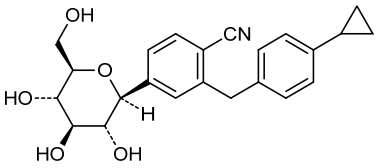
vandefitemcel — human differentiation-restricted descendents (DRCs) of bone-marrow-derived adherent stromal cells (MASCs) isolated from adult donor. To obtain DRCs, MASCs were transiently transfected with a DNA plasmid encoding human Notch-1 intracellular domain (NICD) and expanded in growth media. The transfection does not result in permanent incorporation of the gene into the cells, but does result in changes in a number of proteins and in the methylation pattern of the DNA (there is complete loss of recombinant NICD protein and of the plasmid in the final cell population). The transfection changes the nature of the cells such that they no longer readily differentiate into bone, cartilage or adipose cells, and also results in cells altered in their ability to secrete trophic and chemotactic factors, and extracellular matrix proteins to support damaged neural cells.

	Cells are positive for mesenchymal stem cell (MSC) markers (CD29, CD90, CD105) and negative for hematopoietic markers (CD31, CD34, CD45).
vandéfitemcel	descendants à différenciation restreinte (DRCs) humains de cellules stromales adhérentes dérivées de la moelle osseuse (MASCs) isolées d'un donneur adulte. Pour obtenir les DRCs, les MASCs ont été transitoirement transfectées avec un plasmide dont l'ADN code pour le domaine intracellulaire de Notch-1 humain (NICD) et ont été expansées par des moyens de croissance. La transfection ne résulte pas d'une incorporation permanente du gène dans les cellules, mais de changements dans un nombre de protéines et dans les méthylations de l'ADN (il y a une perte complète de la protéine recombinante NICD et du plasmide dans la population finale). La transfection change la nature des cellules de telle sorte qu'elles ne se différencient plus en cellules osseuses, cartilagineuses ou adipeuses et il en résulte aussi des cellules modifiées dans leur capacité à secréter des facteurs trophiques et chimiotactiques, et des protéines de la matrice extracellulaire qui supportent les cellules neuronales endommagées. Les cellules sont positives pour les marqueurs des cellules souches mésenchymateuses (CD29, CD90, CD105) et négatives pour les marqueurs hématopoïétiques (CD31, CD34, CD45).
vandefitemcel	descendientes humanos de la diferenciación restrictiva (DRCs) de células estromales adherentes derivadas de la médula ósea (MASCs) aisladas de un donante adulto. Para obtener los DRCs, las MASCs se transfectan transitoriamente con un plásmido de ADN que codifica para el dominio intracelular Notch-1 humano (NICD) y se expanden en un medio de crecimiento. La transfección no resulta en una incorporación permanente del gen dentro de las células, pero sí en cambios en el número de proteínas y en el patrón de metilación del DNA (hay una pérdida completa de proteína recombinante NICD y del plásmido en la población final celular). La transfección cambia la naturaleza de las células de tal modo que no se diferencian con más facilidad en células óseas, cartilaginosas o adiposas y también resulta en células modificadas bajo la capacidad de secretar factores tróficos y quimiotácticos, y las proteínas de la matriz extracelular que soportan las células neuronales dañadas. Las células son positivas para los marcadores de las células madres mesenquimales (CD29, CD90, CD105) y negativas para los marcadores hematopoyéticos (CD31, CD34, CD45).
velagliflozinum	
velagliflozin	2-[(4-cyclopropylphenyl)methyl]-4-β-D-glucopyranosylbenzonitrile
vélagliflozine	2-[(4-cyclopropylphényl)méthyl]-4-β-D-glucopyranosylbenzonitrile

velagliflozina

2-[(4-ciclopropilfenil)metil]-4-β-D-glucopiranosilbenzonitrilo

$C_{23}H_{25}NO_5$



vestronidasum alfa #

vestronidase alfa

human β-glucuronidase, natural Leu^{627}>Pro variant, homotetramer, produced in Chinese hamster ovary cells (CHO), glycoform alfa

vestronidase alfa

β-glucuronidase humaine, variant naturel Leu^{627}>Pro, homotétramère, produit dans des cellules ovariennes de hamsters chinois (CHO), glycoforme alfa

vestronidasa alfa

β-glucuronidasa humana, variante natural Leu^{627}>Pro, homotetrámero, producido en células de ovario de hamster chino (CHO), glicoforma alfa

Monomer /Monomère / Monómero

```
LQGGMLYPQE SPSRECKELD GLWSFRADFS DNRRRGFEEQ WYRRPLWESG 50
PTVDMPVPSS FNDISQDWRL RHFVGWVWYE REVILPERWT QDLRTRVVLR 100
IGSAHSYAIV WVNGVDTLEH EGGYLPFEAD ISNLVQVGPL PSRLRITIAI 150
NNTLTPTTLP PGTIQYLTDT SKYPKGYFVQ NTYFDFFNYA GLQRSVLLYT 200
TPTTYIDDIT VTTSVEQDSG LVNYQISVKG SNLFKLEVRL LDAENKVVAN 250
GTGTQGQLKV PGVSLWWPYL MHERPAYLYS LEVQLTAQTS LGPVSDFYTL 300
PVGIRTVAVT KSQFLINGKP FYFHGVNKHE DADIRGKGFD WPLLVKDFNL 350
LRWLGANAFR TSHYPYAEEV MQMCDRYGIV VIDECPGVGL ALPQFFNNVS 400
LHHHMQVMEE VVRRDKNHPA VVMWSVANEP ASHLESAGYY LKMVIAHTKS 450
LDPSRPVTFV SNSNYAADKG APYVDVICLN SYYSWYHDYG HLELIQLQLA 500
TQFENWYKKY QKPIIQSEYG AETIAGFHQD PPLMFTEEYQ KSLLEQYHLG 550
LDQKRRKYVV GELIWNFADF MTEQSPTRVL GNKKGIFTRQ RQPKSAAFLL 600
RERYWKIANE TRYPHSVAKS QCLENSPFT                        629
```

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-151 Asn-250 Asn-398 Asn-609

Disulfide bridges (**C**)
inter-chain 622-622' 622''-622'''
intra-chain not determined

voretigenum neparvovecum #

voretigene neparvovec

recombinant adeno-associated serotype 2 (rAAV-2) virus vector that carries the RPE65 gene, encoding a retinal pigment (RPE)-specific human retinoid isomerohydrolase, containing a modified Kozak sequence at the translation start site and under the control of the cytomegalovirus (CMV) immediate early enhancer and the chicken beta-actin (CBA) promoter.

voretigène néparvovec

vecteur viral adéno-associé de type 2 (rAAV-2) recombinant, contenant le gène RPE65 codant pour l'isomérohydrolase des rétinoïdes, humaine, spécifique de l'épithélium pigmentaire de la rétine, contenant une séquence de Kozak au site de démarrage de la traduction et sous le contrôle de l'activateur immédiat-précoce du cytomégalovirus et du promoteur de l'actine bêta du poulet (ABP, CBA).

voretigén neparvovec

vector viral adeno-associado de tipo 2 (rAAV-2) recombinante, que contiene el gen RPE65 que codifica para la retinoide isomerohidrolasa, humana, especifica del epitelium pigmentario de la retina, que contiene una secuencia de Kozak al sitio del comienzo de la traducción y bajo el control del activador inmediato precoz del citomegalovirus (CMV) y del promotor de la actina beta del pollo (CBA).

vorolanibum

vorolanib

N-[(3*S*)-1-(dimethylcarbamoyl)pyrrolidin-3-yl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidene)methyl]-2,4-dimethyl-1*H*-pyrrole-3-carboxamide

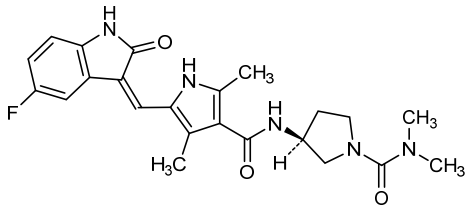
vorolanib

N-[(3*S*)-1-(diméthylcarbamoyl)pyrrolidin-3-yl]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihydro-3*H*-indol-3-ylidène)méthyl]-2,4-diméthyl-1*H*-pyrrole-3-carboxamide

vorolanib

N-[(3*S*)-1-(dimetilcarbamoil)pirrolidin-3-il]-5-[(*Z*)-(5-fluoro-2-oxo-1,2-dihidro-3*H*-indol-3-ilideno)metil]-2,4-dimetil-1*H*-pirrolo-3-carboxamida

$C_{23}H_{26}FN_5O_3$



vunakizumabum #

vunakizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* IL17A (interleukin 17A, IL-17A)], humanized monoclonal antibody;
gamma1 heavy chain (1-453) [humanized VH (*Homo sapiens* IGHV1-2*02 (82.70%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (124-221), hinge (222-236),CH2 (237-346), CH3 D12>E (362), L14>M (364) (347-451), CHS (452-453)) (124-453)], (226-213')-disulfide with kappa light chain (1'-213') [humanized V-KAPPA (*Homo sapiens* IGKV6-21*01 (80.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dimer (232-232":235-235")-bisdisulfide

vunakizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* IL17A (interleukine 17A, IL-17A)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-453) [VH humanisé (*Homo sapiens* IGHV1-2*02 (82.70%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (124-221), charnière (222-236),CH2 (237-346), CH3 D12>E (362), L14>M (364) (347-451), CHS (452-453)) (124-453)], (226-213')-disulfure avec la chaîne légère

kappa (1'-213') [V-KAPPA humanisé (*Homo sapiens* IGKV6-21*01 (80.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dimère (232-232":235-235")-bisdisulfure

vunakizumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* IL17A (interleukina 17A, IL-17A)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-453) [VH humanizado (*Homo sapiens* IGHV1-2*02 (82.70%) -(IGHD)-IGHJ4*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*01, G1m17, nG1m1 (CH1 (124-221), bisagra (222-236),CH2 (237-346), CH3 D12>E (362), L14>M (364) (347-451), CHS (452-453)) (124-453)], (226-213')-disulfuro con la cadena ligera kappa (1'-213') [V-KAPPA humanizado (*Homo sapiens* IGKV6-21*01 (80.00%) -IGKJ1*01) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 (107'-213')]; dímero (232-232":235-235")-bisdisulfuro

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGAE VKKPGASVKV SCKASGYTFT DYEVHWVRQA PGQGLEWMGV  50
IDPGTGGVAY NQKFEGRVTM TADTSTSTAY MELRSLRSDD TAVYYCTRYS 100
LFYGSSPYAM DYWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP 250
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 350
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 400
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPDF QSVTPKEKVT ITCSASSSVN YMHWFQQKPD QSPKLWIYRT  50
SNLASGVPSR FSGSGSGTDY TLTINSLEAE DAATYYCQQR SSYPWTFGQG 100
TKLEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                          213
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	150-206	267-327	373-431
	22"-96"	150"-206"	267"-327"	373"-431"
Intra-L (C23-C104)	23'-87'	133'-193'		
	23'"-87'"	133'"-193'"		
Inter-H-L (h 5-CL 126)	226-213'	226"-213'"		
Inter-H-H (h 11, h 14)	232-232"	235-235"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
303, 303"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
453, 453"

Electronic structure available on Mednet: http://mednet.who.int/
Structure électronique disponible sur Mednet: http://mednet.who.int/
Estructura electrónica disponible en Mednet: http://mednet.who.int/
* http://www.who.int/medicines/services/inn/publication/en/

AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Rec. INN): List 32
Dénominations communes internationales recommandées (DCI Rec.): Liste 32
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 32
(WHO Drug Information, Vol. 6, No. 3, 1992)

p. 9	*suprimáse* tacrolimus	*insertese* tacrólimus

Recommended International Nonproprietary Names (Rec. INN): List 34
Dénominations communes internationales recommandées (DCI Rec.): Liste 34
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 34
(WHO Drug Information, Vol. 8, No. 3, 1994)

p. 19	*suprimáse* sirolimus	*insertese* sirólimus

Recommended International Nonproprietary Names (Rec. INN): List 43
Dénominations communes internationales recommandées (DCI Rec.): Liste 43
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 43
(WHO Drug Information, Vol. 14, No. 1, 2000)

p. 64	*suprimáse* pimecrolimús	*insertese* pimecrólimus

Recommended International Nonproprietary Names (Rec. INN): List 44
Dénominations communes internationales recommandées (DCI Rec.): Liste 44
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 44
(WHO Drug Information, Vol. 14, No. 3, 2000)

p. 194	*suprimáse* everolimus	*insertese* everólimus

Recommended International Nonproprietary Names (Rec. INN): List 54
Dénominations communes internationales recommandées (DCI Rec.): Liste 54
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 54
(WHO Drug Information, Vol. 19, No. 3, 2005)

p. 266	*suprimáse* temsirolimus	*insertese* temsirólimus

Recommended International Nonproprietary Names (Rec. INN): List 56
Dénominations communes internationales recommandées (DCI Rec.): Liste 56
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 56
(WHO Drug Information, Vol. 20, No. 3, 2006)

p. 233	*suprimáse* zotarolimus	*insertese* zotarólimus

Recommended International Nonproprietary Names (Rec. INN): List 65
Dénominations communes internationales recommandées (DCI Rec.): Liste 65
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 65
(WHO Drug Information, Vol. 25, No. 1, 2011)

p. 91	*suprimáse*	*insertese*
	umirolimús	umirólimus

Recommended International Nonproprietary Names (Rec. INN): List 67
Dénominations communes internationales recommandées (DCI Rec.): Liste 67
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 67
(WHO Drug Information, Vol. 26, No. 1, 2012)

p. 77	*suprimáse*	*insertese*
	olcorolimús	olcorólimus

Recommended International Nonproprietary Names (Rec. INN): List 69
Dénominations communes internationales recommandées (DCI Rec.): Liste 69
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 69
(WHO Drug Information, Vol. 27, No. 1, 2013)

p. 44 **antithrombinum gamma #**

antithrombin gamma
antithrombine gamma
antitrombina gamma

replace the structure by the following one
remplacer la structure par la suivante
sustitúyase la estructura por la siguiente

```
HGSPVDICTA KPRDIPMNPM CIYRSPEKKA TEDEGSEQKI PEATNRRVWE 50
LSKANSRFAT TFYQHLADSK NDNDNIFLSP LSISTAFAMT KLGACNDTLQ 100
QLMEVFKFDT ISEKTSDQIH FFFAKLNCRL YRKANKSSKL VSANRLFGDK 150
SLTFNETYQD ISELVYGAKL QPLDFKENAE QSRAAINKWV SNKTEGRITD 200
VIPSEAINEL TVLVLVNTIY FKGLWKSKFS PENTRKELFY KADGESCSAS 250
MMYQEGKFRY RRVAEGTQVL ELPFKGDDIT MVLILPKPEK SLAKVEKELT 300
PEVLQEWLDE LEEMMLVVHM PRFRIEDGFS LKEQLQDMGL VDLFSPEKSK 350
LPGIVAEGRD DLYVSDAFHK AFLEVNEEGS EAAASTAVVI AGRSLNPNRV 400
TFKANRPFLV FIREVPLNTI IFMGRVANPC VK                    432
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
8-128 21-95 247-430

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-96 Asn-135 Asn-155 Asn-192

α-Sia→3-β-Gal→3-β-Gl-*N*→2-α-Man→6-
β-Man→4-β-Gl-*N*→4-β-Gl-*N*→N
α-Sia→3-β-Gal→3-β-Gl-*N*→2-α-Man→3-

Recommended International Nonproprietary Names (Rec. INN): List 69
Dénominations communes internationales recommandées (DCI Rec.): Liste 69
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 69
(WHO Drug Information, Vol. 27, No. 1, 2013)

p. 90	*suprimáse*	*insertese*
	ridaforolimus	ridaforólimus

Recommended International Nonproprietary Names (Rec. INN): List 76
Dénominations communes internationales recommandées (DCI Rec.): Liste 76
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 76
(WHO Drug Information, Vol. 30, No. 3, 2016)

p. 496 **enoblituzumabum #**

enoblituzumab *replace the structure by the following one*
énoblituzumab *remplacer la structure par la suivante*
enoblituzumab *sustitúyase la estructura por la siguiente*

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SFGMHWVRQA PGKGLEWVAY  50
ISSDSSAIYY ADTVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCGRGR 100
ENIYYGSRLD YWGQGTTVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELV GGPSVFLLPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPPEEQ 300
YNSTLRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
LVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
```

Light chain / Chaîne légère / Cadena ligera

```
DIQLTQSPSF LSASVGDRVT ITCKASQNVD TNVAWYQQKP GKAPKALIYS  50
ASYRYSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNNYPFTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                         214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	149-205	266-326	372-430
	22"-96"	149"-205"	266"-326"	372"-430"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)	225-214'	225"-214'"		
Inter-H-H (h 11, h 14)	231-231"	234-234"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

p. 511 **leniolisibum**

leniolisib *replace the chemical name by the following one*
léniolisib *remplacer le nom chimique par le suivant*
leniolisib *sustitúyase el nombre químico por el siguiente*

1-[(3*S*)-3-({6-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl}amino)pyrrolidin-1-yl]propan-1-one

1-[(3*S*)-3-({6-[6-méthoxy-5-(trifluorométhyl)pyridin-3-yl]-5,6,7,8-tétrahydropyrido[4,3-*d*]pyrimidin-4-yl}amino)pyrrolidin-1-yl]propan-1-one

1-[(3*S*)-3-({6-[6-metoxi-5-(trifluorometil)piridin-3-il]-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-il}amino)pirrolidin-1-il]propan-1-ona

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the *Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* will be reproduced in proposed INN lists only.

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* seront publiés seulement dans les listes des DCI proposées.

El texto de los *Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas* y de los *Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas* aparece solamente en las listas de DCI propuestas.

INN Working Doc. 16.395
July 2016
Distr.: PUBLIC
ENGLISH ONLY

62nd Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 12-15 April 2016

Executive Summary

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

62nd Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 12-15 April 2016

EXECUTIVE SUMMARY

INTRODUCTIONS

The meeting was opened and participants welcomed by Dr Marie-Paule Kieny, Assistant Director General, Health Systems and Innovation, who took the opportunity to thank INN Experts for their work in the field of medicines nomenclature, discussion of which is led by WHO on behalf of all member states. The strength of INN is worldwide and its use continues to grow. The increasing number of INN applications is a challenge and requires the diligence of all INN experts whilst the integrated data management system developed by the INN Secretariat has been of great value. The challenge of naming novel substances requires the unique knowledge of the Expert Group whilst the initiative of an innovative school of INN has great potential.

The new Chair, Dr Patience Holland, thanked the ADG for her interest and support. Dr Holland has a background in chemistry and has spent many years in the UK scientific civil service. She informed the Expert Group that two vice chairs had been appointed, one for chemical substances and one for biological substances. With the huge number of requests to assess, she called upon the Group to be efficient and effective, to be pragmatic, and to be scientifically accurate.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, INN Programme, in her turn welcomed all participants. She noted the increased number of applications for INN, the evolving nature of naming substances, and acknowledged the extra work put in by experts in various working groups within the Expert Group.

NOMENCLATURE of INNs

During the 62nd Consultation, a total of 183 INN requests were discussed, including:

- 128 new INN requests, including 68 for biological substances
- 50 outstanding requests
- 5 previously selected proposed INN, against which a formal objection had been raised.

As a result of these discussions, 149 names were selected, which are planned to be published in List 116 of Proposed INNs (p.INN), while 29 requests were deferred for future discussion. Two requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One INN application was withdrawn just before the Consultation. One amendment is planned to be published in a forthcoming List of p.INN and one objection could not be retained. Five new stems/substems were selected and 7 suffixes were promoted to the pre-stem list.

The INN selection process

The Secretariat provided Experts with an insight to its behind-the-scenes work on INN selection. Applications are received by the Secretariat and processed for review on a batch basis by the Experts who make use of the online IDMIS system to provide comment. The Experts' pre-meeting comments are summarized by the Secretariat for face-to-face discussion at INN Consultations, highlighting any consensus and individual opinions provided by the Experts. There is a one month period following a Consultation during which decisions can be reviewed by the Experts, and further checks performed on trademark or other conflicts. Outstanding requests also have to be addressed at Consultations and Experts were reminded on how to make use of the IDMIS system to provide comment on these. Following the one month post-meeting review, the Secretariat informs applicants of the outcome of the Consultation. Information pertaining to the substance involved in a newly adopted name has to be validated by INN Experts, the Secretariat and the applicant prior to publication of a name in a proposed list of INN – the p.INN List. There then follows a 4-month period for objections and comments by stakeholders on the names within a p.INN List. Following this, all fully adopted names

for which there are no objections get published in the WHO recommended list of INN – the r.INN List.

SCHOOL of INN

A small group of INN Experts met in Jan 2016 to discuss the idea of setting up a 'School of INN'. Its role would be to educate the pharmaceutical industry on how to design and construct an INN, and to provide information to healthcare professionals on how to interpret an INN. The school would not only be educational but would raise interest in the science of nomenclature and help cultivate a future generation of INN experts. It has been found also that pharmacy students in general do not learn about INN and the value of the stem in referring to the mode of action of the drug. Further, there is a need to differentiate between INN and generic names that are not INN.

Barriers can exist to the use of INN in teaching and practice, for example, industry sponsored courses sometimes prefer not to use INN for commercial reasons. In addition, the extent of use of INN amongst healthcare professionals varies and there is a perception that INN are difficult to use. Consequently, a school to promote the use and understanding of INN on a global basis would be of tremendous value. It will be difficult to establish INN as a key theme in pharmaceutical textbooks but reaching out to the pharmaceutical industry to encourage them to use the INN would be a good start.

In the initial stages, the school would look to publish papers in scientific educational communities whilst (a revised version of) the INN publication *Guidelines on the Use of INN for Pharmaceutical Substances* would be useful in teaching and the promotion of INN. The school needs to be promoted on the web, with e-learning and the use of info-graphics. Its identity needs to be established, with its own logo, so that it can have a proactive presence in pharmaceutical companies and at industry workshops and conferences. Organising inter-professional online workshops would be useful, for example focusing on a particular theme or disease state that uses a range of drugs with different modes of action, whilst the school would proactively interact with professional pharmaceutical associations and the pharmacopoeias.

The school would be a virtual school and a steering committee of INN Experts should oversee its establishment and development. It is foreseen that a technical officer could assist the steering committee. Its website could be hosted on, or at least linked through, the INN website. Funding would be required for publication, advertising and for a full-time technical officer. Seed funding could be provided from the INN Programme but eventually it should be self-funded, for example with registration fees from courses, and interested partners and funding agencies would be approached for sponsorship.

In the course of discussing the idea of a School of INN, it was felt that a survey of the use of INN in practice and education would be useful, to gather information from the ground and to collect suggestions from practitioners and students. Consequently, a short survey comprising ten statements on the familiarity and usage of INN was developed, in which participants would respond to the statements on a five point scale. A small sample of institutions and organisations was selected for the survey, which was conducted over one month shortly before the 62nd Consultation. The statements addressed issues such as the level of knowledge of INN, their use versus brand names by practitioners and by educational establishments, and the use and meaning of stems.

There were slightly over 1000 respondents from 68 countries involving academics, healthcare providers, scientists, industrialists, regulators and students, with pharmacy students forming the highest proportion. Generally participants were aware of and familiar with INN. Comments were also solicited and the large number submitted provided an overview of the usage of INN in practice and education. Most universities' educational programmes use INN in teaching but the industry and healthcare sectors preferred the use of brand names. However, there is a gap in the education of healthcare professionals and even though INN is used in teaching, students were not familiar with the stem system. A greater understanding of the construct of the INN by the students will help them better appreciate the learning of pharmacology and therapeutics.

A further survey was made of drugs listed in a classical pharmacology text book (Goodman and Gilman's (12th Ed)). About three-quarters of drugs classified according to pharmacological action had useful common stems and classes of drug with no useful stem were typically old drugs.

In surveying the INN Experts present at the Consultation, it became clear that there was a degree of education on INN in their home countries but where this was organised by the pharma industry, there was a tendency for brand names to be used. The Experts also expressed their views that physicians in their home countries tended to use brand names rather than INN. Thus, whilst it would be useful to offer universities educational courses on INN, it was felt that practitioners should also be targeted. It was further highlighted that regulatory personnel tended to have a biological rather than a pharmacy background and these would be good targets for education.

The INN Expert group heartily endorsed the further development of this programme and the Chair congratulated the working group on their efforts on this project.

A draft info-graphics cartoon on the value of INN was shown to, and appreciated by, the Experts.

BIOLOGICAL QUALIFIER

The Expert Group was informed that the original plan to contract out a short study on the application of a BQ had not followed the appropriate WHO procedures and would have to be re-done. With this disruption to the previously agreed plan of action, the situation had been reassessed and it was felt that it would be better to proceed with a provisional implementation of the BQ scheme accompanied by a prospective impact study. This also would have the benefit of not spending a further six months conducting an interim impact study during which time national schemes may get implemented.

To expedite issues it was suggested that the BQ Working Group draw up terms of reference (TOR) for the impact study, which would be used to recruit a suitably qualified body, independent of industry and WHO, to gather data and report back annually to INN. The study would assess countries taking up the scheme, the number of BQs issued and how the database was accessed. Drug funding issues and the quality of the data in the database could be measured using published resources and data from NRAs. In this way, measuring hard rather than virtual data would be a better use of funds. There should be a three-year deadline for the study and if specified parameters were not met, the scheme would be dropped, but if uptake was good with good quality outcomes then it should get fully adopted by WHO. To ensure transparency, it was recommended that the TOR get published so that it would be apparent to all if the scheme is working. The body conducting the study should be announced and annual reports made public.

Consequently, it was proposed to the Expert Group that the BQ be implemented on a provisional basis and that a prospective study gets performed to enable evaluation of the impact of the BQ on access to medicines. Members of the Expert Group expressed support for this plan and agreed to its adoption.

With regard to the impact study, it was felt useful to have countries volunteer to initiate the BQ process and Experts were invited to approach their local regulatory and healthcare authorities in this respect. It would also be useful to gather data from countries not adopting the scheme to better assess the impact in countries that do. It would be important to have a random source of countries in the study so that there would be no perceived bias. Since the FDA has now provided seven biosimilars with random four letter suffixes, essentially the FDA equivalent of the WHO BQ, it would be valuable to include the USA in the impact study. There has been a good degree of communication between INN and FDA personnel on harmonising the BQ and FDA suffix. Assigning identical FDA suffixes and BQ codes would be invaluable.

Technically, a complete BQ system and database would take approximately two months to establish although random BQ codes could be generated within a few days. If needed, codes could be generated in advance and would be available immediately for applicants. Codes would only be assigned when an applicant approached an NRA for drug licensure and so it was likely that very few INN would ultimately be associated with a BQ code as few substances assigned an INN made it through to the licensure process.

NAMING NEUROLEPTICS

In the past, most neuroleptics were derived from phenothiazine or butyrophenone, and their chemical structure was informative regarding antipsychotic activity and side effects. Thus, stems based on chemical structure were appropriate. Currently, there are four stems for neuroleptics: *-peridol* (antipsychotics, haloperidol derivatives), *-peridone* (antipsychotics, risperidone derivatives), *-pride* (sulpiride derivatives) and *-apine* (psychoactive), although the latter two are not specific and many substances with these stems are not antipsychotics. There is no coherence amongst the stems and none of them identify the class as a whole. Also, many neuroleptics on the market have no stem. Whilst none of the stems indicate mode of action, no clinically effective antipsychotic is devoid of dopamine D2 antagonistic activity.

For clozapine and 'atypical antipsychotics' structure-activity is less important whilst emerging data indicate that various neurotransmitters are involved in efficacy and side effects, e.g. 5-HT, glutamate and acetylcholine.

There are many new neuroleptics under development including α-7 nicotinic acetylcholine receptor agonists, 5-HT2A antagonists, and PDE1, PDE9 and PDE10 inhibitors. New neuroleptics could be named on an *ad hoc* basis, creating appropriate stems as and when required, or alternatively a new prospective stem could be defined for DA receptor antagonists, neuroleptics, e.g. *-dant*, *-daleptic* or *-leptic*. The mode of action could be further defined by a substem, for example, *-ser* for action upon serotonin receptors, *-glu* for action upon glutamate receptors and *-col* for action upon cholinergic receptors. However, there would be no need to indicate the subtype of receptor (e.g. 5-HT1, 5-HT2) or the action on receptors (agonist or antagonist).

The INN Experts were requested to consider these comments.

TWO-LETTER STEMS

It was brought to the attention of the INN Expert Group that two-letter (single syllable) INN stems were often used in general language and as such creating new invented names avoiding such stems was difficult. Often they had been missed by regulators as they were such small entities and not easy to pick up. Six two-letter stems had been identified: '*aj*' and '*io*' as infixes ('*io*' also as a prefix), '*ni*' in nicotinic acid or nicotinoyl alcohol derivatives, '*ox*' as antacids, and '*ur*' and '*ac*' as suffixes. Some of these stems were outdated and some had been misused by the INN system in conflicting longer stems, for example, '*ni*' occurs in the stem *nitro-* whilst longer, more specific, stems such as *-fenac*, *-olac* and *-rac* are used instead of '*ac*'. The use of these stems needed to be reviewed. If the commonly used two-letter stems could be defined they should be retained and protected, whereas some did not need to be kept.

The Chair was grateful for this information which would be addressed by the stem review group.

BIOREVIEW REVISON 2016

Assigning INN to biological substances is an increasingly important part of the work of the INN Expert Group and INN Secretariat. The publication, 'International Nonproprietary Names (INN) for biological and biotechnological substances (a review)', otherwise known as the 'Bioreview', describes the stems, systems and General Policies in place for such substances. The current 2014 version is being updated with the new General Policy for cell therapies, an update of stems, a new section on aptamers and siRNAs, and a revised classification of enzymes. This will be available later in 2016. The outcome of current discussions on vaccine-like substances, monoclonal antibodies and the *–cept* stem (see below) will be published in a future version.

INN WORKING GROUPS

Consideration of new therapies

The INN system was established in 1950 by a WHA resolution to create a global nomenclature system for which there could be free and unrestricted use of the names by all interested parties. To achieve this, the INN Programme had to be based upon intellectual property law (within class 5 of the

Nice Agreement). The global recognition of INN as public domain elements of intellectual property legislation and practice resulted in having to have the two step process of proposed INN (p.INN) and recommended INN (r.INN) in order to help protect the rights of existing trademarks. Over several decades, technology has dragged the INN Programme, a small step at a time, into areas that were not in its original remit, with substances that are not exactly defined being named e.g. biopharmaceuticals, and gene and cell therapies. However, even from the start, many substances which were impure and for which there was only a crude definition, e.g. early antibiotics, received INN. In these cases, the benefit of having INN outweighed the lack of homogeneity. Such an approach stands in good stead for substances developed by current modern technologies. In addition, new groups of therapies need new rules (naming scheme + definition requirements).

INN utilisation is expanding along with an increase in the number of INN and pharmaceutical substances/groups. Indeed, the majority of pharmaceutical substances in use today is designated by an INN. The INN system is regulated by the INN Procedure, most recently revised in 2004 and adopted by the Executive Board in 2005, and further revisions are not undertaken lightly. However, INN General Principles (along with the INN Procedure) do not limit the types of therapies the INN Expert Group should be limited to in its selection of names. General Principles can be revised by the Expert Group and the INN Programme has independence in deciding which groups of substances get names and how defined.

Cell therapies working group

An INN scheme for naming cell therapies has been devised and several cell therapy substances have been assigned INN. However, several hurdles remain. One of these is that the border between cell and other therapies needs to be better defined; for example, autologous cells genetically modified *ex vivo* are considered by INN experts to be a gene therapy procedure whereas the USAN considers this to be cell therapy. Consequently, distinct names are being assigned to the same substance. Each cell therapy application also has to be examined thoroughly to understand how to assign the most appropriate name and often there is a paucity of data by which to fully define the cell substance.

The *-cept* stem working group

Following a debate at the 61st INN Consultation on whether the *–cept* stem (for 'receptor molecules, native or modified') was the appropriate stem for three particular INN applications, a working group reviewed the entire *–cept* class and its definition. Currently there are 22 INN with the *–cept* stem: 2 are soluble receptor fragments, 1 is a receptor fused to a toxin, 1 is a receptor conjugated to PEG, 1 is a receptor linked to a myristoyled peptide, while the remaining 17 are Fc-fusion proteins. These substances generally act by ligand trapping rather than being stimulatory substances. There are also 10 Fc-fusion proteins/peptides with alternative stems: several have the *ef*-prefix to indicate the presence of the Fc moiety, whereas prior to the use of this prefix several had been assigned a variety of stems reflecting their mode-of-action (MOA).

Following extensive discussion, the working group agreed that the essential part of the *–cept* stem is the receptor molecule and not the Fc or other moiety that may be fused to it, and therefore Fc should not become part of the stem definition. A receptor is defined typically as a membrane bound protein that receives a chemical signal from outside the cell. The biological response is usually unidirectional but in the case of cell-cell interaction, it can be difficult to define which is a ligand and which is a receptor. Also, several *–cept* substances bind to a cellular target rather than a free ligand. Thus, it was agreed also that the *–cept* stem could include cell surface molecules involved in cell adhesion and designed to block cell-cell interaction so that the stem is not restricted to classical pharmacological receptors.

One Expert emphasised that *-cept* substances are, like monoclonal antibodies (mAbs), major targeted biologics, and that *-cept* substances and mAbs share a similar binding structure (the two arms of the mAb being 'replaced' by the extracellular region of a receptor, for those with an Fc-fusion format), well defined specificity and similar MOA. As *-cept* substances are used more and more as alternative to mAbs, it was proposed to strengthen the parallel by considering that *–cept* substances could be activatory as well as inhibitory (in the same way as mAbs). This meant that *–cept* could include, for

cell-cell interaction, not only 'receptor' but also 'membrane ligand' acting as an agonist of an activatory receptor or an antagonist of an inhibitory receptor. Furthermore, in order to reinforce the coherence of the *–cept* and *–mab* stems, it was proposed that, in addition to the current substem used to define the protein, a second substem (*-ci-*, *-tu-*, etc.) could be used to define the target class, mimicking the substems used for mAbs.

With regard to Fc-fusion peptides, there was full agreement that Fc-peptides should not automatically be assigned a *–cept* stem and that they should continue to be named according to their MOA, making use of the *ef-*prefix and that inserting an infix to indicate the peptide class would be appropriate. However, the term CPCA (composite proteins for clinical applications) should be avoided.

In conclusion, it was agreed by all that *–cept* should not be restricted to Fc-receptor fusion proteins in order to allow for its use with future formats of a receptor protein, but that the working group should consider further whether membrane ligand substances should be included in the definition.

Polyethyene glycol (PEG) working group

The main issue currently being debated by the PEG working group concerns the nature and naming of the linker group, the chemical entity that links the PEG moiety to the principle active substance.

Vaccines-like working group

Several recent INN applications have fallen into a grey area of vaccine-like substances and the working group has been tasked with elucidating a way forward. According to the INN Bioreview (2014), traditional vaccines are not assigned INN, vaccine nomenclature being more the remit of the WHO Expert Committee on Biological Standardisation. However, the Bioreview states that recombinant (protein) vaccines may fulfil the requirements of being defined and homogeneous substances and so could be assigned INN, although to date none have. Also, peptide vaccines being defined molecules can be given INN and many have been so with the stem *–motide* being assigned to them. However, the peptides so far named with the *–motide* stem have immunomodulatory activity but are not true vaccines containing microbial-derived antigens that stimulate an immune response. What is not clear is whether entities such as viral/bacterial vectored vaccines (viruses/bacteria that have been genetically modified to express a heterologous antigen) and oncolytic viruses should be assigned INN. It is also not clear whether DNA/RNA vaccines should be assigned INN. There is a precedent for naming such substances in that viruses, bacteria and DNA plasmids used as gene therapies can be and are being assigned INN according to the INN scheme for gene therapy. Consequently, the working group has been tasked to determine to what extent vaccine-like substances should be given INN.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

The British Approved Names (BAN) 2017 will be published in August 2016 with an effective date of 1st January 2017, in line with the publication of the British Pharmacopoeia 2017. The BAN 2017 will contain the BAN 2012 (and Supplements 1-4) along with 31 new names that are being used in the UK market. The BAN 2017 will contain updated 'Action and Use' statements for radiopharmaceuticals and anticancer drugs along with a new appendix for names that are not harmonised across regions. Mr Evans and Dr Holland thanked those members of the Group that participated in the preparation of the new appendix and indicated that it should be a useful addition to the BAN publication.

European Medicines Agency (EMA)

The latest version of the 'Guideline on the acceptability of names for human medicinal products processed through the centralised procedure' came into effect on 1 January 2015. Based upon feedback from the INN Secretariat, it makes clear reference to the WHA resolution on the protection of stems (WHA46.19). The EMA's Name Review Group (NRG) assesses about 500 names per year. Objections to invented names containing INN stems or similar to INNs are frequently endorsed by the NRG in each meeting.

International Union of Pure and Applied Chemistry (IUPAC)

A project to generate a pdf file of the 'Blue Book' (Nomenclature of Organic Chemistry) for free web access has been initiated and is proposed to be completed by 2019 for the centenary of IUPAC. Another part of the project is to prepare an improved index.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs within the PMDA has two main tasks, preparing the draft Japanese Accepted Names (JAN) as the JAN Secretariat and preparing the draft Japanese Pharmacopoeia (JP) as the JP Secretariat. The JAN Expert Committee met on five occasions in 2015; 62 requests were considered and 60 JAN published. The proportion of biological requests over chemical requests has been increasing and reached 40% for 2015.

The 17th Edition of the JP was published in March 2016 and contains 1962 monographs; an English version will be published in September 2016.

The objective of the WHO Good Pharmacopoeial Practices guidance is to harmonise approaches and policies in establishing pharmacopoeial standards and the next International Meeting of world Pharmacopoeias will take place in Tokyo on 13-14 September 2016, co-hosted by PMDA. Following this, on 15 September, the JP will hold its 130th Anniversary Symposium, also in Tokyo.

United States Adopted Names (USAN)

The 2016 winter USAN Council meeting took place on January 7-8, 2016 in Lake Buena Vista, Florida where names for 37 drug substances were reviewed and discussed. Thirteen new stems or infixes with existing stems were approved and added to USAN's stem list. Two stem definition revisions were approved to harmonise with the INN programmes' definitions.

Policy discussions included trademark abandonment requests, biosimilar drug nomenclature, cellular therapy nomenclature harmonisation with the INN, and ISMP medication errors reports. Forty-three INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 62nd INN Consultation in April, 2016.

Through April 1, 2016 USAN staff will have processed, researched and made recommendations for 40 new USAN applications and forwarded this information to the USAN Council for its review and selection. Through March 2016, 23 USAN, 4 modified USAN and 1 revised USAN will have been adopted for 2016. Revenue will be realised for an additional 3 negotiations.

The 2016 summer meeting of the USAN Council is scheduled to take place July 21-22 at the American Pharmacists Association headquarters in Washington D.C.

United States Food and Drug Administration (FDA)

The FDA Office of Safety Evaluation, Division of Medication Errors Prevention and Analysis (DMEPA) examines invented names in relationship to USAN stems. As of this time, there is no provision for the default permission to utilize two-letter stems within the invented names (see above discussion on 'Two-Letter Stems'). The current policy is that all USAN stems are protected and should not be utilized as part of an invented name.

The FDA issued a draft Guidance entitled "Nonproprietary Naming of Biological Products", which addresses the definitions of and nomenclature of related biological products, biosimilar products, and interchangeable biological products. FDA documents designed for use by sponsor and applicants are classified as guidance.

A new Commissioner of the FDA, Dr. Robert M. Califf, has been appointed after approval by the US Congress.

United States Pharmacopoeia (USP)

The schedule for publication of the 'USP Dictionary of USAN and International Drug Names' has changed to coincide with the calendar year, and so the 2016 version is now available.

Dr Raffaella Balocco-Mattavelli, Group Lead of the INN Programme, was invited to the USP's Nomenclature and Labeling Expert Committee meeting of March 2016, to give a short introduction to the proposed WHO Biological Qualifier, which was well received.

The USP continued its Global Health Programs (GHP) to help improve quality of medicines by activities such as education, outreach, standards resources, consulting. A notable example is the Center for Pharmaceutical Advancement and Training (CePAT) in Ghana, a laboratory and education facility that was recently expanded.

World Customs Organisation (WCO)

The WCO provides leadership, guidance and support to Customs administrations to secure and facilitate legitimate trade, realise revenues, protect society and build capacity. Many members of the World Trade Organisation have undertaken to eliminate customs duties on medicaments and pharmaceutical active substances described in INN Lists. In order to ensure such duty free treatment, it is important to decide the WCO's Harmonised System Customs Tariff Classification (HS Classification) of INN substances, the HS being the International Convention for customs classification. Consequently, when new INN Lists are published, the WCO examines the List and decides upon the HS Classification of new INN substances. So far during 2016, the HS Classification for approx. 200 substances described in INN Lists 112 and 113 has been made and overall more than 4,500 INN substances have been subjected to HS Classification. In order to decide the HS Classification of INN substances, detailed information on chemical structure and pharmaceutical activity is often required. If additional information is needed, this is obtained directly from WHO. Moreover, a representative of the INN Secretariat is usually invited to attend WCO meetings on HS Classification of new INN substances. The WCO greatly appreciates the support offered by WHO in this way and hopes to continue the close cooperation between the INN and WCO.

EU Openmedicine Project

The goal of the EU funded 'openMedicine' project is to enhance the safety and continuity of cross-border (and national level) healthcare through interoperable 'ePrescriptions' and to propose concrete solutions to the delivery problem. It plans to achieve this by univocal identification of a medicinal product dispensed in another country, and if and where substitution is permitted or required, dispensation of an equivalent or similar product in line with national regulations. Overcoming the challenges will involve development of a common data model, common nomenclature, harmonisation of therapeutic and economic substitution, and coordination of the practical solutions and policy recommendations of the openMedicine project with the policy recommendations of the EU/US roadmap process for eHealth cooperation.

CLOSE OF MEETING

The Chair was grateful for the support of the INN Secretariat and Experts in this her first role as Chairperson of the INN Expert Group. She also thanked everyone for their diligence both before and during the Consultation.

Next Meeting

The 63rd INN Consultation will take place in Geneva on 18-21 October, 2016.

Open Session for INN Stakeholders

62nd INN Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 12 April, 2016

Dr Patience Holland, Chair of the INN Expert Group, welcomed stakeholders and INN colleagues to the Open Session for Stakeholders Meeting adjoining the 62nd INN Consultation. Stakeholders provide valuable information that assists INN Experts in assigning INN whilst the progressiveness of the WHO in inviting presentations on policy issues from stakeholders was acknowledged. All participants were requested to respect the confidentiality of the information shared during the meeting until the meeting report is in the public domain.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team welcomed participants on behalf of WHO and thanked Dr Holland for taking on the position of chair of the INN Expert Group.

Dr Raffaella Balocco-Mattavelli, Group Lead INN, INN Programme, similarly welcomed all to the meeting and expressed her pleasure in meeting stakeholders face-to-face.

PRESENTATIONS on INN ASSIGNMENTS

Jazz Pharmaceuticals

Jazz Pharmaceuticals continued to object to the INN *dexamfetanol carbamate* assigned to their product JZP-110 on the grounds that the *–bamate* stem was inconsistent with its known pharmacology. Since stems should define pharmacologically related groups, it would be more appropriate to use the *–faxine* stem with *solrifaxine* the proposed INN. JZP-110 is a selective inhibitor of norepinephrine and dopamine uptake and the *–faxine* stem includes such inhibitors, amongst other activities. In contrast, the *–bamate* stem does not include such substances. New information from a phase II clinical trial on narcolepsy treatment also showed therapeutic effects directly opposite from the *–bamate* class, whilst further new data showed a low potential for abuse in a human study (previously the low abuse potential had only been demonstrated in rats).

A second argument against the assigned INN was that *dexamfetanol* lacked distinctive sound and spelling. In a Phonetic and Orthographic Computer Analysis (POCA), *dexamfetanol* scored >70% against *dexamfetamine* which suggests a high risk of medication errors; *solrifaxine* would be much more distinct.

A third concern was that the similarity between *dexamfetanol carbamate* and *dexamfetamine* would lead to confusion and misunderstanding amongst patients and health professionals resulting in an inappropriate perception of abuse potential and thus reduced access to JZP-110. In contrast, *solrifaxine* would provide for clear identification, safe prescribing and dispensing.

A consultant pharmacologist to Jazz Pharmaceuticals reinforced the arguments presented by the company, that the INN *dexamfetanol carbamate* would create an erroneous impression that JZP-110 was an amphetamine and as a consequence would limit appropriate patient access to JZP-110.

erytech

erytech is a small late stage biotech oncology company, focusing on its 'erycaps' technology platform which involves entrapment of therapeutic compounds inside donor-derived red blood cells (RBCs) using controlled hypotonic swelling followed by hypertonic stress. Its product eryaspase comprises a homologous dispersion of erythrocytes encapsulating asparaginase and was described as a circulating bioreactor manufactured from recombinant *E coli* derived asparaginase and erythrocytes from blood transfusion centres. Eryaspase is not simply asparaginase combined with RBCs, but combines the capacity of erythrocytes to actively pump asparagine from plasma followed by its cleavage into aspartic acid and ammonia by the entrapped enzyme, leading to plasma asparagine depletion.

Assignment of an INN to eryaspase would distinguish it from other available preparations of marketed free asparaginase and aid prescribing and dispensing.

Further, eryaspase does not deplete glutamine as does the free enzyme and so has an improved toxicity profile, as demonstrated in a phase 2/3 clinical trial. The company is investigating two further enzymes – methionine-γ-lyase and arginine deiminase – for RBC entrapment as additional tumour starvation candidates, and an INN for eryaspase would be useful when developing further products using the erycaps technology platform.

In discussion, an INN Expert opined that the company was seeking an INN for a process and that perhaps the more appropriate route would be to consider this as a cell therapy and name accordingly.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologic Medicines (ASBM)

The ASBM congratulated the INN Group on its leadership on the issue of biologics naming. Its message at this critical moment was to proceed expeditiously with a pilot study. Its data indicate strong physician support for clear, distinguishable naming. Patient groups in multiple countries have expressed interest in the BQ programme and distinguishable naming is essential to promote widespread biosimilar adoption and confidence in their use. The ASBM has conducted surveys amongst physicians on distinguishable naming and has presented its data to national regulators, often at their invitation. Its most recent survey amongst US physicians shows overwhelming support for distinguishable naming although a good fraction of physicians bearing 'no opinion', suggests a lack of familiarity with biologics and that education on biosimilars remains a clear need.

Pharmacists typically use three names, tradename, non-proprietary name and the (US) NDC code. Interestingly, whilst US pharmacist organisations have opposed distinguishable names, individual pharmacists attending continuing education programmes on the complexity of biologics compared to simple chemical molecules, showed clear support for distinguishable naming. So despite past objections, ASBM continues to work with pharmacists' organisations to emphasise the importance of distinguishable naming. It will continue to pursue its educational programme on this and to respond to concerns that exist. In conclusion, the ASBM urged the INN Group to proceed with BQ implementation.

Generic Pharmaceutical Association (GPhA)

GPhA represents the manufacturers and distributors of a variety pharmaceutical products, including finished generic products. Many members have developed and manufactured biosimilars for some time and the GPhA Council works to ensure a positive regulatory, reimbursement, political and policy environment for them.

The 2015 WHO proposal for a 'biologics qualifier' composed of a non-meaningful 4-letter code with an optional 2-digit checksum, would be voluntary, would not be part of the INN, would be assigned by WHO and be applied to all biosimilars. The GPhA felt that a BQ will increase naming complexity and the risk of confusion regarding prescribing, dispensing and substitution. It would be unclear whether or not the increased complexity would provide the desired benefit of enhanced pharmacovigilance or create more reporting confusion. Due to these risks, the GPhA stated that the proposed system must be independently tested to ensure it improves identification and reduces risks. Indeed, the BQ scheme should not be implemented until a consensus has been reached and is supported by an impartial and thorough impact assessment.

The GPhA felt that the historic naming system of tradename plus INN works well. Indeed other identifiers are also present such as the company name, lot number and (in USA) the national drug code, which are used successfully for identification and tracking. Thus, whilst GPhA applauds the WHO's interest in developing a global identification system for biologics, it expressed concern that a random 4-letter BQ code will be meaningless and difficult to remember and transcribe. In addition, uncertainty around retrospective application of the BQ may lead to a discriminatory and anticompetitive situation between existing reference and future biosimilar medicines. Finally,

extremely short timelines for a WHO final BQ report will hamper a comprehensive and meaningful impact assessment and there has been a lack of transparency regarding the few national drug authorities that have requested the development of such a system.

Safety is enhanced by the global use of non-proprietary names and the GPhA expressed support for the WHO proposal to keep the INN the same for reference products and biosimilars. The US is an emerging market for biosimilars with the first one approved by FDA in March 2015. The GPhA is concerned also about the FDA proposal to attach a 4-letter suffix to the INN and advocated that biologic products with the same drug substance should contain the same INN.

The WHO BQ needs to be voluntary and should not be implemented in countries with measures that already assure unambiguous identification of biological products. If used it must be applied to all biologics and be applied both retrospectively and prospectively. It should not be required for prescribing and should not include a manufacturing site designation.

In conclusion, the GPhA requested WHO to make fully transparent the positions of all stakeholders during the consultation process, especially the DRAs that requested this action by the WHO. A thorough impact assessment study needs to be conducted and the WHO must be prepared to abandon the BQ concept if the impartial assessment highlights problems with the proposal.

In discussion, the Chair clarified that the BQ would be for all biologics and not just biosimilars. Furthermore, the proposal advocates retrospective application although it is recognised that local legislation may not allow this to occur. The INN Experts also acknowledged that whilst a thorough assessment study is needed, there was a need to move ahead as already some national authorities were activating their own biosimilar identification scheme. All agreed that time was of the essence.

International federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The IFPMA expressed strong support for the BQ. It would enhance patient safety by linking all global systems in use today around the world. The IFPMA recommended that the BQ should now be used in conjunction with the INN, as a tool for pharmacovigilance, should form part of the official record of authorisation of a biological medicine, and should be given to all biologic drug substances awarded an INN. The IFPMA also recommended that all drug regulatory authorities (DRAs) should implement the BQ as soon as possible, and that DRAs using the system passively can choose to permit marketing authorisation holders to include the BQ in product information and labelling. The WHO should also develop practical advice for DRAs for their implementation of the scheme to reduce their administrative burden.

The IFPMA further recommended that subsequent to implementation, DRAs should provide regular feedback to WHO on the operation of the BQ, that surveys of patients and health professionals should be undertaken to assess awareness and impact, and finally that WHO should coordinate educational workshops for all stakeholders.

In conclusion, the IFPMA repeated its strong support for the BQ scheme, that it would achieve its intended outcomes and that it should be implemented as soon as possible.

Medicines for Europe

Medicines for Europe (formerly European Generic and biosimilar medicines Association – EGA) and its Biosimilar Medicines Group continued to appreciate the INN Expert Group's efforts to counteract the proliferation of divergent global schemes for naming biologic medicines. However, it could not support the current final INN proposal for a Biological Qualifier (BQ) as concerns remained regarding its added value over other existing and validated systems. There was also a lack of transparency regarding which WHO member states supported the BQ scheme and with retrospective application only being recommended and not mandated, there was the possibility of creating an undue differentiation among biologic medicines. In contrast, regulatory science supported that 'comparable' and 'highly similar' biologics share the same INN and the scientific principle of comparability should be applied to all biologics including biosimilars.

Introducing a BQ has far reaching consequences and could only be feasible if the need for it was clear and documented, and the proposal was shown to be effectively and safely addressing this need. The INN approach to assessing impact was appreciated and had been a long standing request from the Biosimilar Medicines Group. The reference to the WHA resolution on access to biotherapeutic medicines was welcomed.

The scope of the BQ impact study should cover all intended areas of use of the BQ and ideally should focus on gathering input from all concerned stakeholders on an international basis. Medicines for Europe was concerned that the timelines of the study were overly ambitious and had questions regarding when the study methodology and outcome would be made public, how WHO member states would be consulted, and what the next steps would be.

Different approaches to biologics remain a fact. Developments are underway in the USA and the Japanese system is working well. Consequently, the organisation wished to know which WHO member states supported the BQ, why use was not being made of validated international tools such as ISO IDMP, what would happen if the impact study did not confirm the supposed benefits of the scheme, and finally what was the status of discussions with the FDA and the proposed FDA naming scheme.

The Biosimilar Medicines Group's recommendations were that the basic science-based approach of INN plus brand-name is by far the best approach, that the BQ must be evidence based approach, that there must be transparency on WHO member states official position and that in the long run any system must be robust and fair.

In discussion, the Chair reminded the meeting that divergent schemes were already in place, which was why the WHO INN was developing the BQ scheme, that the BQ would apply to all biological substances and that it had been made clear from the start that the BQ would not be part of the INN. Stakeholders were also informed that the timeline of an assessment study was still being discussed internally and that dialogue especially with the US FDA was ongoing, with comments forwarded to the FDA being publicly posted (by FDA).

The FDA observer at INN, who also liaises with the USAN council, confirmed that the FDA is working with INN to harmonise as much as possible, as having different identifiers would be detrimental. To date, the FDA and INN proposals appear similar. The differences are that the FDA system has no checksum and has a hyphen linking the code to the USAN; however, the FDA system did not intend to change the USAN, the suffix being added to label the product.

The Medicines for Europe's contention that the sole use of INN plus brand name as in the EU was adequate, was challenged. The EU system works relatively well but where similar practices have been adopted in other jurisdictions, there have been problems where biosimilars have the same INN. For example, Australia has registered three *filgrastims* and almost 40% of adverse events are listed simply as *filgrastim* with no way of knowing which one. Similar data has derived from The Netherlands. The idea behind the BQ was to add a bit of extra checking; it would not be perfect but it would add value.

DISCUSSION on MONOCLONAL ANTIBODY NOMENCLATURE

The Antibody Society is a non-profit trade association founded in 2007 representing a number of companies, large and small, involved in the research and development of antibody therapeutics. The Society had been charged by its members to challenge the 2014 changes to mAb INN assignment and so had been invited to attend the open session to discuss naming issues face-to-face with INN Experts. The issues had been documented in a paper by Jones et al, 2016[1], whilst the Society involvement was further backed by a petition signed by 290 individuals from 98 commercial and academic institutions from 23 countries.

The INN designation of the source of an antibody by use of a specific substem (*-omab* for murine, *-ximab* for chimeric, *-zumab* for humanised and *–umab* for human) had been straightforward. But with

[1] Jones et al, MAbs 8:1-9, 2016.

the field growing explosively with highly varied and sophisticated approaches to generate mAbs, an expanding repertoire of Ab engineering options and an increasing number of antibody-based therapeutic platforms, the Society considered that the naming scheme had become outdated and a system identifying source was no longer relevant. Furthermore, in the current (2014) version, source substems are now defined, not by their origin, but by amino acid sequence comparison of the end product to sequences in IMGT, the ImMunoGeneTics international information system. On the other hand, the USAN system requires a >85% sequence identity with human sequences to determine humanisation. This leads to strong inconsistences. Of the 19 marketed humanised mAbs (those with a *-zumab* stem), none would be classified as humanised under the new rules.

The Society felt that the new rules are scientifically flawed as the amino acid sequence does not define human-ness, are inconsistent with previously assigned INN, and do not consider advances in technology. A further criticism was that the designated IMGT database and search tool were not freely available, with payment required for commercial entities. The Society foresaw a risk that companies were already designing mAb therapeutics simply to obtain the humanised (*-zumab*) stem and so alternative approaches are needed. They suggested that the source substem should be dropped and a system developed for near future developments that concentrates more on functional properties should be considered. In conclusion, the Society requested the INN Programme to work with key stakeholders in finding an optimal solution to these issues.

Following this presentation, it was highlighted for information that IMGT is freely available for academics; however, it was correct that there is a cost for companies to cover copyright.

There followed a presentation by the members of the INN mAb Working Group.

INN for mAbs were introduced in 1991. The naming process had to accommodate an enormous number of mAb substances, which form the largest class of biological medicines. INN are given to mAbs well in advance of regulatory licensure and with many not making it to the approval stage, many names are not used. MAb INN need to provide information on the target, the sequence and need to be able to accommodate advances in technology. The Experts acknowledged that recent modifications to the naming process had been criticised in the paper by Jones *et al*., 2016 and by the Antibody Society, which was the reason for the current discussion.

The criticisms levelled by Jones *et al*., 2016 were that the revised system is critically flawed, ambiguous and contradicts scientific literature. Also that classification was inconsistent and that omission of the sequences encoded by the J-region genes was a major flaw. The paper further stated that the 85% sequence threshold was arbitrary, did not correlate with improved therapeutic outcomes such as reduced immunogenicity, and that there was no specific definition of what constitutes a human antibody and what differentiates it from a humanised antibody. A yet further criticism was that the new rules had been applied retrospectively with no notice period. An initial rebuttal from the INN Experts was that threshold percentages to define INN infixes had not been published by the INN Expert Group.

The basics of mAb nomenclature, as described in the BioReview, were summarised. INN for mAbs are composed of a fantasy prefix, two substems and a common stem *–mab*, as the suffix. The *–mab* suffix is used for all substances with an immunoglobulin variable domain. The substem (or infix) adjacent to the *–mab* stem denotes the species upon which the immunoglobulin sequence is based with the substem preceding that in the INN indicating the target class.

In a chimeric antibody, the chains contain a foreign variable domain (originating from one species other than human, or synthetic, or engineered from any species including human) linked to a human constant region; the variable domain has V region amino acid sequence which when analysed as a whole is closer to non-human species than to human. A humanised mAb has CDRs that are foreign (originating from one species other than human, or synthetic) but with the remainder of the antibody being human; the variable domain has a V region amino acid sequence which when analysed as a whole is closer to human than to other species. Humanisation assessment is based on the resulting amino acid sequence and not on the methodology *per se*, which allows protocols other than grafting to be used.

In addressing the four major issues highlighted by the Jones *et al*., 2016 paper, the INN Experts explained firstly that inclusion of the J region in the assessment would be unrealistic and that for sequence comparison the most relevant part of the molecule is the V region. Secondly, the criticism that the inclusion of macaque variable regions in the IMGT database can skew the comparison away from human was considered unfounded and that these are valuable with respect to having the maximum amount of available information. In response to the Society's comment that choosing an 85% cut-off for 'human' is purely arbitrary, the INN Experts reiterated that the INN system does not in fact prescribe any percentage thresholds for distinguishing human/humanised/chimeric mAbs[2]. Finally, the criticism that even human antibodies may fail the 85% threshold was unfounded again because the INN system does not prescribe a percentage cut-off. The decision of the INN Expert Group is based on the results of V region amino acid sequence alignment as a whole (IMGT/DomainGapAlign) and information on the source of the mAb provided by the applicant.

Keeping in mind the main goal in assigning mAb INN, sequence alignment should remain a major tool; however, other data such as 3D conformation could be a useful adjunct for example by analysis of superimposed structures. In general 3D structures are becoming more routine, including for mAbs, and indeed the recently published Annex document for INN requests that a Protein Data Bank (PDB) file be provided, if available.

In conclusion, INN experts are responsible for selecting INN and the mAb Working Group had noted the concerns raised in the Jones *et al*., 2016 paper. The Bioreview 2014 provides the current reference for mAb INN but percent thresholds are not official INN policy. The INN Experts welcomed dialogue with stakeholders, now and in the future.

General Discussion

The Antibody Society acknowledged that whilst the reason to move from murine to more human-like antibodies was to improve the immunogenicity profile, the source substems do not implicitly imply immunogenicity, although undoubtedly the substem does have an impact on the product. Ultimately this was why the discussion was being held. The INN Experts now look at the amino acid sequence to categorise mAbs but it was not clear that this was the best way as the sequence says nothing? about immunogenicity. In addition, the impending addition of monkey sequences to the IMGT database was likely to impact adversely the outcome of sequence comparison analyses. The Society expressed concern about creating an artificial boundary between humanised and chimeric mAbs since there is a continuum between various animal sources and human.

Nonetheless, the INN Experts felt that there was no alternative to the use of sequence data in classifying mAbs. It had value, as a humanised mAb was expected to have sequences closer to human than non-human and anything not closer to human was chimeric. But the ultimate aim had to be to obtain antibodies that were highly effective in patients even if that meant having a sequence further from human; other aspects are more important for the Ab than the sequence, such as specificity. The INN does not predict whether an antibody will be good or bad medicine. What is important is what should be reflected in the name, or not.

The FDA representative pointed out that the 85% homology threshold between chimeric and humanised mAbs is applied by USAN but not used by the INN. Since at least half the mAbs have both a USAN and an INN, this needed to be clarified. The INN confirmed that its approach is based on an assessment of the totality of evidence presented and not simply on a percent cut-off. Too much was being read into the INN, which says nothing about clinical efficacy, and the limitations of the INN have to be appreciated.

In bringing the discussion to a close, the Chair noted that there was no right or wrong, but inferences were being drawn by stakeholders so the Experts need to improve clarity and explain what has been done.

In conclusion, the Society had enjoyed the discussion. It was all about having a biological medicine that works in patients and not about sequences. All participants need to engage in constructive

[2] An 85% cut-off is used by the USAN naming system, but not the INN

discussion to work towards how best to catch that in a name without negative connotations. The connotations in old names and differences in defining boundaries within a gradient argue for a fresh start with names that have no previous connotation.

Close of Open Session meeting

The Chair had found the discussions enlightening. In closing the meeting, she thanked all participants for their presentations and discussion.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 February 2014 (06.02.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/019727 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *G01N 33/53* (2006.01)

(21) International Application Number:
PCT/EP2013/059802

(22) International Filing Date:
13 May 2013 (13.05.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1208370.5 14 May 2012 (14.05.2012) GB

(71) Applicant: **UCB PHARMA S.A.** [BE/BE]; 60 Allée de la Recherche, B-1070 Brussels (BE).

(72) Inventors: **FINNEY, Helene Margaret**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **LAWSON, Alastair David Griffiths**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **SHAW, Stevan Graham**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **SMITH, Bryan John**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **TYSON, Kerry Louise**; c/o IPD, UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB). **KEVORKIAN, Lara**; c/o IPD, UCB Celltech, 208 Bath Road, Slough, Berkshire SL1 3WE (GB).

(74) Agent: **THOMPSON, John**; UCB Celltech, 208 Bath Road, Slough Berkshire SL1 3WE (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

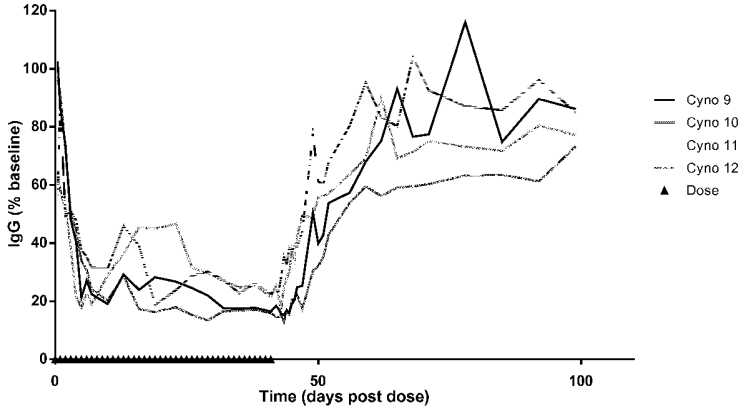
— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

(54) **Title**: ANTI-FCRN ANTIBODIES

Figure 18 **Change in plasma IgG levels in cynomolgus monkeys treated with 30 mg/Kg 1519.g57 IgG4P on day 0 followed by 5mg/Kg 1519.g57 IgG4P daily for 41 days**



(57) **Abstract**: The disclosure relates to antibodies specific to FcRn, formulations comprising the same, use of each in therapy, processes for expressing and optionally formulating said antibody, DNA encoding the antibodies and hosts comprising said DNA.

WO 2014/019727 A1

Anti-FcRn Antibodies

The disclosure relates to antibodies specific to FcRn, formulations comprising the same, use of each in therapy, processes for expressing and optionally formulating said antibody, DNA encoding the antibodies and hosts comprising said DNA.

FcRn is a non-covalent complex of membrane protein FcRn α chain and β2 microglobulin (β2M). In adult mammals FcRn plays a key role in maintaining serum antibody levels by acting as a receptor that binds and salvages antibodies of the IgG isotype. IgG molecules are endocytosed by endothelial cells, and if they bind to FcRn, are recycled transcytosed out into, for example circulation. In contrast, IgG molecules that do not bind to FcRn enter the cells and are targeted to the lysosomal pathway where they are degraded. A variant IgG1 in which His435 is mutated to alanine results in the selective loss of FcRn binding and a significantly reduced serum half-life (Firan et al. 2001, International Immunology 13:993).

It is hypothesised that FcRn is a potential therapeutic target for certain autoimmune disorders caused at least in part by autoantibodies. The current treatment for certain such disorders includes plasmapheresis. Sometimes the plasmapheresis is employed along with immunosuppressive therapy for long-term management of the disease. Plasma exchange offers the quickest short-term answer to removing harmful autoantibodies. However, it may also be desirable to suppress the production of autoantibodies by the immune system for example by the use of medications such as prednisone, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab or a mixture of these.

Examples of diseases that can be treated with plasmapheresis include: Guillain-Barré syndrome; Chronic inflammatory demyelinating polyneuropathy; Goodpasture's syndrome; hyperviscosity syndromes; cryoglobulinemia; paraproteinemia; Waldenström macroglobulinemia; myasthenia gravis; thrombotic thrombocytopenic purpura (TTP)/hemolytic uremic syndrome; Wegener's granulomatosis; Lambert-Eaton Syndrome; antiphospholipid antibody syndrome (APS or APLS); microscopic polyangiitis; recurrent focal and segmental glomerulosclerosis in the transplanted kidney; HELLP syndrome; PANDAS syndrome; Refsum disease; Behcet syndrome; HIV-related neuropathy; Graves' disease in infants and neonates; pemphigus vulgaris; multiple sclerosis, rhabdomyolysis and alloimune diseases.

Plasmapheresis is sometimes used as a rescue therapy for removal of Fc containing therapeutics, for example in emergencies to reduced serious side effects.

Though plasmapheresis is helpful in certain medical conditions there are potential risks and complications associated with the therapy. Insertion of a rather large intravenous catheter can lead to bleeding, lung puncture (depending on the site of catheter insertion), and, if the catheter is left in too long, it can lead to infection and/or damage to the veins giving limited opportunity to repeat the procedure.

The procedure has further complications associated with it, for example when a patient's blood is outside of the body passing through the plasmapheresis instrument, the blood has a tendency to

clot. To reduce this tendency, in one common protocol, citrate is infused while the blood is running through the circuit. Citrate binds to calcium in the blood, calcium being essential for blood to clot. Citrate is very effective in preventing blood from clotting; however, its use can lead to life-threateningly low calcium levels. This can be detected using the Chvostek's sign or Trousseau's sign. To prevent this complication, calcium is infused intravenously while the patient is undergoing the plasmapheresis; in addition, calcium supplementation by mouth may also be given.

Other complications of the procedure include: hypotension; potential exposure to blood products, with risk of transfusion reactions or transfusion transmitted diseases, suppression of the patient's immune system and bleeding or hematoma from needle placement.

Additionally facilities that provide plasmapheresis are limited and the procedure is very expensive.

An alternative to plasmapheresis is intravenous immunoglobulin (IVIG), which is a blood product containing pooled polyclonal IgG extracted from the plasma of over one thousand blood donors. The therapy is administered intravenously and lasts in the region of 2 weeks to 3 months.

Complications of the IVIG treatment include headaches, dermatitis, viral infection from contamination of the therapeutic product, for example HIV or hepatitis, pulmonary edema, allergic reactions, acute renal failure, venous thrombosis and aseptic meningitis.

Thus there is a significant unmet need for therapies for autoimmune disorders which are less invasive and which expose the patients to less medical complications.

Thus there is a significant unmet need for therapies for immunological disorders and/or autoimmune disorders which are less invasive and which expose the patients to less medical complications.

Accordingly agents that block or reduce the binding of IgG to FcRn may be useful in the treatment or prevention of such autoimmune and inflammatory diseases. Anti-FcRn antibodies have been described previously in WO2009/131702, WO2007/087289 and WO2006/118772.

However, there remains a need for improved anti-FcRn antibodies.

Summary of the Disclosure

Thus in one aspect there is provided an anti-FcRn antibody or binding fragment thereof comprising a heavy chain or heavy chain fragment having a variable region, wherein said variable region comprises one, two or three CDRs independently selected from SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3, for example wherein CDR H1 is SEQ ID NO: 1, CDR H2 is SEQ ID NO: 2 and CDR H3 is SEQ ID NO: 3.

In another aspect there is provided an antibody or fragment comprising a sequence or combinations of sequences as defined herein, for example a cognate pair variable region.

The antibodies of the disclosure block binding of IgG to FcRn and are thought to be useful in reducing one or more biological functions of FcRn, including reducing half-life of circulating antibodies. This may be beneficial in that it allows the patient to more rapidly clear antibodies, such as autoantibodies.

Importantly the antibodies of the present invention are able to bind human FcRn at both pH6 and pH7.4 with comparable and high binding affinity. Advantageously therefore the antibodies are able to continue to bind FcRn even within the endosome, thereby maximising the blocking of FcRn binding to IgG, see Figure 10 for an illustration of the mechanism.

In one embodiment the antibodies or binding fragments according to the present disclosure comprise a light chain or light chain fragment having a variable region, for example comprising one, two or three CDRs independently selected from SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6, in particular wherein CDR L1 is SEQ ID NO: 4, CDR L2 is SEQ ID NO: 5 and CDR L3 is SEQ ID NO: 6.

In one embodiment the antibodies or binding fragments according to the present disclosure comprise CDR sequences of SEQ ID NOs: 1 to 6, for example wherein CDR H1 is SEQ ID NO: 1, CDR H2 is SEQ ID NO: 2, CDR H3 is SEQ ID NO: 3, CDR L1 is SEQ ID NO: 4, CDR L2 is SEQ ID NO: 5 and CDR L3 is SEQ ID NO: 6.

The disclosure also extends to a polynucleotide, such as DNA, encoding an antibody or fragment as described herein.

Also provided is a host cell comprising said polynucleotide.

Methods of expressing an antibody or fragment are provided herein as are methods of conjugating an antibody or fragment to a polymer, such as PEG.

The present disclosure also relates to pharmaceutical compositions comprising said antibodies and fragments.

In one embodiment there is provided a method of treatment comprising administering a therapeutically effective amount of an antibody, fragment or composition as described herein.

The present disclosure also extends to an antibody, fragment or composition according to the present disclosure for use in treatment, particularly in the treatment of an immunological and/or autoimmune disorder.

Thus the present disclosure provides antibodies, fragments thereof and methods for removal of pathogenic IgG, which is achieved by accelerating the body's natural mechanism for catabolising IgG.

In essence the antibodies and fragments according to the disclosure block the system that recycles IgG in the body.

The present therapy is likely to provide a replacement or supplement for certain diseases where plasmapheresis is a therapy or IVIg therapy, which is advantageous for patients.

Brief Description of the Figures

Figure 1 shows certain amino acid and polynucleotide sequences.

Figure 2 shows alignments of certain sequences.

Figure 3 shows a comparison of binding on human MDCK II for a Fab' fragment according to the present disclosure and a PEGylated version thereof

Figure 4 shows a Fab' fragment according to the present disclosure and a PEGylated version thereof inhibiting IgG recycling on MDCK II cells

Figure 5 shows a PEGylated Fab' fragment according to the present disclosure inhibits apical to basolateral IgG trancytosis in MDCK II cells

Figure 6 shows a comparison of binding of cyno monkey MDCK II for a Fab' fragment according to the present disclosure and a PEGylated version thereof

Figure 7 shows a PEGylated Fab' fragment according to the present inhibiting IgG recycling on MDCK II cells for human and cyno monkey versions thereof

Figure 8 shows the effect of a single dose of a PEGylated Fab' molecule according to the disclosure on plasma IgG levels in cynomolgus monkeys

Figure 9 shows the effect of four weekly doses of a PEGylated Fab' molecule according to the disclosure on plasma IgG levels

Figure 10 shows a diagrammatic representation of antibody recycling function of FcRn inhibited by a blocking protein

Figure 11 shows flow cytometry based human IgG blocking assay using purified gamma 1 IgG antibodies

Figure 12 shows Fab'PEG single/intermittent IV doses in normal cyno 20mg/Kg days 1 and 67 IgG pharmacodynamics

Figure 13 shows Fab'PEG: repeat IV doses in normal cyno- 4x 20 or 100 mg/Kg per week IgG pharmacodynamics

Figure 14 shows Fab'PEG single/intermittent IV doses in normal cyno -20 mg/Kg and 100 mg/Kg days 1 and 67 IgG Pharmacodynamics

Figure 15 shows plasma IgG levels in 4 cynomolgus monkeys after 2 IV doses of 20mg/Kg 1519.g57 Fab'PEG

Figure 16 shows plasma IgG levels in 4 cynomolgus monkeys receiving 10 IV doses of 20mg/Kg 1519.g57 Fab'PEG, one every 3 days

Figure 17 shows the effect of two 30mg/Kg IV doses of 1519.g57 IgG4P on the endogenous plasma IgG in cynomolgus monkeys

Figure 18 shows the effect of 30 mg/Kg if followed by 41 daily doses of 5mg/Kg 1519.g57 IgG4P on plasma IgG in cynomolgus monkeys

Figure 19 shows the result of daily dosing with vehicle on the plasma IgG in cynomolgus monkeys

Figure 20 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'PEG or PBS IV

Figure 21 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 IgG1 or IgG4 or PBS IV

Figure 22 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'-human serum albumin or PBS IV

Figure 23 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 FabFv or PBS IV

Figure 24 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab or Fab'PEG or PBS IV

Figure 25 shows a bispecific antibody fusion protein of the present invention, referred to as a Fab-dsFv.

Details of the Disclosure

FcRn as employed herein refers to the non-covalent complex between the human IgG receptor alpha chain, also known as the neonatal Fc receptor, the amino acid sequence of which is in UniProt under number P55899 together with β2 microglobulin (β2M), the amino acid sequence of which is in UniProt under number P61769.

Antibody molecule as employed herein refers to an antibody or binding fragment thereof.

The term 'antibody' as used herein generally relates to intact (whole) antibodies i.e. comprising the elements of two heavy chains and two light chains. The antibody may comprise further additional binding domains for example as per the molecule DVD-Ig as disclosed in WO 2007/024715, or the so-called $(FabFv)_2Fc$ described in WO2011/030107. Thus antibody as employed herein includes bi, tri or tetra-valent full length antibodies.

Binding fragments of antibodies include single chain antibodies (i.e. a full length heavy chain and light chain); Fab, modified Fab, Fab', modified Fab', $F(ab')_2$, Fv, Fab-Fv, Fab-dsFv, single domain antibodies (e.g. VH or VL or VHH), scFv, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, tribodies, triabodies, tetrabodies and epitope-binding fragments of any of the above (see for example Holliger and Hudson, 2005, Nature Biotech. 23(9):1126-1136; Adair and Lawson, 2005, Drug Design Reviews - Online 2(3), 209-217). The methods for creating and manufacturing these antibody fragments are well known in the art (see for example Verma et al., 1998, Journal of Immunological Methods, 216, 165-181). The Fab-Fv format was first disclosed in WO2009/040562 and the disulphide stabilised versions thereof, the Fab-dsFv was first disclosed in WO2010/035012, see also Figure 25 herein. Other antibody fragments for use in the present invention include the Fab and Fab' fragments described in International patent applications WO2005/003169, WO2005/003170 and WO2005/003171. Multi-valent antibodies may comprise multiple specificities e.g. bispecific or may be monospecific (see for example WO 92/22583 and WO05/113605). One such example of the latter is a Tri-Fab (or TFM) as described in WO92/22583.

A typical Fab' molecule comprises a heavy and a light chain pair in which the heavy chain comprises a variable region V_H, a constant domain C_H1 and a natural or modified hinge region and the light chain comprises a variable region V_L and a constant domain C_L.

In one embodiment there is provided a dimer of a Fab' according to the present disclosure to create a $F(ab')_2$ for example dimerisation may be through the hinge.

In one embodiment the antibody or binding fragment thereof comprises a binding domain. A binding domain will generally comprises 6 CDRs, three from a heavy chain and three from a light chain. In one embodiment the CDRs are in a framework and together form a variable region. Thus in one embodiment an antibody or binding fragment comprises a binding domain specific for antigen comprising a light chain variable region and a heavy chain variable region.

It will be appreciated that one or more (for example 1, 2, 3 or 4) amino acid substitutions, additions and/or deletions may be made to the CDRs or other sequences (e.g variable domains) provided by the present invention without significantly altering the ability of the antibody to bind to FcRn. The effect of any amino acid substitutions, additions and/or deletions can be readily tested by one skilled in the art, for example by using the methods described herein, in particular in the Examples, to determine FcRn.

In one or more (for example 1, 2, 3 or 4) amino acid substitutions, additions and/or deletions may be made to the framework region employed in the antibody or fragment provided by the present invention and wherein binding affinity to FcRn is retained or increased.

The residues in antibody variable domains are conventionally numbered according to a system devised by Kabat *et al.* This system is set forth in Kabat *et al.*, 1987, in Sequences of Proteins of Immunological Interest, US Department of Health and Human Services, NIH, USA (hereafter "Kabat *et al.* (*supra*)"). This numbering system is used in the present specification except where otherwise indicated.

The Kabat residue designations do not always correspond directly with the linear numbering of the amino acid residues. The actual linear amino acid sequence may contain fewer or additional amino acids than in the strict Kabat numbering corresponding to a shortening of, or insertion into, a structural component, whether framework or complementarity determining region (CDR), of the basic variable domain structure. The correct Kabat numbering of residues may be determined for a given antibody by alignment of residues of homology in the sequence of the antibody with a "standard" Kabat numbered sequence.

The CDRs of the heavy chain variable domain are located at residues 31-35 (CDR-H1), residues 50-65 (CDR-H2) and residues 95-102 (CDR-H3) according to the Kabat numbering system. However, according to Chothia (Chothia, C. and Lesk, A.M. J. Mol. Biol., 196, 901-917 (1987)), the loop equivalent to CDR-H1 extends from residue 26 to residue 32. Thus unless indicated otherwise 'CDR-H1' as employed herein is intended to refer to residues 26 to 35, as described by a combination of the Kabat numbering system and Chothia's topological loop definition.

The CDRs of the light chain variable domain are located at residues 24-34 (CDR-L1), residues 50-56 (CDR-L2) and residues 89-97 (CDR-L3) according to the Kabat numbering system.

Antibodies and fragments of the present disclosure block FcRn and may thereby prevent it functioning in the recycling of IgG. Blocking as employed herein refers to physically blocking such as occluding the receptor but will also include where the antibody or fragments binds an epitope that causes, for example a conformational change which means that the natural ligand to the receptor no longer binds. Antibody molecules of the present invention bind to FcRn and thereby decrease or prevent (e.g. inhibit) FcRn binding to an IgG constant region.

In one embodiment the antibody or fragment thereof binds FcRn competitively with respect to IgG.

In one example the antibody or binding fragment thereof functions as a competitive inhibitor of human FcRn binding to human IgG. In one example the antibody or binding fragment thereof binds to the IgG binding site on FcRn. In one example the antibody or binding fragment thereof does not bind β2M.

Antibodies for use in the present disclosure may be obtained using any suitable method known in the art. The FcRn polypeptide/protein including fusion proteins, cells (recombinantly or naturally) expressing the polypeptide (such as activated T cells) can be used to produce antibodies which specifically recognise FcRn. The polypeptide may be the 'mature' polypeptide or a biologically active fragment or derivative thereof. The human protein is registered in Swiss-Prot under the number P55899. The extracellular domain of human FcRn alpha chain is provided in SEQ ID NO:94. The sequence of β2M is provided in SEQ ID NO:95.

In one embodiment the antigen is a mutant form of FcRn which is engineered to present FcRn on the surface of a cell, such that there is little or no dynamic processing where the FcRn is internalised in the cell, for example this can be achieved by making a mutation in the cytoplasmic tail of the FcRn alpha chain, wherein di-leucine is mutated to di-alanine as described in Ober et al 2001 Int. Immunol. 13, 1551–1559.

Polypeptides, for use to immunize a host, may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems or they may be recovered from natural biological sources. In the present application, the term "polypeptides" includes peptides, polypeptides and proteins. These are used interchangeably unless otherwise specified. The FcRn polypeptide may in some instances be part of a larger protein such as a fusion protein for example fused to an affinity tag or similar.

Antibodies generated against the FcRn polypeptide may be obtained, where immunisation of an animal is necessary, by administering the polypeptides to an animal, preferably a non-human animal, using well-known and routine protocols, see for example Handbook of Experimental Immunology, D. M. Weir (ed.), Vol 4, Blackwell Scientific Publishers, Oxford, England, 1986. Many warm-blooded animals, such as rabbits, mice, rats, sheep, cows, camels or pigs may be immunized. However, mice, rabbits, pigs and rats are generally most suitable.

Monoclonal antibodies may be prepared by any method known in the art such as the hybridoma technique (Kohler & Milstein, 1975, Nature, 256:495-497), the trioma technique, the human B-

cell hybridoma technique (Kozbor *et al.,* 1983, Immunology Today, 4:72) and the EBV-hybridoma technique (Cole *et al.,* Monoclonal Antibodies and Cancer Therapy, pp77-96, Alan R Liss, Inc., 1985).

Antibodies for use in the invention may also be generated using single lymphocyte antibody methods by cloning and expressing immunoglobulin variable region cDNAs generated from single lymphocytes selected for the production of specific antibodies by, for example, the methods described by Babcook, J. *et al.*, 1996, Proc. Natl. Acad. Sci. USA 93(15):7843-7848l; WO92/02551; WO2004/051268 and International Patent Application number WO2004/106377.

Screening for antibodies can be performed using assays to measure binding to human FcRn and/or assays to measure the ability to block IgG binding to the receptor. An example of a binding assay is an ELISA, in particular, using a fusion protein of human FcRn and human Fc, which is immobilized on plates, and employing a secondary antibody to detect anti-FcRn antibody bound to the fusion protein. Examples of suitable antagonistic and blocking assays are described in the Examples herein.

Humanised antibodies (which include CDR-grafted antibodies) are antibody molecules having one or more complementarity determining regions (CDRs) from a non-human species and a framework region from a human immunoglobulin molecule (see, *e.g.* US 5,585,089; WO91/09967). It will be appreciated that it may only be necessary to transfer the specificity determining residues of the CDRs rather than the entire CDR (see for example, Kashmiri *et al.*, 2005, Methods, 36, 25-34). Humanised antibodies may optionally further comprise one or more framework residues derived from the non-human species from which the CDRs were derived. The latter are often referred to as donor residues.

Specific as employed herein is intended to refer to an antibody that only recognises the antigen to which it is specific or an antibody that has significantly higher binding affinity to the antigen to which it is specific compared to binding to antigens to which it is non-specific, for example at least 5, 6, 7, 8, 9, 10 times higher binding affinity. Binding affinity may be measured by techniques such as BIAcore as described herein below. In one example the antibody of the present invention does not bind β2 microglobulin (β2M). In one example the antibody of the present invention binds cynomolgus FcRn. In one example the antibody of the present invention does not bind rat or mouse FcRn.

The amino acid sequences and the polynucleotide sequences of certain antibodies according to the present disclosure are provided in the Figures.

In one embodiment the antibody or fragments according to the disclosure are humanised.

As used herein, the term 'humanised antibody molecule' refers to an antibody molecule wherein the heavy and/or light chain contains one or more CDRs (including, if desired, one or more modified CDRs) from a donor antibody (e.g. a non-human antibody such as a murine monoclonal antibody) grafted into a heavy and/or light chain variable region framework of an acceptor antibody (e.g. a human antibody). For a review, see Vaughan *et al*, Nature

Biotechnology, 16, 535-539, 1998. In one embodiment rather than the entire CDR being transferred, only one or more of the specificity determining residues from any one of the CDRs described herein above are transferred to the human antibody framework (see for example, Kashmiri *et al.*, 2005, Methods, 36, 25-34). In one embodiment only the specificity determining residues from one or more of the CDRs described herein above are transferred to the human antibody framework. In another embodiment only the specificity determining residues from each of the CDRs described herein above are transferred to the human antibody framework.

When the CDRs or specificity determining residues are grafted, any appropriate acceptor variable region framework sequence may be used having regard to the class/type of the donor antibody from which the CDRs are derived, including mouse, primate and human framework regions.

Suitably, the humanised antibody according to the present invention has a variable domain comprising human acceptor framework regions as well as one or more of the CDRs provided specifically herein. Thus, provided in one embodiment is blocking humanised antibody which binds human FcRn wherein the variable domain comprises human acceptor framework regions and non-human donor CDRs.

Examples of human frameworks which can be used in the present invention are KOL, NEWM, REI, EU, TUR, TEI, LAY and POM (Kabat *et al., supra*). For example, KOL and NEWM can be used for the heavy chain, REI can be used for the light chain and EU, LAY and POM can be used for both the heavy chain and the light chain. Alternatively, human germline sequences may be used; these are available at: http://vbase.mrc-cpe.cam.ac.uk/

In a humanised antibody of the present invention, the acceptor heavy and light chains do not necessarily need to be derived from the same antibody and may, if desired, comprise composite chains having framework regions derived from different chains.

One such suitable framework region for the heavy chain of the humanised antibody of the present invention is derived from the human sub-group VH3 sequence 1-3 3-07 together with JH4 (SEQ ID NO: 56).

Accordingly, in one example there is provided a humanised antibody comprising the sequence given in SEQ ID NO: 1 for CDR-H1, the sequence given in SEQ ID NO: 2 for CDR-H2 and the sequence given in SEQ ID NO: 3 for CDRH3, wherein the heavy chain framework region is derived from the human subgroup VH3 sequence 1-3 3-07 together with JH4.

The sequence of human JH4 is as follows: (YFDY)WGQGTLVTVS (Seq ID No: 70). The YFDY motif is part of CDR-H3 and is not part of framework 4 (Ravetch, JV. *et al.*, 1981, *Cell*, 27, 583-591).

In one example the heavy chain variable domain of the antibody comprises the sequence given in SEQ ID NO: 29.

A suitable framework region for the light chain of the humanised antibody of the present invention is derived from the human germline sub-group VK1 sequence 2-1-(1) A30 together with JK2 (SEQ ID NO: 54).

Accordingly, in one example there is provided a humanised antibody comprising the sequence given in SEQ ID NO: 4 for CDR-L1, the sequence given in SEQ ID NO: 5 for CDR-L2 and the sequence given in SEQ ID NO: 6 for CDRL3, wherein the light chain framework region is derived from the human subgroup VK1 sequence 2-1-(1) A30 together with JK2.

The JK2 sequence is as follows: (YT)FGQGTKLEIK (Seq ID No: 71). The YT motif is part of CDR-L3 and is not part of framework 4 (Hieter, PA., *et al.*, 1982, J. Biol. Chem., 257, 1516-1522).

In one example the light chain variable domain of the antibody comprises the sequence given in SEQ ID NO: 15.

In a humanised antibody of the present invention, the framework regions need not have exactly the same sequence as those of the acceptor antibody. For instance, unusual residues may be changed to more frequently-occurring residues for that acceptor chain class or type. Alternatively, selected residues in the acceptor framework regions may be changed so that they correspond to the residue found at the same position in the donor antibody (see Reichmann *et al.*, 1998, Nature, 332, 323-324). Such changes should be kept to the minimum necessary to recover the affinity of the donor antibody. A protocol for selecting residues in the acceptor framework regions which may need to be changed is set forth in WO91/09967.

Thus in one embodiment 1, 2, 3, 4, or 5 residues in the framework are replaced with an alternative amino acid residue.

Accordingly, in one example there is provided a humanised antibody, wherein at least the residues at each of positions 3, 24, 76, 93 and 94 of the variable domain of the heavy chain (Kabat numbering) are donor residues, see for example the sequence given in SEQ ID NO: 29.

In one embodiment residue 3 of the heavy chain variable domain is replaced with an alternative amino acid, for example glutamine.

In one embodiment residue 24 of the heavy chain variable domain is replaced with an alternative amino acid, for example alanine.

In one embodiment residue 76 of the heavy chain variable domain is replaced with an alternative amino acid, for example asparagine.

In one embodiment residue 93 of the heavy chain is replaced with an alternative amino acid, for example alanine.

In one embodiment residue 94 of the heavy chain is replaced with an alternative amino acid, for example arginine.

In one embodiment residue 3 is glutamine, residue 24 is alanine, residue 76 is aspargine, residue 93 is alanine and residue 94 is arginine in the humanised heavy chain variable region according to the present disclosure.

Accordingly, in one example there is provided a humanised antibody, wherein at least the residues at each of positions 36, 37 and 58 of the variable domain of the light chain (Kabat numbering) are donor residues, see for example the sequence given in SEQ ID NO: 15

In one embodiment residue 36 of the light chain variable domain is replaced with an alternative amino acid, for example tyrosine.

In one embodiment residue 37 of the light chain variable domain is replaced with an alternative amino acid, for example glutamine.

In one embodiment residue 58 of the light chain variable domain is replaced with an alternative amino acid, for example valine.

In one embodiment residue 36 is tyrosine, residue 37 is glutamine and residue 58 is valine, in the humanised heavy chain variable region according to the present disclosure.

In one embodiment the disclosure provides an antibody sequence which is 80% similar or identical to a sequence disclosed herein, for example 85%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% over part or whole of the relevant sequence, for example a variable domain sequence, a CDR sequence or a variable domain sequence, excluding the CDRs. In one embodiment the relevant sequence is SEQ ID NO: 15. In one embodiment the relevant sequence is SEQ ID NO: 29.

In one embodiment, the present invention provides an antibody molecule which binds human FcRn comprising a heavy chain, wherein the variable domain of the heavy chain comprises a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% identity or similarity to the sequence given in SEQ ID NO:29.

In one embodiment, the present invention provides an antibody molecule which binds human FcRn comprising a light chain, wherein the variable domain of the light chain comprises a sequence having at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% identity or similarity to the sequence given in SEQ ID NO:15.

In one embodiment the present invention provides an antibody molecule which binds human FcRn wherein the antibody has a heavy chain variable domain which is at least 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% similar or identical to the sequence given in SEQ ID NO:29 but wherein the antibody molecule has the sequence given in SEQ ID NO: 1 for CDR-H1, the sequence given in SEQ ID NO: 2 for CDR-H2 and the sequence given in SEQ ID NO: 3 for CDR-H3.

In one embodiment the present invention provides an antibody molecule which binds human FcRn wherein the antibody has a light chain variable domain which is at least 90%, 91%, 92%,

93%, 94%, 95% 96%, 97%, 98% or 99% similar or identical to the sequence given in SEQ ID NO:15 but wherein the antibody molecule has the sequence given in SEQ ID NO: 4 for CDR-L1, the sequence given in SEQ ID NO: 5 for CDR-L2 and the sequence given in SEQ ID NO:6 for CDR-L3.

In one embodiment the present invention provides an antibody molecule which binds human FcRn wherein the antibody has a heavy chain variable domain which is at least 90% , 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% similar or identical to the sequence given in SEQ ID NO:29 and a light chain variable domain which is at least 90%, 91%, 92%, 93%, 94%, 95% 96%, 97%, 98% or 99% similar or identical to the sequence given in SEQ ID NO:15 but wherein the antibody molecule has the sequence given in SEQ ID NO: 1 for CDR-H1, the sequence given in SEQ ID NO: 2 for CDR-H2, the sequence given in SEQ ID NO: 3 for CDR-H3, the sequence given in SEQ ID NO: 4 for CDR-L1, the sequence given in SEQ ID NO: 5 for CDR-L2 and the sequence given in SEQ ID NO:6 for CDR-L3.

"Identity", as used herein, indicates that at any particular position in the aligned sequences, the amino acid residue is identical between the sequences. "Similarity", as used herein, indicates that, at any particular position in the aligned sequences, the amino acid residue is of a similar type between the sequences. For example, leucine may be substituted for isoleucine or valine. Other amino acids which can often be substituted for one another include but are not limited to:

- phenylalanine, tyrosine and tryptophan (amino acids having aromatic side chains);

- lysine, arginine and histidine (amino acids having basic side chains);

- aspartate and glutamate (amino acids having acidic side chains);

- asparagine and glutamine (amino acids having amide side chains); and

- cysteine and methionine (amino acids having sulphur-containing side chains). Degrees of identity and similarity can be readily calculated (Computational Molecular Biology, Lesk, A.M., ed., Oxford University Press, New York, 1988; Biocomputing. Informatics and Genome Projects, Smith, D.W., ed., Academic Press, New York, 1993; Computer Analysis of Sequence Data, Part 1, Griffin, A.M., and Griffin, H.G., eds., Humana Press, New Jersey, 1994; Sequence Analysis in Molecular Biology, von Heinje, G., Academic Press, 1987, Sequence Analysis Primer, Gribskov, M. and Devereux, J., eds., M Stockton Press, New York, 1991, the BLAST™ software available from NCBI (Altschul, S.F. *et al.,* 1990, J. Mol. Biol. 215:403-410; Gish, W. & States, D.J. 1993, Nature Genet. 3:266-272. Madden, T.L. *et al.,* 1996, Meth. Enzymol. 266:131-141; Altschul, S.F. *et al.,* 1997, Nucleic Acids Res. 25:3389-3402; Zhang, J. & Madden, T.L. 1997, Genome Res. 7:649-656,).

The antibody molecules of the present invention may comprise a complete antibody molecule having full length heavy and light chains or a fragment thereof and may be, but are not limited to Fab, modified Fab, Fab', modified Fab', $F(ab')_2$, Fv, single domain antibodies (e.g. VH or VL or VHH), scFv, bi, tri or tetra-valent antibodies, Bis-scFv, diabodies, triabodies, tetrabodies and epitope-binding fragments of any of the above (see for example Holliger and Hudson, 2005,

Nature Biotech. 23(9):1126-1136; Adair and Lawson, 2005, Drug Design Reviews - Online 2(3), 209-217). The methods for creating and manufacturing these antibody fragments are well known in the art (see for example Verma et al., 1998, Journal of Immunological Methods, 216, 165-181). Other antibody fragments for use in the present invention include the Fab and Fab' fragments described in International patent applications WO2005/003169, WO2005/003170 and WO2005/003171. Multi-valent antibodies may comprise multiple specificities e.g bispecific or may be monospecific (see for example WO 92/22853, WO05/113605, WO2009/040562 and WO2010/035012).

In one embodiment the antibody molecule of the present disclosure is an antibody Fab' fragment comprising the variable regions shown in SEQ ID NOs: 15 and 29 for example for the light and heavy chain respectively. In one embodiment the antibody molecule has a light chain comprising the sequence given in SEQ ID NO:22 and a heavy chain comprising the sequence given in SEQ ID NO:36.

In one embodiment the antibody molecule of the present disclosure is a full length IgG1 antibody comprising the variable regions shown in SEQ ID NOs: 15 and 29 for example for the light and heavy chain respectively. In one embodiment the antibody molecule has a light chain comprising the sequence given in SEQ ID NO:22 and a heavy chain comprising the sequence given in SEQ ID NO:72.

In one embodiment the antibody molecule of the present disclosure is a full length IgG4 format comprising the variable regions shown in SEQ ID NOs: 15 and 29 for example for the light and heavy chain respectively. In one embodiment the antibody molecule has a light chain comprising the sequence given in SEQ ID NO:22 and a heavy chain comprising the sequence given in SEQ ID NO:87.

In one embodiment the antibody molecule of the present disclosure is a full length IgG4P format comprising the variable regions shown in SEQ ID NOs: 15 and 29 for example for the light and heavy chain respectively. In one embodiment the antibody molecule has a light chain comprising the sequence given in SEQ ID NO:22 and a heavy chain comprising the sequence given in SEQ ID NO:43.

IgG4P as employed herein is a mutation of the wild-type IgG4 isotype where amino acid 241 is replaced by proline see for example where serine at position 241 has been changed to proline as described in Angal *et al.*, Molecular Immunology, 1993, 30 (1), 105-108.

In one embodiment the antibody according to the present disclosure is provided as FcRn binding antibody fusion protein which comprises an immunoglobulin moiety, for example a Fab or Fab' fragment, and one or two single domain antibodies (dAb) linked directly or indirectly thereto, for example as described in WO2009/040562, WO2010035012, WO2011/030107, WO2011/061492 and WO2011/086091 all incorporated herein by reference.

In one embodiment the fusion protein comprises two domain antibodies, for example as a variable heavy (VH) and variable light (VL) pairing, optionally linked by a disulphide bond.

In one embodiment the Fab or Fab' element of the fusion protein has the same or similar specificity to the single domain antibody or antibodies. In one embodiment the Fab or Fab' has a different specificity to the single domain antibody or antibodies, that is to say the fusion protein is multivalent. In one embodiment a multivalent fusion protein according to the present invention has an albumin binding site, for example a VH/VL pair therein provides an albumin binding site. In one such embodiment the heavy chain comprises the sequence given in SEQ ID NO:50 and the light chain comprises the sequence given in SEQ ID NO:46 or SEQ ID NO:78. This Fab-dsFv format is illustrated in Figure 25 herein.

In one embodiment the Fab or Fab' according to the present disclosure is conjugated to a PEG molecule or human serum albumin.

CA170_01519g57 and 1519 and 1519.g57 are employed inchangeably herein and are used to refer to a specific pair of antibody variable regions which may be used in a number of different formats. These variable regions are the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15 (Figure 1).

The constant region domains of the antibody molecule of the present invention, if present, may be selected having regard to the proposed function of the antibody molecule, and in particular the effector functions which may be required. For example, the constant region domains may be human IgA, IgD, IgE, IgG or IgM domains. In particular, human IgG constant region domains may be used, especially of the IgG1 and IgG3 isotypes when the antibody molecule is intended for therapeutic uses and antibody effector functions are required. Alternatively, IgG2 and IgG4 isotypes may be used when the antibody molecule is intended for therapeutic purposes and antibody effector functions are not required. It will be appreciated that sequence variants of these constant region domains may also be used. For example IgG4 molecules in which the serine at position 241 has been changed to proline as described in Angal *et al.*, Molecular Immunology, 1993, 30 (1), 105-108 may be used. It will also be understood by one skilled in the art that antibodies may undergo a variety of posttranslational modifications. The type and extent of these modifications often depends on the host cell line used to express the antibody as well as the culture conditions. Such modifications may include variations in glycosylation, methionine oxidation, diketopiperazine formation, aspartate isomerization and asparagine deamidation. A frequent modification is the loss of a carboxy-terminal basic residue (such as lysine or arginine) due to the action of carboxypeptidases (as described in Harris, RJ. *Journal of Chromatography* 705:129-134, 1995). Accordingly, the C-terminal lysine of the antibody heavy chain may be absent.

In one embodiment the antibody heavy chain comprises a CH1 domain and the antibody light chain comprises a CL domain, either kappa or lambda.

In one embodiment the light chain has the sequence given in SEQ ID NO:22 and the heavy chain has the sequence given in SEQ ID NO:43.

In one embodiment the light chain has the sequence given in SEQ ID NO:22 and the heavy chain has the sequence given in SEQ ID NO:72.

In one embodiment a C-terminal amino acid from the antibody molecule is cleaved during post-translation modifications.

In one embodiment an N-terminal amino acid from the antibody molecule is cleaved during post-translation modifications.

Also provided by the present invention is a specific region or epitope of human FcRn which is bound by an antibody provided by the present invention, in particular an antibody comprising the heavy chain sequence gH20 (SEQ ID NO:29) and/or the light chain sequence gL20 (SEQ ID NO:15).

This specific region or epitope of the human FcRn polypeptide can be identified by any suitable epitope mapping method known in the art in combination with any one of the antibodies provided by the present invention. Examples of such methods include screening peptides of varying lengths derived from FcRn for binding to the antibody of the present invention with the smallest fragment that can specifically bind to the antibody containing the sequence of the epitope recognised by the antibody. The FcRn peptides may be produced synthetically or by proteolytic digestion of the FcRn polypeptide. Peptides that bind the antibody can be identified by, for example, mass spectrometric analysis. In another example, NMR spectroscopy or X-ray crystallography can be used to identify the epitope bound by an antibody of the present invention. Once identified, the epitopic fragment which binds an antibody of the present invention can be used, if required, as an immunogen to obtain additional antibodies which bind the same epitope.

In one embodiment the antibody of the present disclosure binds the human FcRn alpha chain extracellular sequence as shown below:

AESHLSLLYH LTAVSSPAPG TPAFWVSGWL GPQQYLSYNS LRGEAEPCGA WVWENQVSWY WEKETTDLRI KEKLFLEAFK ALGGKGPYTL QGLLGCELG**P** DNTS**VPTAK**F ALNG**EEFMNF DLKQ**GTW**GGD WPE**ALAISQR WQQQDKAANK ELTFLLFSCP HRLREHLERG RGNLEWKEPP SMRLKARPSS PGFSVLTCSA FSFYPPELQL RFLRNGLAAG TGQGDFGPNS DGSFHASSSL TVKSGDEHHY CCIVQHAGLA QPLRVELESPAKSS (SEQ ID NO: 94).

The residues underlined are those known to be critical for the interaction of human FcRn with the Fc region of human IgG and those residues highlighted in bold are those involved in the interaction of FcRn with the 1519 antibody of the present disclosure comprising the heavy chain sequence gH20 (SEQ ID NO:29) and the light chain sequence gL20 (SEQ ID NO:15).

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises at least one amino acid selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue, for example at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues selected from the group consisting of P100, E115, E116, F117, M118, N119, F120, D121, L122, K123, Q124, G128, G129, D130, W131, P132 and E133 of SEQ ID NO:94.

In one example the epitope of the antibody molecule is determined by X-ray crystallography using the FcRn alpha chain extracellular sequence (SEQ ID NO:94) in complex with β2M.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises at least one amino acid selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue, for example at least 2, 3, 4, 5, 6, 7, 8, 9 or 10 residues, selected from the group consisting of E115, E116, F117, M118, N119, F120, D121, L122, K123 and Q124 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises at least two, three, four or five amino acids selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of E115, E116, F117, M118, N119, F120, D121, L122, K123 and Q124 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises at least one amino acid selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of P100, E115, E116, F117, M118, N119, F120, D121, L122, K123, Q124, G128, G129, D130, W131, P132 and E133 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises at least one amino acid selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of P100, M118, N119, F120, D121, L122, K123, Q124 and G128 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of P100, M118, N119, F120, D121, L122, K123, Q124 and G128 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of P100, E115, E116, F117, M118, N119, F120, D121, L122, K123, Q124, G128, G129, D130, W131, P132 and E133 of SEQ ID NO:94.

In one example, the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises residues P100, V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of E115, E116, F117, M118, N119, F120, D121, L122, K123, Q124, G128, G129, D130, W131, P132 and E133 of SEQ ID NO:94.

In one example 'at least one residue' may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 or 16 residues.

In one example the present invention provides an anti-FcRn antibody molecule which binds an epitope of human FcRn which comprises or consists of residues 100, 105 to 109, 115 to 124 and 129 to 133 of SEQ ID NO: 94.

Antibodies which cross-block the binding of an antibody molecule according to the present invention in particular, an antibody molecule comprising the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15 may be similarly useful in blocking FcRn activity. Accordingly, the present invention also provides an anti-FcRn antibody molecule, which cross-blocks the binding of any one of the antibody molecules described herein above to human FcRn and/or is cross-blocked from binding human FcRn by any one of those antibodies. In one embodiment, such an antibody binds to the same epitope as an antibody described herein above. In another embodiment the cross-blocking neutralising antibody binds to an epitope which borders and/or overlaps with the epitope bound by an antibody described herein above.

Cross-blocking antibodies can be identified using any suitable method in the art, for example by using competition ELISA or BIAcore assays where binding of the cross blocking antibody to human FcRn prevents the binding of an antibody of the present invention or *vice versa*. Such cross blocking assays may use isolated natural or recombinant FcRn or a suitable fusion protein/polypeptide. In one example binding and cross-blocking is measured using recombinant human FcRn extracellular domain (SEQ ID NO:94). In one example the recombinant human FcRn alpha chain extracellular domain is used in a complex with β2 microglobulin (β2M) (SEQ ID NO:95).

In one embodiment there is provided an anti-FcRn antibody molecule which blocks FcRn binding to IgG and which cross-blocks the binding of an antibody whose heavy chain comprises the sequence given in SEQ ID NO:29 and whose light chain comprises the sequence given in SEQ ID NO:15 to human FcRn. In one embodiment the cross-blocking antibodies provided by the present invention inhibit the binding of an antibody comprising the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15 by greater than 80%, for example by greater than 85%, such as by greater than 90%, in particular by greater than 95%.

Alternatively or in addition, anti-FcRn antibodies according to this aspect of the invention may be cross-blocked from binding to human FcRn by an antibody comprising the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15. Also provided therefore is an anti-FcRn antibody molecule which blocks FcRn binding to IgG and which is cross-blocked from binding human FcRn by an antibody comprising the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15. In one embodiment the anti-FcRn antibodies provided by this aspect of the invention are inhibited from binding human FcRn by an antibody comprising the heavy chain sequence given in SEQ ID NO:29 and the light chain sequence given in SEQ ID NO:15 by greater than 80%, for example by greater than 85%, such as by greater than 90%, in particular by greater than 95%.

In one embodiment the cross-blocking antibodies provided by the present invention are fully human. In one embodiment the cross-blocking antibodies provided by the present invention are humanised. In one embodiment the cross-blocking antibodies provided by the present invention have an affinity for human FcRn of 100pM or less. In one embodiment the cross-blocking antibodies provided by the present invention have an affinity for human FcRn of 50pM or less. Affinity can be measured using the methods described herein below.

Biological molecules, such as antibodies or fragments, contain acidic and/or basic functional groups, thereby giving the molecule a net positive or negative charge. The amount of overall "observed" charge will depend on the absolute amino acid sequence of the entity, the local environment of the charged groups in the 3D structure and the environmental conditions of the molecule. The isoelectric point (pI) is the pH at which a particular molecule or solvent accessible surface thereof carries no net electrical charge. In one example, the FcRn antibody and fragments of the invention may be engineered to have an appropriate isoelectric point. This may lead to antibodies and/or fragments with more robust properties, in particular suitable solubility and/or stability profiles and/or improved purification characteristics.

Thus in one aspect the invention provides a humanised FcRn antibody engineered to have an isoelectric point different to that of the originally identified antibody. The antibody may, for example be engineered by replacing an amino acid residue such as replacing an acidic amino acid residue with one or more basic amino acid residues. Alternatively, basic amino acid residues may be introduced or acidic amino acid residues can be removed. Alternatively, if the molecule has an unacceptably high pI value acidic residues may be introduced to lower the pI, as required. It is important that when manipulating the pI care must be taken to retain the desirable activity of the antibody or fragment. Thus in one embodiment the engineered antibody or fragment has the same or substantially the same activity as the "unmodified" antibody or fragment.

Programs such as ** ExPASY http://www.expasy.ch/tools/pi_tool.html, and

http://www.iut-arles.up.univ-mrs.fr/w3bb/d_abim/compo-p.html, may be used to predict the isoelectric point of the antibody or fragment.

The antibody molecules of the present invention suitably have a high binding affinity, in particular in the nanomolar range. Affinity may be measured using any suitable method known in the art, including BIAcore, as described in the Examples herein, using isolated natural or recombinant FcRn or a suitable fusion protein/polypeptide. In one example affinity is measured using recombinant human FcRn extracellular domain as described in the Examples herein (SEQ ID NO:94). In one example affinity is measured using the recombinant human FcRn alpha chain extracellular domain (SEQ ID NO:94) in association with β2 microglobulin (β2M) (SEQ ID NO:95). Suitably the antibody molecules of the present invention have a binding affinity for isolated human FcRn of about 1nM or lower. In one embodiment the antibody molecule of the present invention has a binding affinity of about 500pM or lower (i.e. higher affinity). In one embodiment the antibody molecule of the present invention has a binding affinity of about 250pM or lower. In one embodiment the antibody molecule of the present invention has a binding affinity of about 200pM or lower. In one embodiment the present invention provides an anti-FcRn antibody with a binding affinity of about 100pM or lower. In one embodiment the present invention provides a humanised anti-FcRn antibody with a binding affinity of about 100pM or lower. In one embodiment the present invention provides an anti-FcRn antibody with a binding affinity of 50pM or lower.

Importantly the antibodies of the present invention are able to bind human FcRn at both pH6 and pH7.4 with comparable binding affinity. Advantageously therefore the antibodies are able to continue to bind FcRn even within the endosome, thereby maximising the blocking of FcRn binding to IgG, see Figure 10 for an illustration of the mechanism.

In one embodiment the present invention provides an anti-FcRn antibody with a binding affinity of 100pM or lower when measured at pH6 and pH7.4.

The affinity of an antibody or binding fragment of the present invention, as well as the extent to which a binding agent (such as an antibody) inhibits binding, can be determined by one of ordinary skill in the art using conventional techniques, for example those described by Scatchard et al. (Ann. KY. Acad. Sci. 51:660-672 (1949)) or by surface plasmon resonance (SPR) using systems such as BIAcore. For surface plasmon resonance, target molecules are immobilized on a solid phase and exposed to ligands in a mobile phase running along a flow cell. If ligand binding to the immobilized target occurs, the local refractive index changes, leading to a change in SPR angle, which can be monitored in real time by detecting changes in the intensity of the reflected light. The rates of change of the SPR signal can be analyzed to yield apparent rate constants for the association and dissociation phases of the binding reaction. The ratio of these values gives the apparent equilibrium constant (affinity) (see, e.g., Wolff et al, Cancer Res. 53:2560-65 (1993)).

In the present invention affinity of the test antibody molecule is typically determined using SPR as follows. The test antibody molecule is captured on the solid phase and human FcRn alpha chain extracellular domain in non-covalent complex with β2M is run over the captured antibody in the mobile phase and affinity of the test antibody molecule for human FcRn determined. The test antibody molecule may be captured on the solid phase chip surface using any appropriate

method, for example using an anti-Fc or anti Fab' specific capture agent. In one example the affinity is determined at pH6. In one example the affinity is determined at pH7.4.

It will be appreciated that the affinity of antibodies provided by the present invention may be altered using any suitable method known in the art. The present invention therefore also relates to variants of the antibody molecules of the present invention, which have an improved affinity for FcRn. Such variants can be obtained by a number of affinity maturation protocols including mutating the CDRs (Yang *et al.*, J. Mol. Biol., 254, 392-403, 1995), chain shuffling (Marks *et al.*, Bio/Technology, 10, 779-783, 1992), use of mutator strains of *E. coli* (Low *et al.*, J. Mol. Biol., 250, 359-368, 1996), DNA shuffling (Patten *et al.*, Curr. Opin. Biotechnol., 8, 724-733, 1997), phage display (Thompson *et al.*, J. Mol. Biol., 256, 77-88, 1996) and sexual PCR (Crameri *et al.*, Nature, 391, 288-291, 1998). Vaughan *et al.* (*supra*) discusses these methods of affinity maturation.

In one embodiment the antibody molecules of the present invention block human FcRn activity. Assays suitable for determining the ability of an antibody to block FcRn are described in the Examples herein. Suitable assays for determining whether antibodies block FcRn interaction with circulating IgG molecules as described in the Examples herein. A suitable assay for determining the ability of an antibody molecule to block IgG recycling in vitro is described herein below.

If desired an antibody for use in the present invention may be conjugated to one or more effector molecule(s). It will be appreciated that the effector molecule may comprise a single effector molecule or two or more such molecules so linked as to form a single moiety that can be attached to the antibodies of the present invention. Where it is desired to obtain an antibody fragment linked to an effector molecule, this may be prepared by standard chemical or recombinant DNA procedures in which the antibody fragment is linked either directly or via a coupling agent to the effector molecule. Techniques for conjugating such effector molecules to antibodies are well known in the art (see, Hellstrom *et al.*, Controlled Drug Delivery, 2nd Ed., Robinson *et al.*, eds., 1987, pp. 623-53; Thorpe *et al.*, 1982 , Immunol. Rev., 62:119-58 and Dubowchik *et al.*, 1999, Pharmacology and Therapeutics, 83, 67-123). Particular chemical procedures include, for example, those described in WO 93/06231, WO 92/22583, WO 89/00195, WO 89/01476 and WO 03/031581. Alternatively, where the effector molecule is a protein or polypeptide the linkage may be achieved using recombinant DNA procedures, for example as described in WO 86/01533 and EP0392745.

The term effector molecule as used herein includes, for example, antineoplastic agents, drugs, toxins, biologically active proteins, for example enzymes, other antibody or antibody fragments, synthetic or naturally occurring polymers, nucleic acids and fragments thereof e.g. DNA, RNA and fragments thereof, radionuclides, particularly radioiodide, radioisotopes, chelated metals, nanoparticles and reporter groups such as fluorescent compounds or compounds which may be detected by NMR or ESR spectroscopy.

Examples of effector molecules may include cytotoxins or cytotoxic agents including any agent that is detrimental to (*e.g.* kills) cells. Examples include combrestatins, dolastatins, epothilones, staurosporin, maytansinoids, spongistatins, rhizoxin, halichondrins, roridins, hemiasterlins, taxol, cytochalasin B, gramicidin D, ethidium bromide, emetine, mitomycin, etoposide, tenoposide, vincristine, vinblastine, colchicin, doxorubicin, daunorubicin, dihydroxy anthracin dione, mitoxantrone, mithramycin, actinomycin D, 1-dehydrotestosterone, glucocorticoids, procaine, tetracaine, lidocaine, propranolol, and puromycin and analogs or homologs thereof.

Effector molecules also include, but are not limited to, antimetabolites (*e.g.* methotrexate, 6-mercaptopurine, 6-thioguanine, cytarabine, 5-fluorouracil decarbazine), alkylating agents (*e.g.* mechlorethamine, thioepa chlorambucil, melphalan, carmustine (BSNU) and lomustine (CCNU), cyclothosphamide, busulfan, dibromomannitol, streptozotocin, mitomycin C, and cis-dichlorodiamine platinum (II) (DDP) cisplatin), anthracyclines (*e.g.* daunorubicin (formerly daunomycin) and doxorubicin), antibiotics (*e.g.* dactinomycin (formerly actinomycin), bleomycin, mithramycin, anthramycin (AMC), calicheamicins or duocarmycins), and anti-mitotic agents (*e.g.* vincristine and vinblastine).

Other effector molecules may include chelated radionuclides such as ^{111}In and ^{90}Y, Lu^{177}, Bismuth^{213}, Californium^{252}, Iridium^{192} and Tungsten^{188}/Rhenium^{188}; or drugs such as but not limited to, alkylphosphocholines, topoisomerase I inhibitors, taxoids and suramin.

Other effector molecules include proteins, peptides and enzymes. Enzymes of interest include, but are not limited to, proteolytic enzymes, hydrolases, lyases, isomerases, transferases. Proteins, polypeptides and peptides of interest include, but are not limited to, immunoglobulins, toxins such as abrin, ricin A, pseudomonas exotoxin, or diphtheria toxin, a protein such as insulin, tumour necrosis factor, α-interferon, β-interferon, nerve growth factor, platelet derived growth factor or tissue plasminogen activator, a thrombotic agent or an anti-angiogenic agent, *e.g.* angiostatin or endostatin, or, a biological response modifier such as a lymphokine, interleukin-1 (IL-1), interleukin-2 (IL-2), granulocyte macrophage colony stimulating factor (GM-CSF), granulocyte colony stimulating factor (G-CSF), nerve growth factor (NGF) or other growth factor and immunoglobulins.

Other effector molecules may include detectable substances useful for example in diagnosis. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, radioactive nuclides, positron emitting metals (for use in positron emission tomography), and nonradioactive paramagnetic metal ions. See generally U.S. Patent No. 4,741,900 for metal ions which can be conjugated to antibodies for use as diagnostics. Suitable enzymes include horseradish peroxidase, alkaline phosphatase, beta-galactosidase, or acetylcholinesterase; suitable prosthetic groups include streptavidin, avidin and biotin; suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride and phycoerythrin; suitable luminescent materials include luminol; suitable bioluminescent materials include luciferase, luciferin, and aequorin; and suitable radioactive nuclides include ^{125}I, ^{131}I, ^{111}In and ^{99}Tc.

In another example the effector molecule may increase the half-life of the antibody *in vivo*, and/or reduce immunogenicity of the antibody and/or enhance the delivery of an antibody across an epithelial barrier to the immune system. Examples of suitable effector molecules of this type include polymers, albumin, albumin binding proteins or albumin binding compounds such as those described in WO05/117984.

In one embodiment a half-life provided by an effector molecule which is independent of FcRn is advantageous.

Where the effector molecule is a polymer it may, in general, be a synthetic or a naturally occurring polymer, for example an optionally substituted straight or branched chain polyalkylene, polyalkenylene or polyoxyalkylene polymer or a branched or unbranched polysaccharide, e.g. a homo- or hetero- polysaccharide.

Specific optional substituents which may be present on the above-mentioned synthetic polymers include one or more hydroxy, methyl or methoxy groups.

Specific examples of synthetic polymers include optionally substituted straight or branched chain poly(ethyleneglycol), poly(propyleneglycol) poly(vinylalcohol) or derivatives thereof, especially optionally substituted poly(ethyleneglycol) such as methoxypoly(ethyleneglycol) or derivatives thereof.

Specific naturally occurring polymers include lactose, amylose, dextran, glycogen or derivatives thereof.

In one embodiment the polymer is albumin or a fragment thereof, such as human serum albumin or a fragment thereof.

"Derivatives" as used herein is intended to include reactive derivatives, for example thiol-selective reactive groups such as maleimides and the like. The reactive group may be linked directly or through a linker segment to the polymer. It will be appreciated that the residue of such a group will in some instances form part of the product as the linking group between the antibody fragment and the polymer.

The size of the polymer may be varied as desired, but will generally be in an average molecular weight range from 500Da to 50000Da, for example from 5000 to 40000Da such as from 20000 to 40000Da. The polymer size may in particular be selected on the basis of the intended use of the product for example ability to localize to certain tissues such as tumors or extend circulating half-life (for review see Chapman, 2002, Advanced Drug Delivery Reviews, 54, 531-545). Thus, for example, where the product is intended to leave the circulation and penetrate tissue, for example for use in the treatment of a tumour, it may be advantageous to use a small molecular weight polymer, for example with a molecular weight of around 5000Da. For applications where the product remains in the circulation, it may be advantageous to use a higher molecular weight polymer, for example having a molecular weight in the range from 20000Da to 40000Da.

Suitable polymers include a polyalkylene polymer, such as a poly(ethyleneglycol) or, especially, a methoxypoly(ethyleneglycol) or a derivative thereof, and especially with a molecular weight in the range from about 15000Da to about 40000Da.

In one example antibodies for use in the present invention are attached to poly(ethyleneglycol) (PEG) moieties. In one particular example the antibody is an antibody fragment and the PEG molecules may be attached through any available amino acid side-chain or terminal amino acid functional group located in the antibody fragment, for example any free amino, imino, thiol, hydroxyl or carboxyl group. Such amino acids may occur naturally in the antibody fragment or may be engineered into the fragment using recombinant DNA methods (see for example US 5,219,996; US 5,667,425; WO98/25971, WO2008/038024). In one example the antibody molecule of the present invention is a modified Fab fragment wherein the modification is the addition to the C-terminal end of its heavy chain one or more amino acids to allow the attachment of an effector molecule. Suitably, the additional amino acids form a modified hinge region containing one or more cysteine residues to which the effector molecule may be attached. Multiple sites can be used to attach two or more PEG molecules.

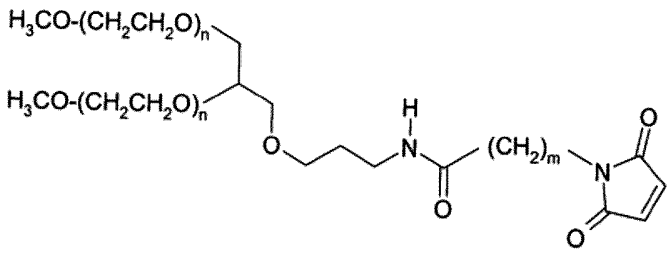
Suitably PEG molecules are covalently linked through a thiol group of at least one cysteine residue located in the antibody fragment. Each polymer molecule attached to the modified antibody fragment may be covalently linked to the sulphur atom of a cysteine residue located in the fragment. The covalent linkage will generally be a disulphide bond or, in particular, a sulphur-carbon bond. Where a thiol group is used as the point of attachment appropriately activated effector molecules, for example thiol selective derivatives such as maleimides and cysteine derivatives may be used. An activated polymer may be used as the starting material in the preparation of polymer-modified antibody fragments as described above. The activated polymer may be any polymer containing a thiol reactive group such as an α-halocarboxylic acid or ester, e.g. iodoacetamide, an imide, e.g. maleimide, a vinyl sulphone or a disulphide. Such starting materials may be obtained commercially (for example from Nektar, formerly Shearwater Polymers Inc., Huntsville, AL, USA) or may be prepared from commercially available starting materials using conventional chemical procedures. Particular PEG molecules include 20K methoxy-PEG-amine (obtainable from Nektar, formerly Shearwater; Rapp Polymere; and SunBio) and M-PEG-SPA (obtainable from Nektar, formerly Shearwater).

In one embodiment, the antibody is a modified Fab fragment, Fab' fragment or diFab which is PEGylated, *i.e.* has PEG (poly(ethyleneglycol)) covalently attached thereto, *e.g.* according to the method disclosed in EP 0948544 or EP1090037 [see also "Poly(ethyleneglycol) Chemistry, Biotechnical and Biomedical Applications", 1992, J. Milton Harris (ed), Plenum Press, New York, "Poly(ethyleneglycol) Chemistry and Biological Applications", 1997, J. Milton Harris and S. Zalipsky (eds), American Chemical Society, Washington DC and "Bioconjugation Protein Coupling Techniques for the Biomedical Sciences", 1998, M. Aslam and A. Dent, Grove Publishers, New York; Chapman, A. 2002, Advanced Drug Delivery Reviews 2002, 54:531-545]. In one example PEG is attached to a cysteine in the hinge region. In one example, a PEG modified Fab fragment has a maleimide group covalently linked to a single thiol group in a modified hinge region. A lysine residue may be covalently linked to the maleimide group and to

each of the amine groups on the lysine residue may be attached a methoxypoly(ethyleneglycol) polymer having a molecular weight of approximately 20,000Da. The total molecular weight of the PEG attached to the Fab fragment may therefore be approximately 40,000Da.

Particular PEG molecules include 2-[3-(N-maleimido)propionamido]ethyl amide of N,N'-bis(methoxypoly(ethylene glycol) MW 20,000) modified lysine, also known as PEG2MAL40K (obtainable from Nektar, formerly Shearwater).

Alternative sources of PEG linkers include NOF who supply GL2-400MA3 (wherein m in the structure below is 5) and GL2-400MA (where m is 2) and n is approximately 450:

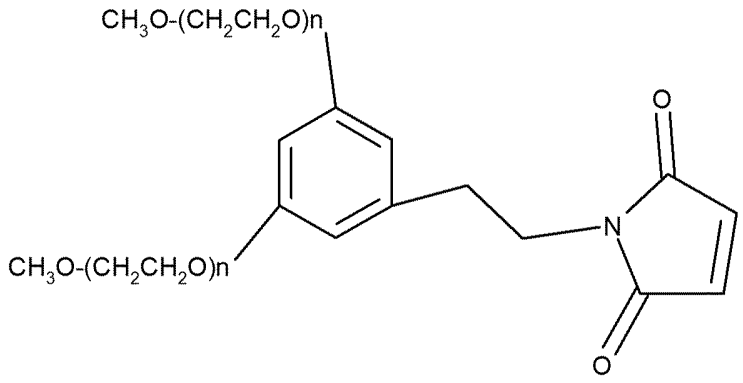


m is 2 or 5

That is to say each PEG is about 20,000Da.

Thus in one embodiment the PEG is 2,3-Bis(methylpolyoxyethylene-oxy)-1-{[3-(6-maleimido-1-oxohexyl)amino]propyloxy} hexane (the 2 arm branched PEG, $-CH_2)_3NHCO(CH_2)_5$-MAL, Mw 40,000 known as SUNBRIGHT GL2-400MA3.

Further alternative PEG effector molecules of the following type:



are available from Dr Reddy, NOF and Jenkem.

In one embodiment there is provided an antibody which is PEGylated (for example with a PEG described herein), attached through a cysteine amino acid residue at or about amino acid 226 in the chain, for example amino acid 226 of the heavy chain (by sequential numbering), for example amino acid 226 of SEQ ID NO:36.

In one embodiment the present disclosure provides a Fab'PEG molecule comprising one or more PEG polymers, for example 1 or 2 polymers such as a 40kDa polymer or polymers.

Fab'-PEG molecules according to the present disclosure may be particularly advantageous in that they have a half-life independent of the Fc fragment. In one example the present invention provides a method treating a disease ameliorated by blocking human FcRn comprising administering a therapeutically effective amount of an anti-FcRn antibody or binding fragment thereof wherein the antibody or binding fragment thereof has a half life that is independent of Fc binding to FcRn.

In one embodiment there is provided a Fab' conjugated to a polymer, such as a PEG molecule, a starch molecule or an albumin molecule.

In one embodiment there is provided a scFv conjugated to a polymer, such as a PEG molecule, a starch molecule or an albumin molecule.

In one embodiment the antibody or fragment is conjugated to a starch molecule, for example to increase the half life. Methods of conjugating starch to a protein as described in US 8,017,739 incorporated herein by reference.

In one embodiment there is provided an anti-FcRn binding molecule which:

- Causes 70% reduction of plasma IgG concentration,
- With not more than 20% reduction of plasma albumin concentration, and/or
- With the possibility of repeat dosing to achieve long-term maintenance of low plasma IgG concentration.

The present invention also provides an isolated DNA sequence encoding the heavy and/or light chain(s) of an antibody molecule of the present invention. Suitably, the DNA sequence encodes the heavy or the light chain of an antibody molecule of the present invention. The DNA sequence of the present invention may comprise synthetic DNA, for instance produced by chemical processing, cDNA, genomic DNA or any combination thereof.

DNA sequences which encode an antibody molecule of the present invention can be obtained by methods well known to those skilled in the art. For example, DNA sequences coding for part or all of the antibody heavy and light chains may be synthesised as desired from the determined DNA sequences or on the basis of the corresponding amino acid sequences.

DNA coding for acceptor framework sequences is widely available to those skilled in the art and can be readily synthesised on the basis of their known amino acid sequences.

Standard techniques of molecular biology may be used to prepare DNA sequences coding for the antibody molecule of the present invention. Desired DNA sequences may be synthesised completely or in part using oligonucleotide synthesis techniques. Site-directed mutagenesis and polymerase chain reaction (PCR) techniques may be used as appropriate.

Examples of suitable DNA sequences are provided in herein.

Examples of suitable DNA sequences encoding the 1519 light chain variable region are provided in SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:90. Examples of suitable DNA sequences encoding the 1519 heavy chain variable region are provided in SEQ ID NO:30, SEQ ID NO:31 and SEQ ID NO:92.

Examples of suitable DNA sequences encoding the 1519 light chain (variable and constant) are provided in SEQ ID NO:23, SEQ ID NO:75 and SEQ ID NO:91.

Examples of suitable DNA sequences encoding the 1519 heavy chain (variable and constant, depending on format) are provided in SEQ ID NOs:37, 38 and 76 (Fab'), SEQ ID NO:72 or 85 (IgG1), SEQ ID NO: 44 or 93 (IgG4P) and SEQ ID:88 (IgG4).

Accordingly in one example the present invention provides an isolated DNA sequence encoding the heavy chain of an antibody Fab' fragment of the present invention which comprises the sequence given in SEQ ID NO:37. Also provided is an isolated DNA sequence encoding the light chain of an antibody Fab' fragment of the present invention which comprises the sequence given in SEQ ID NO:23.

In one example the present invention provides an isolated DNA sequence encoding the heavy chain and the light chain of an IgG4(P) antibody of the present invention in which the DNA encoding the heavy chain comprises the sequence given in SEQ ID NO:44 or SEQ ID NO:93 and the DNA encoding the light chain comprises the sequence given in SEQ ID NO:75 or SEQ ID NO:91.

In one example the present invention provides an isolated DNA sequence encoding the heavy chain and the light chain of a Fab-dsFv antibody of the present invention in which the DNA encoding the heavy chain comprises the sequence given in SEQ ID NO:51 or SEQ ID NO:80 and the DNA encoding the light chain comprises the sequence given in SEQ ID NO:47 or SEQ ID NO:79.

The present invention also relates to a cloning or expression vector comprising one or more DNA sequences of the present invention. Accordingly, provided is a cloning or expression vector comprising one or more DNA sequences encoding an antibody of the present invention. Suitably, the cloning or expression vector comprises two DNA sequences, encoding the light chain and the heavy chain of the antibody molecule of the present invention, respectively and suitable signal sequences. In one example the vector comprises an intergenic sequence between the heavy and the light chains (see WO03/048208).

General methods by which the vectors may be constructed, transfection methods and culture methods are well known to those skilled in the art. In this respect, reference is made to "Current

Protocols in Molecular Biology", 1999, F. M. Ausubel (ed), Wiley Interscience, New York and the Maniatis Manual produced by Cold Spring Harbor Publishing.

Also provided is a host cell comprising one or more cloning or expression vectors comprising one or more DNA sequences encoding an antibody of the present invention. Any suitable host cell/vector system may be used for expression of the DNA sequences encoding the antibody molecule of the present invention. Bacterial, for example *E. coli*, and other microbial systems may be used or eukaryotic, for example mammalian, host cell expression systems may also be used. Suitable mammalian host cells include CHO, myeloma or hybridoma cells.

Suitable types of Chinese Hamster Ovary (CHO cells) for use in the present invention may include CHO and CHO-K1 cells including dhfr- CHO cells, such as CHO-DG44 cells and CHO-DXB11 cells and which may be used with a DHFR selectable marker or CHOK1-SV cells which may be used with a glutamine synthetase selectable marker. Other cell types of use in expressing antibodies include lymphocytic cell lines, e.g., NSO myeloma cells and SP2 cells, COS cells.

The present invention also provides a process for the production of an antibody molecule according to the present invention comprising culturing a host cell containing a vector of the present invention under conditions suitable for leading to expression of protein from DNA encoding the antibody molecule of the present invention, and isolating the antibody molecule.

The antibody molecule may comprise only a heavy or light chain polypeptide, in which case only a heavy chain or light chain polypeptide coding sequence needs to be used to transfect the host cells. For production of products comprising both heavy and light chains, the cell line may be transfected with two vectors, a first vector encoding a light chain polypeptide and a second vector encoding a heavy chain polypeptide. Alternatively, a single vector may be used, the vector including sequences encoding light chain and heavy chain polypeptides.

The antibodies and fragments according to the present disclosure are expressed at good levels from host cells. Thus the properties of the antibodies and/or fragments are conducive to commercial processing.

Thus there is a provided a process for culturing a host cell and expressing an antibody or fragment thereof, isolating the latter and optionally purifying the same to provide an isolated antibody or fragment. In one embodiment the process further comprises the step of conjugating an effector molecule to the isolated antibody or fragment, for example conjugating to a PEG polymer in particular as described herein.

In one embodiment there is provided a process for purifiying an antibody (in particular an antibody or fragment according to the invention) comprising the steps: performing anion exchange chromatography in non-binding mode such that the impurities are retained on the column and the antibody is eluted.

In one embodiment the purification employs affinity capture on an FcRn column.

In one embodiment the purification employs cibacron blue or similar for purification of albumin fusion or conjugate molecules.

Suitable ion exchange resins for use in the process include Q.FF resin (supplied by GE-Healthcare). The step may, for example be performed at a pH about 8.

The process may further comprise an intial capture step employing cation exchange chromatography, performed for example at a pH of about 4 to 5, such as 4.5. The cation exchange chromatography may, for example employ a resin such as CaptoS resin or SP sepharose FF (supplied by GE-Healthcare). The antibody or fragment can then be eluted from the resin employing an ionic salt solution such as sodium chloride, for example at a concentration of 200mM.

Thus the chromatograph step or steps may include one or more washing steps, as appropriate.

The purification process may also comprise one or more filtration steps, such as a diafiltration step.

Thus in one embodiment there is provided a purified anti-FcRn antibody or fragment, for example a humanised antibody or fragment, in particular an antibody or fragment according to the invention, in substantially purified from, in particular free or substantially free of endotoxin and/or host cell protein or DNA.

Purified form as used *supra* is intended to refer to at least 90% purity, such as 91, 92, 93, 94, 95, 96, 97, 98, 99% w/w or more pure.

Substantially free of endotoxin is generally intended to refer to an endotoxin content of 1 EU per mg antibody product or less such as 0.5 or 0.1 EU per mg product.

Substantially free of host cell protein or DNA is generally intended to refer to host cell protein and/or DNA content 400μg per mg of antibody product or less such as 100μg per mg or less, in particular 20μg per mg, as appropriate.

The antibody molecule of the present invention may also be used in diagnosis, for example in the *in vivo* diagnosis and imaging of disease states involving FcRn.

As the antibodies of the present invention are useful in the treatment and/or prophylaxis of a pathological condition, the present invention also provides a pharmaceutical or diagnostic composition comprising an antibody molecule of the present invention in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier. Accordingly, provided is the use of an antibody molecule of the invention for the manufacture of a medicament. The composition will usually be supplied as part of a sterile, pharmaceutical composition that will normally include a pharmaceutically acceptable carrier. A pharmaceutical composition of the present invention may additionally comprise a pharmaceutically-acceptableexcipient.

The present invention also provides a process for preparation of a pharmaceutical or diagnostic composition comprising adding and mixing the antibody molecule of the present invention together with one or more of a pharmaceutically acceptable excipient, diluent or carrier.

The antibody molecule may be the sole active ingredient in the pharmaceutical or diagnostic composition or may be accompanied by other active ingredients including other antibody ingredients or non-antibody ingredients such as steroids or other drug molecules, in particular drug molecules whose half-life is independent of FcRn binding.

The pharmaceutical compositions suitably comprise a therapeutically effective amount of the antibody of the invention. The term "therapeutically effective amount" as used herein refers to an amount of a therapeutic agent needed to treat, ameliorate or prevent a targeted disease or condition, or to exhibit a detectable therapeutic or preventative effect. For any antibody, the therapeutically effective amount can be estimated initially either in cell culture assays or in animal models, usually in rodents, rabbits, dogs, pigs or primates. The animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

The precise therapeutically effective amount for a human subject will depend upon the severity of the disease state, the general health of the subject, the age, weight and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities and tolerance/response to therapy. This amount can be determined by routine experimentation and is within the judgement of the clinician. Generally, a therapeutically effective amount will be from 0.01 mg/kg to 500 mg/kg, for example 0.1 mg/kg to 200 mg/kg, such as 100mg/Kg. Pharmaceutical compositions may be conveniently presented in unit dose forms containing a predetermined amount of an active agent of the invention per dose.

Therapeutic doses of the antibodies according to the present disclosure show no apparent toxicology effects *in vivo*.

In one embodiment of an antibody or fragment according to the invention a single dose may provide up to a 70% reduction in circulating IgG levels.

The maximal therapeutic reduction in circulating IgG may be observed about 1 week after administration of the relevant therapeutic dose. The levels of IgG may recover over about a six week period if further therapeutic doses are not delivered.

Advantageously, the levels of IgG *in vivo* may be maintained at an appropriately low level by administration of sequential doses of the antibody or fragments according to the disclosure.

Compositions may be administered individually to a patient or may be administered in combination (*e.g.* simultaneously, sequentially or separately) with other agents, drugs or hormones.

In one embodiment the antibodies or fragments according to the present disclosure are employed with an immunosuppressant therapy, such as a steroid, in particular prednisone.

In one embodiment the antibodies or fragments according to the present disclosure are employed with Rituximab or other B cell therapies.

In one embodiment the antibodies or fragments according to the present disclosure are employed with any B cell or T cell modulating agent or immunomodulator. Examples include methotrexate, microphenyolate and azathioprine.

The dose at which the antibody molecule of the present invention is administered depends on the nature of the condition to be treated, the extent of the inflammation present and on whether the antibody molecule is being used prophylactically or to treat an existing condition.

The frequency of dose will depend on the half-life of the antibody molecule and the duration of its effect. If the antibody molecule has a short half-life (e.g. 2 to 10 hours) it may be necessary to give one or more doses per day. Alternatively, if the antibody molecule has a long half life (e.g. 2 to 15 days) and/or long lasting pharmacodynamics (PD) profile it may only be necessary to give a dosage once per day, once per week or even once every 1 or 2 months.

In one embodiment the dose is delivered bi-weekly, i.e. twice a month.

Half life as employed herein is intended to refer to the duration of the molecule in circulation, for example in serum/plasma.

Pharmacodynamics as employed herein refers to the profile and in particular duration of the biological action of the molecule according the present disclosure.

The pharmaceutically acceptable carrier should not itself induce the production of antibodies harmful to the individual receiving the composition and should not be toxic. Suitable carriers may be large, slowly metabolised macromolecules such as proteins, polypeptides, liposomes, polysaccharides, polylactic acids, polyglycolic acids, polymeric amino acids, amino acid copolymers and inactive virus particles.

Pharmaceutically acceptable salts can be used, for example mineral acid salts, such as hydrochlorides, hydrobromides, phosphates and sulphates, or salts of organic acids, such as acetates, propionates, malonates and benzoates.

Pharmaceutically acceptable carriers in therapeutic compositions may additionally contain liquids such as water, saline, glycerol and ethanol. Additionally, auxiliary substances, such as wetting or emulsifying agents or pH buffering substances, may be present in such compositions. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries and suspensions, for ingestion by the patient.

Suitable forms for administration include forms suitable for parenteral administration, e.g. by injection or infusion, for example by bolus injection or continuous infusion. Where the product is for injection or infusion, it may take the form of a suspension, solution or emulsion in an oily or aqueous vehicle and it may contain formulatory agents, such as suspending, preservative,

stabilising and/or dispersing agents. Alternatively, the antibody molecule may be in dry form, for reconstitution before use with an appropriate sterile liquid.

Once formulated, the compositions of the invention can be administered directly to the subject. The subjects to be treated can be animals. However, in one or more embodiments the compositions are adapted for administration to human subjects.

Suitably in formulations according to the present disclosure, the pH of the final formulation is not similar to the value of the isoelectric point of the antibody or fragment, for example if the pI of the protein is in the range 8-9 or above then a formulation pH of 7 may be appropriate. Whilst not wishing to be bound by theory it is thought that this may ultimately provide a final formulation with improved stability, for example the antibody or fragment remains in solution.

In one example the pharmaceutical formulation at a pH in the range of 4.0 to 7.0 comprises: 1 to 200mg/mL of an antibody molecule according to the present disclosure, 1 to 100mM of a buffer, 0.001 to 1% of a surfactant, a) 10 to 500mM of a stabiliser, b) 10 to 500mM of a stabiliser and 5 to 500 mM of a tonicity agent, or c) 5 to 500 mM of a tonicity agent.

The pharmaceutical compositions of this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, transcutaneous (for example, see WO98/20734), subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, intravaginal or rectal routes. Hyposprays may also be used to administer the pharmaceutical compositions of the invention. Typically, the therapeutic compositions may be prepared as injectables, either as liquid solutions or suspensions. Solid forms suitable for solution in, or suspension in, liquid vehicles prior to injection may also be prepared.

Direct delivery of the compositions will generally be accomplished by injection, subcutaneously, intraperitoneally, intravenously or intramuscularly, or delivered to the interstitial space of a tissue. The compositions can also be administered into a lesion. Dosage treatment may be a single dose schedule or a multiple dose schedule.

It will be appreciated that the active ingredient in the composition will be an antibody molecule. As such, it will be susceptible to degradation in the gastrointestinal tract. Thus, if the composition is to be administered by a route using the gastrointestinal tract, the composition will need to contain agents which protect the antibody from degradation but which release the antibody once it has been absorbed from the gastrointestinal tract.

A thorough discussion of pharmaceutically acceptable carriers is available in Remington's Pharmaceutical Sciences (Mack Publishing Company, N.J. 1991).

In one embodiment the formulation is provided as a formulation for topical administrations including inhalation.

Suitable inhalable preparations include inhalable powders, metering aerosols containing propellant gases or inhalable solutions free from propellant gases. Inhalable powders according

to the disclosure containing the active substance may consist solely of the abovementioned active substances or of a mixture of the abovementioned active substances with physiologically acceptable excipient.

These inhalable powders may include monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose), oligo- and polysaccharides (e.g. dextranes), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these with one another. Mono- or disaccharides are suitably used, the use of lactose or glucose, particularly but not exclusively in the form of their hydrates.

Particles for deposition in the lung require a particle size less than 10 microns, such as 1-9 microns for example from 1 to 5 μm. The particle size of the active ingredient (such as the antibody or fragment) is of primary importance.

The propellent gases which can be used to prepare the inhalable aerosols are known in the art. Suitable propellent gases are selected from among hydrocarbons such as n-propane, n-butane or isobutane and halohydrocarbons such as chlorinated and/or fluorinated derivatives of methane, ethane, propane, butane, cyclopropane or cyclobutane. The abovementioned propellent gases may be used on their own or in mixtures thereof.

Particularly suitable propellent gases are halogenated alkane derivatives selected from among TG 11, TG 12, TG 134a and TG227. Of the abovementioned halogenated hydrocarbons, TG134a (1,1,1,2-tetrafluoroethane) and TG227 (1,1,1,2,3,3,3-heptafluoropropane) and mixtures thereof are particularly suitable.

The propellent-gas-containing inhalable aerosols may also contain other ingredients such as cosolvents, stabilisers, surface-active agents (surfactants), antioxidants, lubricants and means for adjusting the pH. All these ingredients are known in the art.

The propellant-gas-containing inhalable aerosols according to the invention may contain up to 5 % by weight of active substance. Aerosols according to the invention contain, for example, 0.002 to 5 % by weight, 0.01 to 3 % by weight, 0.015 to 2 % by weight, 0.1 to 2 % by weight, 0.5 to 2 % by weight or 0.5 to 1 % by weight of active ingredient.

Alternatively topical administrations to the lung may also be by administration of a liquid solution or suspension formulation, for example employing a device such as a nebulizer, for example, a nebulizer connected to a compressor (e.g., the Pari LC-Jet Plus(R) nebulizer connected to a Pari Master(R) compressor manufactured by Pari Respiratory Equipment, Inc., Richmond, Va.).

The antibody of the invention can be delivered dispersed in a solvent, e.g., in the form of a solution or a suspension. It can be suspended in an appropriate physiological solution, e.g., saline or other pharmacologically acceptable solvent or a buffered solution. Buffered solutions known in the art may contain 0.05 mg to 0.15 mg disodium edetate, 8.0 mg to 9.0 mg NaCl, 0.15 mg to 0.25 mg polysorbate, 0.25 mg to 0.30 mg anhydrous citric acid, and 0.45 mg to 0.55 mg sodium

citrate per 1 ml of water so as to achieve a pH of about 4.0 to 5.0. A suspension can employ, for example, lyophilised antibody.

The therapeutic suspensions or solution formulations can also contain one or more excipients. Excipients are well known in the art and include buffers (e.g., citrate buffer, phosphate buffer, acetate buffer and bicarbonate buffer), amino acids, urea, alcohols, ascorbic acid, phospholipids, proteins (e.g., serum albumin), EDTA, sodium chloride, liposomes, mannitol, sorbitol, and glycerol. Solutions or suspensions can be encapsulated in liposomes or biodegradable microspheres. The formulation will generally be provided in a substantially sterile form employing sterile manufacture processes.

This may include production and sterilization by filtration of the buffered solvent/solution used for the formulation, aseptic suspension of the antibody in the sterile buffered solvent solution, and dispensing of the formulation into sterile receptacles by methods familiar to those of ordinary skill in the art.

Nebulizable formulation according to the present disclosure may be provided, for example, as single dose units (e.g., sealed plastic containers or vials) packed in foil envelopes. Each vial contains a unit dose in a volume, e.g., 2 mL, of solvent/solutionbuffer.

The antibodies disclosed herein may be suitable for delivery via nebulisation.

It is also envisaged that the antibody of the present invention may be administered by use of gene therapy. In order to achieve this, DNA sequences encoding the heavy and light chains of the antibody molecule under the control of appropriate DNA components are introduced into a patient such that the antibody chains are expressed from the DNA sequences and assembled *in situ*.

The present invention also provides an antibody molecule (or compositions comprising same) for use in the control of autoimmune diseases, for example Acute Disseminated Encephalomyelitis (ADEM), Acute necrotizing hemorrhagic leukoencephalitis, Addison's disease, Agammaglobulinemia, Alopecia areata, Amyloidosis, ANCA-associated vasculitis, Ankylosing spondylitis, Anti-GBM/Anti-TBM nephritis, Antiphospholipid syndrome (APS), Autoimmune angioedema, Autoimmune aplastic anemia, Autoimmune dysautonomia, Autoimmune hepatitis, Autoimmune hyperlipidemia, Autoimmune immunodeficiency , Autoimmune inner ear disease (AIED), Autoimmune myocarditis, Autoimmune pancreatitis, Autoimmune retinopathy, Autoimmune thrombocytopenic purpura (ATP), Autoimmune thyroid disease, Autoimmune urticarial, Axonal & nal neuropathies, Balo disease, Behcet's disease, Bullous pemphigoid, Cardiomyopathy, Castleman disease, Celiac disease, Chagas disease, Chronic inflammatory demyelinating polyneuropathy (CIDP), Chronic recurrent multifocal ostomyelitis (CRMO), Churg-Strauss syndrome, Cicatricial pemphigoid/benign mucosal pemphigoid, Crohn's disease, Cogans syndrome, Cold agglutinin disease, Congenital heart block, Coxsackie myocarditis, CREST disease, Essential mixed cryoglobulinemia, Demyelinating neuropathies, Dermatitis herpetiformis, Dermatomyositis, Devic's disease (neuromyelitis optica), Dilated cardiomyopathy, Discoid lupus, Dressler's syndrome, Endometriosis, Eosinophilic angiocentric fibrosis,

Eosinophilic fasciitis, Erythema nodosum, Experimental allergic encephalomyelitis, Evans syndrome, Fibrosing alveolitis, Giant cell arteritis (temporal arteritis), Glomerulonephritis, Goodpasture's syndrome, Granulomatosis with Polyangiitis (GPA) see Wegener's, Graves' disease, Guillain-Barre syndrome, Hashimoto's encephalitis, Hashimoto's thyroiditis, Hemolytic anemia, Henoch-Schonlein purpura, Herpes gestationis, Hypogammaglobulinemia, Idiopathic hypocomplementemic tubulointestitial nephritis, Idiopathic thrombocytopenic purpura (ITP), IgA nephropathy, IgG4-related disease, IgG4-related sclerosing disease, Immunoregulatory lipoproteins, Inflammatory aortic aneurysm, Inflammatory pseudotumour, Inclusion body myositis, Insulin-dependent diabetes (type1), Interstitial cystitis, Juvenile arthritis, Juvenile diabetes, Kawasaki syndrome, Kuttner's tumour, Lambert-Eaton syndrome, Leukocytoclastic vasculitis, Lichen planus, Lichen sclerosus, Ligneous conjunctivitis, Linear IgA disease (LAD), Lupus (SLE), Lyme disease, chronic, Mediastinal fibrosis, Meniere's disease, Microscopic polyangiitis, Mikulicz's syndrome, Mixed connective tissue disease (MCTD), Mooren's ulcer, Mucha-Habermann disease, Multifocal fibrosclerosis, Multiple sclerosis, Myasthenia gravis, Myositis, Narcolepsy, Neuromyelitis optica (Devic's), Neutropenia, Ocular cicatricial pemphigoid, Optic neuritis, Ormond's disease (retroperitoneal fibrosis), Palindromic rheumatism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcus), Paraneoplastic cerebellar degeneration, Paraproteinemic polyneuropathies, Paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, Parsonnage-Turner syndrome, Pars planitis (peripheral uveitis), Pemphigus vulgaris, Periaortitis, Periarteritis, Peripheral neuropathy, Perivenous encephalomyelitis, Pernicious anemia, POEMS syndrome, Polyarteritis nodosa, Type I, II, & III autoimmune polyglandular syndromes, Polymyalgia rheumatic, Polymyositis, Postmyocardial infarction syndrome, Postpericardiotomy syndrome, Progesterone dermatitis, Primary biliary cirrhosis, Primary sclerosing cholangitis, Psoriasis, Psoriatic arthritis, Idiopathic pulmonary fibrosis, Pyoderma gangrenosum, Pure red cell aplasia, Raynauds phenomenon, Reflex sympathetic dystrophy, Reiter's syndrome, Relapsing polychondritis, Restless legs syndrome, Retroperitoneal fibrosis (Ormond's disease), Rheumatic fever, Rheumatoid arthritis, Riedel's thyroiditis, Sarcoidosis, Schmidt syndrome, Scleritis, Scleroderma, Sjogren's syndrome, Sperm & testicular autoimmunity, Stiff person syndrome, Subacute bacterial endocarditis (SBE), Susac's syndrome, Sympathetic ophthalmia, Takayasu's arteritis, Temporal arteritis/Giant cell arteritis, Thrombotic, thrombocytopenic purpura (TTP), Tolosa-Hunt syndrome, Transverse myelitis, Ulcerative colitis, Undifferentiated connective tissue disease (UCTD), Uveitis, Vasculitis, Vesiculobullous dermatosis, Vitiligo, Waldenstrom Macroglobulinaemia, Warm idiopathic haemolytic anaemia and Wegener's granulomatosis (now termed Granulomatosis with Polyangiitis (GPA).

In one embodiment the antibodies or fragments according to the disclosure are employed in the treatment or prophylaxis of epilepsy or seizures.

In one embodiment the antibodies or fragments according to the disclosure are employed in the treatment or prophylaxis of multiple sclerosis.

In embodiment the antibodies and fragments of the disclosure are employed in alloimmune disease/indications which includes:

- Transplantation donor mismatch due to anti-HLA antibodies
- Foetal and neonatal alloimmune thrombocytopenia, FNAIT (or neonatal alloimmune thrombocytopenia, NAITP or NAIT or NAT, or foeto-maternal alloimmune thrombocytopenia, FMAITP or FMAIT).

Additional indications include: rapid clearance of Fc-containing biopharmaceutical drugs from human patients and combination of anti-FcRn therapy with other therapies – IVIg, Rituxan, plasmapheresis. For example anti-FcRn therapy may be employed following Rituxan therapy.

In embodiment the antibodies and fragments of the disclosure are employed in a neurology disorder such as:

- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Guillain-Barre syndrome
- Paraproteinemic polyneuropathies
- Neuromyelitis optica (NMO, NMO spectrum disorders or NMO spectrum diseases), and
- Myasthenia gravis.

In embodiment the antibodies and fragments of the disclosure are employed in a dermatology disorder such as:

- Bullous pemphigoid
- Pemphigus vulgaris
- ANCA-associated vasculitis
- Dilated cardiomyopathy

In embodiment the antibodies and fragments of the disclosure are employed in an Immunology, haematology disorder such as:

- Idiopathic thrombocytopenic purpura (ITP)
- Thrombotic thrombocytopenic purpura (TTP)
- Warm idiopathic haemolytic anaemia
- Goodpasture's syndrome
- Transplantation donor mismatch due to anti-HLA antibodies

In one embodiment the disorder is selected from Myasthenia Gravis, Neuro- myelitis Optica, CIDP, Guillaume-Barre Syndrome, Para-proteinemic Poly neuropathy, Refractory Epilepsy, ITP/TTP, Hemolytic Anemia, Goodpasture's Syndrome, ABO mismatch, Lupus nephritis, Renal Vasculitis, Sclero-derma, Fibrosing alveolitis, Dilated cardio-myopathy, Grave's Disease, Type 1 diabetes, Auto-immune diabetes, Pemphigus, Sclero-derma, Lupus, ANCA vasculitis, Dermato-myositis, Sjogren's Disease and Rheumatoid Arthritis.

In one embodiment the disorder is selected from autoimmune polyendocrine syndrome types 1 (APECED or Whitaker's Syndrome) and 2 (Schmidt's Syndrome); alopecia universalis; myasthenic crisis; thyroid crisis; thyroid associated eye disease; thyroid ophthalmopathy; autoimmune diabetes; autoantibody associated encephalitis and/or encephalopathy; pemphigus

foliaceus; epidermolysis bullosa; dermatitis herpetiformis; Sydenham's chorea; acute motor axonal neuropathy (AMAN); Miller-Fisher syndrome; multifocal motor neuropathy (MMN); opsoclonus; inflammatory myopathy; Isaac's syndrome (autoimmune neuromyotonia), Paraneoplastic syndromes and Limbic encephalitis.

The antibodies and fragments according to the present disclosure may be employed in treatment or prophylaxis.

The present invention also provides a method of reducing the concentration of undesired antibodies in an individual comprising the steps of administering to an individual a therapeutically effective dose of an anti-FcRn antibody or binding fragment thereof described herein.

In one embodiment the present disclosure comprises use of antibodies or fragments thereof as a reagent for diagnosis, for example conjugated to a reporter molecule. Thus there is provided antibody or fragment according to the disclosure which is labelled. In one aspect there is provided a column comprising an antibody or fragment according to the disclosure.

Thus there is provided an anti-FcRn antibody or binding fragment for use as a reagent for such uses as:

1) purification of FcRn protein (or fragments thereof) – being conjugated to a matrix and used as an affinity column, or (as a modified form of anti-FcRn) as a precipitating agent (e.g. as a form modified with a domain recognised by another molecule, which may be modified by addition of an Fc (or produced as full length IgG), which is optionally precipitated by an anti-Fc reagent)

2) detection and/or quantification of FcRn on cells or in cells, live or fixed (cells in vitro or in tissue or cell sections). Uses for this may include quantification of FcRn as a biomarker, to follow the effect of anti-FcRn treatment. For these purposes, the candidate might be used in a modified form (e.g. by addition of an Fc domain, as in full length IgG, or some other moiety, as a genetic fusion protein or chemical conjugate, such as addition of a fluorescent tag used for the purposes of detection).

3) purification or sorting of FcRn-bearing cells labeled by binding to candidate modified by ways exemplified in (1) and (2).

Also provided by the present invention is provided an assay suitable for assessing the ability of a test molecule such as an antibody molecule to block FcRn activity and in particular the ability of the cells to recycle IgG. Such an assay may be useful for identifying inhibitors of FcRn activity, such as antibody molecules or small molecules and as such may also be useful as a batch release assay in the production of such an inhibitor.

In one aspect there is provided an assay suitable for assessing the ability of a test molecule such as an antibody molecule to block human FcRn activity and in particular the ability of human FcRn to recycle IgG, wherein the method comprises the steps of:

a) coating onto a surface non-human mammalian cells recombinantly expressing human FcRn alpha chain and human β2 microglobulin (β2M),
b) contacting the cells under mildly acidic conditions such as about pH5.9 with a test molecule and an IgG to be recycled by the cell for a period of time sufficient to allow binding of both the test molecule and the IgG to FcRn, optionally adding the test molecule before the IgG to be recycled and incubating for a period of time sufficient to allow binding of the test molecule to FcRn.
c) washing with a slightly acidic buffer, and
d) detecting the amount of IgG internalised and/or recycled by the cells.

In one aspect there is provided an assay suitable for assessing the ability of a test molecule such as an antibody molecule to block human FcRn activity and in particular the ability of human FcRn to recycle IgG, wherein the method comprises the steps of:

a) coating onto a surface non-human mammalian cells recombinantly expressing human FcRn alpha chain and human β2 microglobulin (β2M),
b) contacting the cells under mildly acidic conditions such as about pH5.9 with a test antibody molecule and an IgG to be recycled by the cell for a period of time sufficient to allow binding of both the test antibody molecule and the IgG to FcRn, optionally adding the test antibody molecule before the IgG to be recycled and incubating for a period of time sufficient to allow binding of the test antibody molecule to FcRn.
c) washing with a slightly acidic buffer to remove unbound IgG and test antibody molecule, and
d) detecting the amount of IgG recycled by the cells.

In one aspect there is provided an assay suitable for assessing the ability of a test molecule such as an antibody molecule to block human FcRn activity and in particular the ability of human FcRn to recycle IgG, wherein the method comprises the steps of:

a) coating onto a surface non-human mammalian cells recombinantly expressing human FcRn alpha chain and human β2 microglobulin (β2M),
b) contacting the cells under mildly acidic conditions such as about pH5.9 with a test antibody molecule and an IgG to be recycled by the cell for a period of time sufficient to allow binding of both the test antibody molecule and IgG to FcRn, optionally adding the test antibody molecule before the IgG to be recycled and incubating for a period of time sufficient to allow binding of the test antibody molecule to FcRn.
c) washing with a slightly acidic buffer to remove unbound IgG and test antibody molecule,
d) incubating the cells in a neutral buffer such as about pH 7.2
e) detecting the amount of IgG recycled by the cells by determining the amount of IgG released into the supernatant.

Suitable cells include Madin-Darby Canine Kidney (MDCK) II cells. Transfection of MDCKII cells with human FcRn alpha chain and human β2 microglobulin (β2M) has previously been

described by Claypool *et al.,* 2002, Journal of Biological Chemistry, 277, 31, 28038-28050. This paper also describes recycling of IgG by these transfected cells.

Media for supporting the cells during testing includes complete media comprising MEM (Gibco #21090-022), 1 x non-essential amino acids (Gibco 11140-035), 1 x sodium pyruvate (Gibco #11360-039), and L-glutamine (Gibco # 25030-024).

Acidic wash can be prepared by taking HBSS+ (PAA #H15-008) and adding 1M MES until a pH 5.9 +/- 0.5 is reached. BSA about 1% may also be added (Sigma # A9647).

A neutral wash can be prepared by taking HBSS+ (PAA #H15-008) and adding 10M Hepes pH 7.2 +/- 0.5 is reached. BSA about 1% may also be added (Sigma # A9647).

Washing the cells with acidic buffer removes the unbound test antibody and unbound IgG and allows further analysis to be performed. Acidic conditions used in step (b) encourage the binding of the IgG to FcRn and internalisation and recycling of the same.

The amount of test antibody or fragment and IgG on only the surface of the cells may be determined by washing the cells with neutral wash and analysing the supernatant/washings to detect the quantity of test antibody or IgG. Importantly a lysis buffer is not employed. To determine the amount of IgG internalised by the cells the antibody may first be removed from the surface of the cell with a neutral wash and the cells lysed by a lysis buffer and then the internal contents analysed. To determine the amount of IgG recycled by the cells the cells are incubated under neutral conditions for a suitable period of time and the surrounding buffer analysed for IgG content. If the surface and internal antibody content of the cell is required then the cell can be washed with acid wash to maintain the antibody presence on the cell surface, followed by cell lysis and analysis of the combined material.

Where it is desired to measure both internalisation and recycling of the IgG samples are run in duplicate and testing for internalisation and recycling conducted separately.

A suitable lysis buffer includes 150mM NaCl, 20mM Tris, pH 7.5, 1mM EDTA, 1mM EGTA, 1% Triton-X 100, for each 10ml add protease inhibitors/phosphate inhibitors as described in manufacturer's guidelines.

Typically the IgG to be recycled is labelled, in one example a biotinylated human IgG may be used. The IgG can then be detected employing, for example a streptavidin sulfo-tag detection antibody (such as MSD # r32ad-5) 25mL at 0.2ug/mL of MSD blocking buffer. Blocking buffer may comprise 500mM Tris, pH7.5. 1.5M NaCl and 0.2% Tween-20 and 1.5% BSA.

Alternatively the IgG may be pre-labelled with a fluorophore or similar label.

In one embodiment a suitable surface is a plastic plate or well such as a 96 well plate or similar, a glass slide or a membrane. In one example cells are coated onto the surface at a density that results in the formation of a monolayer.

In one embodiment the assay described herein is not a measurement of transcytosis of an antibody top to bottom across a membrane with a pH gradient there-across, for example acid conditions one side of the membrane and neutral conditions on the underside of the membrane.

In one example the test antibody or fragment and IgG may be incubated with the cells in step (b) for about 1 hour for example at ambient temperature under acidic conditions to allow binding.

In one example the test antibody or fragment may be incubated with the cells in step (b) for about 1 hour for example at ambient temperature under acidic conditions to allow binding before addition of the IgG to be recycled. Subsequently the IgG to be recycled by the cell may be incubated with the cells in step (b) for about 1 hour for example at ambient temperature under acidic conditions to allow binding.

Neutral conditions facilitate release of the IgG into the supernatant.

Comprising in the context of the present specification is intended to meaning including.

Where technically appropriate embodiments of the invention may be combined.

Embodiments are described herein as comprising certain features/elements. The disclosure also extends to separate embodiments consisting or consisting essentially of said features/elements.

Technical references such as patents and applications are incorporated herein by reference.

The present invention is further described by way of illustration only in the following examples, which refer to the accompanying Figures, in which:

Figure 1 shows certain amino acid and polynucleotide sequences.

Figure 2 shows alignments of certain sequences.

Figure 3 shows a comparison of binding on human MDCK II for a Fab' fragment according to the present disclosure and a PEGylated version thereof

Figure 4 shows a Fab' fragment according to the present disclosure and a PEGylated version thereof inhibiting IgG recycling on MDCK II cells

Figure 5 shows a PEGylated Fab' fragment according to the present disclosure inhibits apical to basolateral IgG trancytosis in MDCK II cells

Figure 6 shows a comparison of binding of cyno monkey MDCK II for a Fab' fragment according to the present disclosure and a PEGylated version thereof

Figure 7 shows a PEGylated Fab' fragment according to the present inhibiting IgG recycling on MDCK II cells for human and cyno monkey versions thereof

Figure 8 shows the effect of a single dose of a PEGylated Fab' molecule according to the disclosure on plasma IgG levels in cynomolgus monkeys

Figure 9 shows the effect of four weekly doses of a PEGylated Fab' molecule according to the disclosure on plasma IgG levels

Figure 10 shows a diagrammatic representation of antibody recycling function of FcRn inhibited by a blocking protein

Figure 11 shows flow cytometry based human IgG blocking assay using purified gamma 1 IgG antibodies

Figure 12 shows Fab'PEG single/intermittent IV doses in normal cyno 20mg/Kg days 1 and 67 IgG pharmacodynamics

Figure 13 shows Fab'PEG: repeat IV doses in normal cyno- 4x 20 or 100 mg/Kg per week IgG pharmacodynamics

Figure 14 shows Fab'PEG single/intermittent IV doses in normal cyno -20 mg/Kg and 100 mg/Kg days 1 and 67 IgG Pharmacodynamics

Figure 15 shows plasma IgG levels in 4 cynomolgus monkeys after 2 IV doses of 20mg/Kg 1519.g57 Fab'PEG

Figure 16 shows plasma IgG levels in 4 cynomolgus monkeys receiving 10 IV doses of 20mg/Kg 1519.g57 Fab'PEG, one every 3 days

Figure 17 shows the effect of two 30mg/Kg IV doses of 1519.g57 IgG4P on the endogenous plasma IgG in cynomolgus monkeys

Figure 18 shows the effect of 30 mg/Kg if followed by 41 daily doses of 5mg/Kg 1519.g57 IgG4P on plasma IgG in cynomolgus monkeys

Figure 19 shows the result of daily dosing with vehicle on the plasma IgG in cynomolgus monkeys

Figure 20 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'PEG or PBS IV

Figure 21 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 IgG1 or IgG4 or PBS IV

Figure 22 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'-human serum albumin or PBS IV

Figure 23 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 FabFv or PBS IV

Figure 24 shows the increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab or Fab'PEG or PBS IV

Figure 25 shows a bispecific antibody fusion protein of the present invention, referred to as a Fab-dsFv.

EXAMPLES

The following immunizations were performed in order to generate material for B cell culture and antibody screening:

Sprague Dawley rats were immunized with three shots of NIH3T3 mouse fibroblasts co-expressing mutant human FcRn (L320A; L321A) (Ober et al., 2001 Int. Immunol. 13, 1551–1559) and mouse β2M with a fourth final boost of human FcRn extracellular domain.

Sera were monitored for both binding to mutant FcRn on HEK-293 cells and for its ability to prevent binding of Alexafluor 488-labelled human IgG. Both methods were performed by flow cytometry. For binding, phycoerythrin (PE)-labelled anti mouse or rat Fc specific secondary reagents were used to reveal binding of IgG in sera.

B cell cultures were prepared using a method similar to that described by Zubler *et al.* (1985). Briefly, B cells at a density of approximately 5000 cells per well were cultured in bar-coded 96-well tissue culture plates with 200 µl/well RPMI 1640 medium (Gibco BRL) supplemented with 10% FCS (PAA laboratories ltd), 2% HEPES (Sigma Aldrich), 1% L-Glutamine (Gibco BRL), 1% penicillin/streptomycin solution (Gibco BRL), 0.1% β-mercaptoethanol (Gibco BRL), 2-5%

activated rabbit splenocyte culture supernatant and gamma-irradiated EL-4-B5 murine thymoma cells ($5x10^4$/well) for seven days at 37°C in an atmosphere of 5% CO_2.

The presence of FcRn-specific antibodies in B cell culture supernatants was determined using a homogeneous fluorescence-based binding assay using HEK-293 cells transiently transfected with mutant FcRn (surface-stabilised) as a source of target antigen. 10 ul of supernatant was transferred from barcoded 96-well tissue culture plates into barcoded 384-well black-walled assay plates containing 5000 transfected HEK-293 cells per well using a Matrix Platemate liquid handler. Binding was revealed with a goat anti-rat or mouse IgG Fcγ-specific Cy-5 conjugate (Jackson). Plates were read on an Applied Biosystems 8200 cellular detection system. From 3800 x 96-well culture plates, representing 38 different immunized animals, 9800 anti-human FcRn binders were identified. It was estimated that this represented the screening of approximately 2.5 billion B cells.

Following primary screening, positive supernatants were consolidated on 96-well bar-coded master plates using an Aviso Onyx hit-picking robot and B cells in cell culture plates frozen at -80C. Master plates were then screened in a Biacore assay in order to identify wells containing antibodies of high affinity and those which inhibited the binding of human IgG to FcRn (see below).

Biomolecular interaction analysis using surface plasmon resonance technology (SPR) was performed on a BIAcore T200 system (GE Healthcare). Goat anti-rat IgG, Fc gamma (Chemicon International Inc.) in 10mM NaAc, pH 5 buffer was immobilized on a CM5 Sensor Chip via amine coupling chemistry to a capture level of approx. 19500 response units (RU) using HBS-EP$^+$ as the running buffer. 50mM Phosphate, pH6 + 150mM NaCl was used as the running buffer for the affinity and blocking assay. B cell culture supernatants were diluted 1 in 5 in 200mM Phosphate, pH6 +150mM NaCl. A 600s injection of diluted B cell supernatant at 5µl/min was used for capture by the immobilized anti-rat IgG,Fc. Human FcRn at 100nM was injected over the captured B cell culture supernatant for 180s at 30µl/min followed by 360s dissociation. Human IgG (Jackson ImmunoResearch) was injected over for 60s with 180s dissociation at 30µl/min.

The data was analysed using T200 evaluation software (version 1.0) to determine affinity constants (K_D) of antibodies and determine those which blocked IgG binding.

As an alternative assay, master plate supernatants were also screened in a cell-based human IgG blocking assay. 25 ul of B cell culture supernatant from master plates were added to 96 well U-bottomed polypropylene plate. Mutant hFcRn-transfected HEK-293 cells (50,000 cells per well in 25 ul PBS pH6/1% FCS) were then added to each well and incubated for 1 hour at 4°C. Cells were washed twice with 150 ul of PBS media. Cells were then resuspended in 50 ul/well PBS/FCS media containing human IgG labelled with Alexafluor 488 or 649 at 7.5ug/ml and incubated 1 hour at 4°C. Cells were then washed twice with 150 ul of media and then resuspended in 35 ul / well of PBS/FCS media containing 1% formaldehyde as fixative. Plates were then read on a FACS Canto 2 flow cytometer. Example data is given in Figure 11.

To allow recovery of antibody variable region genes from a selection of wells of interest, a deconvolution step had to be performed to enable identification of the antigen-specific B cells in a given well that contained a heterogeneous population of B cells. This was achieved using the

Fluorescent foci method. Briefly, Immunoglobulin-secreting B cells from a positive well were mixed with streptavidin beads (New England Biolabs) coated with biotinylated human FcRn and a 1:1200 final dilution of a goat anti-rat or mouse Fcγ fragment-specific FITC conjugate (Jackson). After static incubation at 37°C for 1 hour, antigen-specific B cells could be identified due to the presence of a fluorescent halo surrounding that B cell. These individual B cells, identified using an Olympus microscope, were then picked with an Eppendorf micromanipulator and deposited into a PCR tube. Fluorescent foci were generated from 268 selected wells.

Antibody variable region genes were recovered from single cells by reverse transcription polymerase chain reaction (RT)-PCR using heavy and light chain variable region-specific primers. Two rounds of PCR were performed on an Aviso Onyx liquid handling robot, with the nested 2° PCR incorporating restriction sites at the 3' and 5' ends allowing cloning of the variable regions into a mouse γ1 IgG (VH) or mouse kappa (VL) mammalian expression vector. Paired heavy and light chain constructs were co-transfected into HEK-293 cells using Fectin 293 (Invitrogen) and cultured in 48-well plates in a volume of 1 ml. After 5-7 days expression, supernatants were harvested and antibody subjected to further screening.

PCR successfully recovered heavy and light chain cognate pairs from single B cells from 156 of the selected wells. DNA sequence analysis of the cloned variable region genes identified a number of unique families of recombinant antibody. Following expression, transient supernatants were interrogated in both human IgG FACS blocking (described above) and IgG recycling assays. In some cases, purified mouse γ1 IgG was produced and tested (data labeled accordingly).

The recycling assay used MDCK II cells (clone 34 as described in Examples 4 and 5 below) over-expressing human FcRn and beta 2 microglobulin plated out at 25,000 cells per well of a 96 well plate. These were incubated overnight at 37°C, 5% CO_2. The cells were washed with HBSS+ Ca/Mg pH 7.2+1% BSA and then incubated with 50µl of varying concentrations of HEK-293 transient supernatant or purified antibody for 1 hour at 37°C, 5% CO_2. The supernatant was removed and 500ng/ml of biotinylated human IgG (Jackson) in 50µl of HBSS+ Ca/Mg pH 5.9 +1%BSA was added to the cells and incubated for 1 hour at 37°C, 5% CO_2. The cells were then washed three times in HBSS+ Ca/Mg pH 5.9 and 100µl of HBSS+ Ca/Mg pH 7.2 added to the cells and incubated at 37°C, 5% CO_2 for 2 hours. The supernatant was removed from the cells and analysed for total IgG using an MSD assay with an anti-human IgG capture antibody (Jackson) and a streptavidin-sulpho tag reveal antibody (MSD). The inhibition curve was analysed by non-linear regression to determine IC50 values.

Based on performance in these assays a family of antibodies was selected comprising the six CDRs given in SEQ ID NOs 1 to 6. Antibody CA170_01519 had the best activity and was selected for humanisation.

Example 1 Humanisation Method

Antibody CA170_01519 was humanised by grafting the CDRs from the rat antibody V-regions onto human germline antibody V-region frameworks. In order to recover the activity of the antibody, a number of framework residues from the rat V-regions were also retained in the humanised sequence. These residues were selected using the protocol outlined by Adair *et al.*

(1991) (Humanised antibodies WO91/09967). Alignments of the rat antibody (donor) V-region sequences with the human germline (acceptor) V-region sequences are shown in Figures 2A and 2B, together with the designed humanised sequences. The CDRs grafted from the donor to the acceptor sequence are as defined by Kabat (Kabat *et al.*, 1987), with the exception of CDR-H1 where the combined Chothia/Kabat definition is used (see Adair *et al.,* 1991 Humanised antibodies. WO91/09967). Human V-region VK1 2-1-(1) A30 plus JK2 J-region (V BASE, http://vbase.mrc-cpe.cam.ac.uk/) was chosen as the acceptor for the light chain CDRs. Human V-region VH3 1-3 3-07 plus JH4 J-region (V BASE, http://vbase.mrc-cpe.cam.ac.uk/) was chosen as the acceptor for the heavy chain CDRs.

Genes encoding a number of variant heavy and light chain V-region sequences were designed and these were constructed by an automated synthesis approach by Entelechon GmbH. Further variants of both heavy and light chain V-regions were created by modifying the VH and VK genes by oligonucleotide-directed mutagenesis. These genes were cloned into a number of vectors to enable expression of humanised 1519 Fab' in mammalian and *E. coli* cells. The variant chains, and combinations thereof, were assessed for their expression in *E. coli*, their potency relative to the parent antibody, their biophysical properties and suitability for downstream processing, leading to the selection of the gL20 light chain graft and gH20 heavy chain graft. The final selected gL20 and gH20 graft sequences are shown in Figures 2A and 2B, respectively. This V-region pairing was named 1519.g57.

The light chain framework residues in graft gL20 are all from the human germline gene, with the exception of residues 36, 37 and 58 (Kabat numbering), where the donor residues Leucine (L36), Phenylalanine (F37) and Isoleucine (I58) were retained, respectively. Retention of these three residues was essential for full potency of the humanised Fab'. The heavy chain framework residues in graft gH20 are all from the human germline gene, with the exception of residues 3, 24, 76, 93 and 94 (Kabat numbering), where the donor residues Proline (P3), Valine (V24), Serine (S76), Threonine (T93) and Threonine (T94) were retained, respectively. Retention of these five residues was important for full potency of the humanised Fab'.

For expression in *E. coli*, the humanised heavy and light chain V-region genes were cloned into the UCB expression vector pTTOD, which contains DNA encoding the human C-kappa constant region (K1m3 allotype) and the human gamma-1 CH1-hinge region (G1m17 allotype). The *E.coli* FkpA gene was also introduced into the expression plasmid, as co-expression of this chaperone protein was found to improve the yield of the humanised Fab' in *E. coli* strain MXE016 (disclosed in WO2011/086136) during batch-fed fermentation, using IPTG to induce Fab' expression. The 1519 Fab' light and heavy chains and FkpA polypeptide were all expressed from a single multi-cistron under the control of the IPTG-inducible tac promoter.

For expression in mammalian cells, the humanised light chain V-region genes were cloned into the UCB-Celltech human light chain expression vector pMhCK, which contains DNA encoding the human Kappa chain constant region (Km3 allotype). The humanised heavy chain V-region genes were cloned into the UCB-Celltech human gamma-4 heavy chain expression vector pMhg4P FL, which contains DNA encoding the human gamma-4 heavy chain constant region with the hinge stabilising mutation S241P (Angal *et al.*, Mol Immunol. 1993, 30(1):105-8). Co-transfection of light and heavy chain vectors into HEK293 suspension cells was achieved using

293 Fectin (12347-019 Invitrogen), and gave expression of the humanised, recombinant 1519 antibodies.

Example 1A Preparation of 1519.g57 Fab'-PEG conjugate

Fab' expressed in the periplasm of *E.coli* was extracted from cells by heat extraction. Fab' purified by Protein G affinity purification with an acid elution. Fab' reduced and PEGylated with 40kDa PEG (SUNBRIGHT GL2-400MA3). PEG is covalently linked via a maleimide group to one or more thiol groups in the antibody fragment. PEGylation efficiency was confirmed by SE-HPLC. Fab'PEG was separated from un-PEGylated Fab' and diFab' by cation exchange chromatography. Fractions analyzed by SE-HPLC and SDS-PAGE. Pooling carried out to minimize levels of impurities. Final sample concentrated and diafiltered into desired buffer.

Example 1B Preparation of 1519.g57 Fab' (Anti human FcRn) conjugated with human serum albumin

Anti human FcRn Fab' 1519.g57 was chemically conjugated with human serum albumin (recombinant derived) which was then used for animal studies.

- Human serum albumin: Recombumin from Novozyme (Cat No: 200-010) presented as 20%w/v solution produced recombinantly in *Saccharomyces cerevisiae*.
- 1519.g57Fab': 30mg/ml presented in 0.1M Sodium Phosphate, 2mM EDTA, pH6.0 (reduction buffer)
- 1,6-Bismaleimidohexane (BMH) from Thermofisher (Cat No. 22330)

Reduction of Albumin:

Albumin was reduced using freshly prepared cysteamine hydrochloride (Sigma cat no: 30078) which was prepared in reduction buffer. To the albumin solution cysteamine hydrochloride was added at 10 fold molar excess and then incubated at 37°C water bath for 30 minutes. Following reduction the solution was desalted using PD10 columns (GE Healthcare Cat. No: 17-0851-01) to remove any excess reducing agent.

Addition of BMH linker:

A stock solution of 1,6-bismaleimidohexane was prepared in glass vial using dimethylformamide. The solution was vortexed to ensure complete dissolution of BMH. BMH solution was added to the desalted reduced albumin solution at 10 fold molar excess with respect to albumin concentration. The solution was then incubated at 37°C for 30 minutes followed by overnight incubation at room temperature on a roller to ensure proper mixing. A white precipitate was seen which was spun down using bench top centrifuge.
After the completion of the reaction the solution was desalted using PD10 columns.

Reduction of 1519.g57 Fab'

1519.g57 Fab' was reduced using freshly prepared cysteamine hydrochloride (Sigma cat no: 30078) which was prepared in reduction buffer. To the 1519.g57 Fab' solution cysteamine hydrochloride was added at 10 fold molar excess and then incubated at 37°C water bath for 30 minutes. Following reduction the solution was desalted using PD10 columns (from GE Healthcare Cat. No: 17-0851-01) to remove any excess reducing agent.

Mixing of reduced Fab and albumin-BMH

Equal amounts (in molar terms) of the reduced Fab' and albumin-linker was added and incubated at room temperature overnight on a roller mixer.

Affinity purification:

The above mix was then affinity purified using Blue Sepharose which bound to albumin-Fab conjugate and free albumin. Purification was carried out according to manufacturer's instruction which is briefly described here:

Blue sepharose was reconstituted in DPBS pH7.4 and washed thrice with PBS. Following washing the mixture of Fab and linker linked albumin was added and incubated at room temperature for 1 hour on a roller mixer. After incubation the matrix was washed again with PBS to remove any unbound materials and then eluted with PBS7.4 containing 2M KCl.

Size exclusion purification:

The affinity purified material contained albumin conjugated to Fab along with some unreacted HSA. This required further clean-up and this was achieved using size exclusion chromatography (S200 16X60 from GE Healthcare). The final pooled fractions were presented in DPBS pH7.4. The final 1519.g57Fab-HSA conjugate was concentrated up to 20mg/ml in DPBS pH7.4 and analyzed on analytical size exclusion chromatography (Agilent Zorbax GF250 and GF450 in tandem) and was found to be predominantly monomeric conjugate. Endotoxin assay was also carried out and the sample was found to be below the specified lower limit of endotoxin content.

Example 2 Screening of Fab' & Fab'PEG candidate molecules in the IgG recycling assay

To determine the ability of the candidate Fab'PEG molecules to block FcRn activity in a functional cell assay, the molecules were screened in the IgG recycling assay (described in more detail in Example 5). Briefly, MDCK II clone 34 cells were pre-incubated with candidate Fab' or Fab'PEG before addition of biotinylated human IgG in an acidic buffer. The cells were washed to remove all excess IgG and then incubated in a neutral pH buffer to facilitate release of IgG into the supernatant. The amount of IgG released into the supernatant was measured by MSD assay and EC_{50} values calculated. The EC_{50} values of humanised Fab' and Fab'PEG candidate molecules that inhibit IgG recycling are shown in the table below .Upon PEGylation there is a loss of potency for all candidate antibodies, however the extent of this varies depending on candidate.

Table 1

Antibody	Fab' EC_{50} (nM)	(n)	Fab'PEG EC_{50} (nM)	(n)	Fold Change in EC_{50} after pegylation
CA170_0519.g63	1.91	3	5.25	3	2.7
CA170_0519.g57	2.06	7	6.64	6	3.2
CA170_0519.g2	4.22	2	11.01	4	2.6

Mean EC_{50} values for Fab' and Fab'PEG molecules in the IgG Recycling assay.

MDCK II clone 34 cells stably transfected with human FcRn and beta 2 microglobulin were at 25,000 cells per well in a 96 well plate and incubated overnight at 37°C, 5% CO_2. The cells were

incubated with candidate Fab' or Fab'PEG in $HBSS^+$ (Ca/Mg) pH 5.9 + 1% BSA for 1 hour at 37°C, 5% CO_2 before addition of 500 ng/ml of biotinylated human IgG (Jackson) and incubation for a further 1 hour. The cells were washed with $HBSS^+$ pH 5.9 and then incubated at 37°C, 5% CO_2 for 2 hours in $HBSS^+$ pH 7.2. The supernatant was removed from the cells and analysed for total IgG using an MSD assay (using an anti-human IgG capture antibody (Jackson) and a streptavidin-sulpho tag reveal antibody (MSD)). The inhibition curve was analysed by non-linear regression (Graphpad Prism®) to determine the EC_{50}. Table 1 represents combined data from 2 to 7 experiments.

Example 3 Affinity for hFcRn binding

Biomolecular interaction analysis using surface plasmon resonance technology (SPR) was performed on a Biacore T200 system (GE Healthcare) and binding to human FcRn extracellular domain determined. Human FcRn extracellular domain was provided as a non-covalent complex between the human FcRn alpha chain extracellular domain (SEQ ID NO:94) and β2 microglobulin (β2M) (SEQ ID NO:95). Affinipure $F(ab')_2$ fragment goat anti-human IgG, $F(ab')_2$ fragment specific (for Fab'-PEG capture) or Fc fragment specific (for IgG1 or IgG4 capture) (Jackson ImmunoResearch Lab, Inc.) in 10mM NaAc, pH 5 buffer was immobilized on a CM5 Sensor Chip via amine coupling chemistry to a capture level between 4000 - 5000 response units (RU) using $HBS\text{-}EP^+$ (GE Healthcare) as the running buffer.
50mM Phosphate, pH6 + 150mM NaCl + 0.05%P20 or HBS-P, pH7.4 (GE Healthcare) was used as the running buffer for the affinity assay. The relevant antibody, either anti-hFcRn Fab'-PEG, IgG1 or IgG4P was diluted to 5μg/ml (Fab'-PEG), 0.3μg/ml (IgG1) or 4μg/ml (IgG4) in running buffer. A 60s injection of Fab'-PEG or IgG1 or IgG4 at 10μl/min was used for capture by the immobilized anti-human IgG, $F(ab')_2$. Human FcRn extracellular domain was titrated from 20nM to 1.25nM over the captured anti-FcRn antibody (Fab'-PEG, IgG1 or IgG4) for 300s at 30μl/min followed by 1200s dissociation. The surface was regenerated by 2 x 60s 50mM HCl at 10μl/min.
The data was analysed using T200 evaluation software (version 1.0).

Table 2 Affinity data for anti-hFcRn 1519.g57 Fab'-PEG at pH6

1519.g57Fab'-PEG	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	KD (M)
1	4.37E+05	1.59E-05	3.63E-11
2	4.20E+05	2.01E-05	4.78E-11
3	4.35E+05	1.43E-05	3.29E-11
4	4.37E+05	2.75E-05	6.30E-11
5	4.33E+05	1.28E-05	2.97E-11
	4.32E+05	**1.81E-05**	**4.19E-11**

Table 3 Affinity data for anti-hFcRn 1519.g57 Fab'-PEG at pH7.4

1519.g57Fab'-PEG	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	K_D (M)
1	3.40E+05	1.87E-05	5.49E-11
2	3.31E+05	1.85E-05	5.58E-11
3	3.25E+05	1.99E-05	6.13E-11
4	3.23E+05	1.52E-05	4.70E-11
5	3.20E+05	1.99E-05	6.21E-11
	3.28E+05	**1.84E-05**	**5.62E-11**

In these experiments the Fab'PEG had an average affinity of around 42pM at pH6 and around 56pM at pH7.4.

pH7.4

1519.g57	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	KD (M)	KD (pM)
IgG1	3.80E+05	1.25E-05	3.29E-11	33
IgG4P	3.68E+05	1.26E-05	3.43E-11	34

Table 3A Affinity data for anti-hFcRn 1519.g57 as IgG1 and IgG4P at pH7.4 (average of three experiments)

pH6

1519.g57	ka ($M^{-1}s^{-1}$)	kd (s^{-1})	KD (M)	KD (pM)
IgG1	4.56E+05	1.01E-05	2.21E-11	22
IgG4P	4.43E+05	1.00E-05	2.26E-11	23

Table 3B Affinity data for anti-hFcRn 1519.g57 as IgG1 and IgG4P at pH6 (average of three experiments)

Tables 3A and 3B show the affinity of the full length antibodies is consistent with that observed for the Fab'-PEG at both pH6 and pH7.4.

Example 4 Cell-based potency

Cell-based assays were performed using Madin-Darby Canine Kidney (MDCK) II cells which had been stably transfected with a human FcRn and human B2M double gene vector with a Geneticin selection marker. A stable cell clone was selected that was able to recycle and

transcytose human IgG and this was used for all subsequent studies. It will be referred to as MDCK II clone 34.

Cell based Affinity of CA170_01519.g57 Fab'PEG for human FcRn

Quantitative flow cytometry experiments were performed using MDCK II clone 34 cells and AlexaFluor 488-labelled CA170_01519.g57 Fab' or CA170_01519.g57 Fab'PEG. Specific binding of antibody to FcRn across a range of antibody concentrations was used to determine K_D. The analyses were performed in both neutral and acidic buffers to determine whether environmental pH comparable to that found in blood plasma (pH7.4) or endosomes (pH6) had any effect on the antibody binding.

Figure 3 shows representative binding curves for CA170_01519.g57 Fab'(Figure 3A) and Fab'PEG (Figure 3B). The mean K_D values (n = 2 or 3) were 1.66nM and 6.5nM in neutral buffer, and 1.59nM and 5.42nM in acidic buffer, respectively (see Table 4).

Table 4 - Mean K_D values (nM) for CA170_01519.g57 Fab' and Fab'PEG on MDCK II clone 34 cells.

Antibody format	Human FcRnpH 7.4	Human FcRnpH 6.0
1519.g57 Fab'	1.66	1.59
1519.g57 Fab'PEG	6.5	5.42

Figure 3 shows CA170_01519.g57 Fab' (A) and CA170_01519.g57 Fab'PEG (B) binding on MDCK II clone 34 cells in acidic and neutral pH.

MDCK II clone 34 cells were incubated in Facs buffer (PBS with 0.2% w/v BSA, 0.09% w/v NaN3) for 30 mins prior to the addition of Alexa-fluor 488-labelled CA170_01519.g57 Fab' or Fab'PEG for 1 hour in Facs buffer at either pH 7.4 or pH 6. The final antibody concentrations ranged from 931nM to 0.002nM. The cells were washed in ice cold Facs buffer then analysed by flow cytometry using a Guava flow cytometer (Millipore, UK). Titration data sets were also produced for isotype control antibodies for each antibody format to determine non-specific binding. The number of moles of bound antibody was calculated using interpolated values from a standard curve generated from beads comprised of differing amounts of fluorescent dye. Geometric mean fluorescence values were determined in the flow cytometric analyses of cells and beads. Non-specific binding was subtracted from the anti-FcRn antibody values and the specific binding curve generated was analysed by non-linear regression using a one-site binding equation (Graphpad Prism®) to determine the K_D. Data is representative of 2 or 3 experiments. CA170_01519.g57 Fab'PEG can bind human FcRn expressed on cells at both acidic and neutral pH and the determined K_D values are approximately 3.5 to 4 fold below the equivalent Fab' molecule.

Example 5 Functional cell based assays

CA170_01519.g57 Fab'PEG inhibits the recycling of human IgG

FcRn expression is primarily intracellular (Borvak J et al. 1998, Int. Immunol., 10 (9) 1289-98 and Cauza K et al. 2005, J. Invest. Dermatol., 124 (1), 132-139), and associated with endosomal and lysosomal membranes. The Fc portion of IgG binds to FcRn at acidic pH (<6.5), but not at a neutral physiological pH (7.4) (Rhagavan M et al. 1995) and this pH-dependency facilitates the recycling of IgG.

Once it is taken up by pinocytosis and enters the acidic endosome, IgG bound to FcRn will be recycled along with the FcRn to the cell surface, whereas at the physiologically neutral pH the IgG will be released. (Ober RJ et al. 2004, The Journal of Immunology, 172, 2021-2029). Any IgG not bound to FcRn will enter the lysosomal degradative pathway.

An *in vitro* assay was established to examine the ability of CA170_01519.g57 Fab'PEG or Fab' to inhibit the IgG recycling capabilities of FcRn. Briefly, MDCK II clone 34 cells were incubated in the presence or absence of CA170_01519.g57 Fab' or CA170_01519.g57 Fab'PEG before addition of biotinylated human IgG in an acidic buffer (pH 5.9) to allow binding to FcRn. All excess antibody was removed and the cells incubated in a neutral pH buffer (pH 7.2) which allows release of surface-exposed, bound IgG into the supernatant. The inhibition of FcRn was followed using an MSD assay to detect the amount of IgG recycled and thus released into the supernatant.

Figure 4 shows CA170_01519.g57 inhibits IgG recycling in MDCK II clone 34 cells. MDCK II clone 34 cells were plated at 25,000 cells per well in a 96 well plate and incubated overnight at 37°C, 5% CO_2. The cells were incubated with CA170_01519.g57 Fab' or Fab'PEG in $HBSS^+$ (Ca/Mg) pH 5.9 + 1% BSA for 1 hour at 37°C, 5% CO_2 before addition of 500 ng/ml of biotinylated human IgG (Jackson) and incubation for a further 1 hour. The cells were washed with $HBSS^+$ pH 5.9 then incubated at 37°C, 5% CO_2 for 2 hours in $HBSS^+$ pH 7.2. The supernatant was removed from the cells and analysed for total IgG using an MSD assay (using an anti-human IgG capture antibody (Jackson) and a streptavidin-sulpho tag reveal antibody (MSD)). The inhibition curve was analysed by non-linear regression (Graphpad Prism®) to determine the EC_{50}. The graph represents combined data from 6 or 7 experiments.

As shown in **Figure.4** CA170_01519.g57 Fab' and CA170_01519.g57 Fab'PEG inhibit IgG recycling in a concentration dependent manner with mean EC_{50} values (n= 6 or 7) of 1.937nM and 6.034nM respectively. Hence the CA170_01519.g57 Fab'PEG is approximately 3 fold less potent than CA170_01519.g57 Fab' in inhibiting IgG recycling.

CA170_01519.g57 Fab'PEG inhibits the transcytosis of human IgG

FcRn can traffic IgG across polarised epithelial cell layers in both the apical to basolateral and basolateral to apical directions and thus plays an important role in permitting IgG to move between the circulation and lumen at mucosal barriers (Claypool et al. 2004 Mol Biol Cell 15(4):1746-59).

An *in vitro* assay was established to examine the ability of CA170_01519.g57 Fab'PEG to inhibit FcRn dependent IgG transcytosis. Briefly, MDCK II clone 34 cells were plated in a 24 well transwell plate and allowed to form monolayers over 3 days. The cells were then pre-incubated with CA170_01519.g57 Fab'PEG on the apical surface before the addition of

biotinylated human IgG in an acidic buffer which facilitates binding to FcRn. The human IgG is transcytosed through the cells from the apical to basolateral side and released into a neutral buffer in the lower chamber. Levels of IgG on the basolateral side were then measured using an MSD assay.

Figure 5 shows CA170_01519.g57 Fab'PEG inhibits apical to basolateral IgG transcytosis in MDCK II clone 34 cells.
MDCK II clone 34 cells were plated at 500,000 cells per well of a 24 well transwell plate and incubated for 3 days at 37°C, 5% CO_2 until monolayers were formed. The pH of the apical compartment was adjusted to 5.9 and the basolateral side to 7.2 in a $HBSS^{+}$(Ca/Mg) buffer + 1% BSA. Cells on the apical compartment were pre-incubated with CA170_01519.g57 Fab'PEG for 1 hour before addition of 2.5µg/ml biotinylated human IgG (Jackson) at the indicated concentrations for 4 hours at 37°C, 5% CO_2. The basolateral medium was then collected and total IgG measured by MSD assay (using an anti-human IgG capture antibody (Jackson) and a streptavidin-sulpho tag reveal antibody (MSD)). The inhibition curve was analysed by non-linear regression (Graphpad Prism®) to determine the EC_{50}. The graph represents combined data from 3 experiments.
In summary Figure 5 shows that CA170_01519.g57 Fab'PEG can inhibit the apical to basolateral transcytosis of human IgG in a concentration dependent manner with an EC_{50} value of 25.5nM (n=3).

Summary of *in vitro* effects of CA170_01519.g57 Fab'PEG
CA170_01519.g57 Fab'PEG inhibits both IgG recycling and transcytosis. The EC_{50} of 6nM achieved in the IgG recycling assay is comparable to the cell affinity binding data in which K_D values of 6.5nM in neutral buffer and 5.42nM in acidic buffer were obtained. CA170_01519.g57 Fab'PEG does show a slight reduction in potency compared to the Fab' alone, but compared to many of the other candidate molecules assessed showed the lowest drop in potency between the two formats (see *supra*). In the IgG transcytosis assay an EC_{50} of 25.5nM was obtained.
The data in this section have clearly shown that CA170_01519.g57 Fab'PEG can inhibit human FcRn function.

Example 6 Cross reactivity of CA170_01519.g57 Fab'PEG with non-human primate FcRn.
To validate the use of CA170_01519.g57 Fab'PEG in a non-human primate PK/PD study and pre-clinical toxicology, its relative affinity and functional potency with cynomolgus macaque FcRn was examined. MDCK II cells stably transfected with cynomolgus macaque FcRn and B2M (MDCKII (cm)) were used for the following studies alongside the previously described MDCK II cells stably transfected with human FcRn and B2M (MDCK II clone 34).

Cell based affinity of CA170_01519.g57 Fab'PEG for cynomolgus monkey FcRn
To determine the cell based binding affinity of CA170_01519.g57 Fab'PEG for cynomolgus monkey FcRn, quantitative flow cytometry experiments were performed using MDCK II (cm) cells and AlexaFluor 488-labelled CA170_01519.g57 Fab' or Fab'PEG. Specific binding of antibody to cynomolgus macaque FcRn across a range of antibody concentrations was used to

determine K_D. Antibody binding was performed in both neutral and acidic pH to determine the effect of binding FcRn in neutral blood plasma or acidic endosomes and to therefore determine any effect pH may have on CA170_01519.g57 binding to cynomolgus macaque FcRn.

Figure 6– shows CA170_01519.g57 Fab' (A) and CA170_01519.g57 Fab'PEG (B) binding on MDCK II (cm) cells in acidic and neutral pH.

MDCK II (cm) cells were incubated in Facs buffer (PBS with 0.2% w/v BSA, 0.09% w/v NaN3) for 30 mins prior to the addition of Alexa-fluor 488 labelled CA170_01519.g57 Fab' or Fab'PEG for 1 hour in Facs buffer at either pH 7.4 or pH 6. The final antibody concentrations ranged from 931nM to 0.002nM. The cells were washed in ice cold Facs buffer then analysed by flow cytometry using a Guava flow cytometer (Millipore, UK). Titration data sets were also produced for isotype control antibodies for each antibody format to determine non specific binding. The number of moles of bound antibody was calculated by using interpolated values from a standard curve generated from beads carrying varying amounts of fluorescent dye. Geometric mean fluorescence values were determined in the flow cytometric analyses of cells and beads. Non-specific binding was subtracted from the anti-FcRn antibody values and the specific binding curve generated was analysed by non-linear regression using a one-site binding equation (Graphpad Prism®) to determine the K_D. Data is representative of between 2 and 3 experiments.

Table 5 Mean K_D values (nM) for CA170_01519.g57 Fab' & Fab'PEG on MDCK II (cm) cells.

Antibody format	*Cyno FcRnpH 7.4*	*Cyno FcRnpH 6.0*
1519.g57 Fab'	1.16	1.09
1519.g57 Fab'PEG	8.15	5.01

Figure 6 shows representative binding curves for CA17001519.g57 Fab' (Figure 6A) and Fab'PEG (Figure 6B) binding to cynomolgus macaque FcRn. The mean K_D values obtained for CA17001519.g57 Fab' and Fab'PEG are shown in Table 5. These values are comparable to the K_D values obtained for CA170_01519.g57 Fab' and Fab'PEG binding to human FcRn (see table 4)

CA170_01519.g57 Fab'PEG inhibits the recycling of cynomolgus monkey IgG

To determine if CA170_01519.g57 Fab'PEG is functionally active in blocking cynomolgus monkey FcRn, MDCK II (cm) cells were used to examine the ability of CA170_01519.g57 Fab'PEG to inhibit the recycling of cynomolgus macaque IgG as described previously for the human FcRn assay. The assay was run alongside representative human assays to allow for a comparison between the two.

Briefly, MDCK II cells (clone 34 or cm) were pre-incubated with CA170_01519.g57 Fab'PEG before addition of biotinylated human (h) or cynomolgus macaque (c) IgG in an acidic buffer to allow binding to FcRn. All excess CA170_01519.g57 Fab'PEG and biotinylated IgG were removed and the cells incubated in a neutral pH buffer to allow release of IgG into the

supernatant. The inhibition of FcRn was assessed by detecting the amount of IgG present in the supernatant by MSD assay and percent inhibition calculated.

As shown in **Figure 7,** CA170_01519.g57 Fab'PEG can inhibit both human and cynomolgus macaque IgG recycling in a concentration dependent manner, with EC_{50} values of 8.448nM and 5.988nM respectively. Inhibition of FcRn by CA170_01519.g57 Fab'PEG in the human and cynomolgus macaque assays are comparable, although it appears slightly more potent against the cynomolgus FcRn.

Table 6

	1519.g57 Fab'PEG hFcRn:hIgG	1519.g57 Fab'PEG cFcRn:cIgG
EC50 (nM)	8.448	5.988
95% CI (nM)	6.560 to 10.88	5.383 to 6.661

Figure 7 shows CA170_01519.g57 inhibits IgG recycling in MDCK II clone 34 cells & MDCK II (cm) cells.

MDCK II clone 34 and MDCK II (cm) cells were plated at 25,000 cells per well in a 96 well plate and incubated overnight at 37°C, 5% CO_2. The cells were pre- incubated with CA170_01519.g57 Fab' or Fab'PEG in $HBSS^+$ (Ca/Mg) pH 5.9 + 1% BSA for 1 hour at 37°C, 5% CO_2 before addition of 500 ng/ml of biotinylated human or cyno IgG and incubated for a further 1 hour. The cells were then washed with $HBSS^+$ pH 5.9 and incubated at 37°C, 5% CO_2 for 2 hours in $HBSS^+$ pH 7.2. The supernatant was removed from the cells and analysed for total IgG using an MSD assay (using an anti-human IgG capture antibody (Jackson) and a streptavidin-sulpho tag reveal antibody (MSD)). The inhibition curve was analysed by non-linear regression (Graphpad Prism®) to determine the EC_{50}. The graph represents combined data from 2 experiments.

Example 7 Effect of 01519g Fab PEG in cynomolgus monkey

This was a study of the effect of the administration of 01519g Fab PEG in cynomolgus monkeys, in single, intermittent or repeated dosing regimens. 01519g Fab PEG was administered by intravenous infusion, as a single dose or in repeat doses to groups of four cynomolgus monkeys as indicated in Table 7. Plasma IgG and the pharmacokinetics of the 01519g Fab PEG were monitored by immunoassay (see Table 7A for immunoassay methods) and LC-MS/MS. Assay of plasma albumin was conducted at Covance.

Table 7 Dose groups in study NCD2241. Dosing was by intravenous infusion. The redose was the same as the first dose in each case. Repeat doses (4 of) were weekly.

Phase	Group	Antibody	Dose (mg/kg)	Dosing Regimen	Comments
I	1	Control	0	Single Dose	Redose at 67 days
	2	Fab PEG	20	Single Dose	Redose at 67 days
	3	Fab PEG	100	Single Dose	Redose at 67 days
II	4	Control	0	Repeat Dose	
	5	Fab PEG	20	Repeat Dose	
	6	Fab PEG	100	Repeat Dose	

Table 7A Plasma IgG, PK and ADA immunoassay methods

Assay type	Immunoassay	Method
PD	Total plasma IgG	1) Coat immunoassay plate with F(ab')$_2$ goat anti-human Fcγ 2) Incubate with sample. 3) Reveal with horseradish peroxidase conjugated F(ab')$_2$, goat anti-human IgG F(ab')$_2$ & the addition of TMB substrate.
PK	Fab PEG PK	1) Coat immunoassay plate with FcRn. 2) Incubate with sample. 3) Reveal with biotin conjugated murine IgG1 anti-PEG /.Streptavidin-horseradish peroxidase conjugate & the addition of TMB substrate alternatively reveal with MSD sulfo-tagged goat anti-human kappa & the addition of MSD read buffer

Effect on plasma IgG concentration

Immunoassay and LC-MS/MS plasma IgG data were in good agreement. Plasma IgG was reduced by the administration of Fab PEG (see Fig 12 and Figure 14). For both Phase I dose groups, a single dose of Fab PEG reduced plasma IgG by approximately 70-80%, reaching a nadir at approximately 7 days and returning to pre-dosing levels by day 63. Redosing at day 67 achieved similar results.

For both Phase II dose groups, 4 weekly doses of the Fab PEG reduced plasma IgG by approximately 70-80%, again reaching a nadir at about 7 days after the first dose. The results are shown in Figure 13.

Example 8 Effect of CA170_01519.g57 Fab'PEGand CA170_01519.g57 IgG4P in cynomolgus monkeys

The effects of CA170_01519g.57 Fab'PEG and CA170_01519g.57 IgG4P on endogenous plasma IgG were determined in cynomolgus monkeys. Animals were dosed as indicated in Table 8, with 4 animals per treatment group. Plasma IgG and the pharmacokinetics of the anti-FcRn entities were monitored by immunoassay (see Table 8A for immunoassay methods) and LC-MS/MS.

Table 8 Treatment regimens in cynomolgus monkeys.

Anti-FcRn	Dose (mg/kg)	Dosing Regimen	Route	Figure
Fab'PEG	20	Day 0 & 65	i.v.	15
Fab'PEG	20	Every 3 days, day 0-27	i.v.	16
IgG4P	30	Day 0 & 63	i.v.	17
IgG4P	30 & 5	30mg/kg on day 0, 5mg/kg daily day 1-41	i.v.	18
Control	0	Daily day 0-41	i.v.	19

Table 8A Plasma IgG and PK immunoassay methods

Assay type	Immunoassay	Method
PD	Total plasma IgG	1) Coat immunoassay plate with F(ab')$_2$ Goat anti-human Fcγ. 2) Incubate with sample. 3) Reveal with horseradish peroxidase conjugated F(ab')$_2$, goat anti-human IgG F(ab')$_2$ and the addition of TMB substrate.
PK	Fab'PEG PK	1) Coat MSD streptavidin plate with biotinylated FcRn. 2) Incubate with sample. 3) Reveal with MSD sulfo-tagged goat anti-human kappa and the addition of MSD read buffer.

Effect on plasma IgG concentration.

Immunoassay and LC-MS/MS plasma IgG data were in good agreement. Plasma IgG was reduced by the administration of anti-FcRn Fab'PEG or anti-FcRn IgG4P (see Figures 15 and 16 and Figures 17 and 18 respectively; see Figure 19 for control). For both anti-FcRn entities, a single dose reduced plasma IgG by approximately 70-80%, reaching a nadir at approximately 7 days and returning to pre-dosing levels by day 62. Redosing at day 63 or day 65, as described achieved similar results.

Repeated dosing of anti-FcRn Fab'PEG or IgG4P reduced plasma IgG by approximately 60-80% and maintained the level of IgG for the duration of the dose period. Again, the nadir was reached at about 7 days after the first dose. The results are shown in Figure 16 and 18.

Example 9 Effect of CA170_01519.g57 Fab'PEG, CA170_01519.g57 IgG1, CA170_01519.g57 IgG4P, CA170_01519.g57 Fab'HSA, CA170_01519.g57 FabFv and CA170_01519.g57 Fab in hFcRn transgenic mice

The effect of various different formats of antibody CA170_01519.g57 on the clearance of human IVIG was determined in human FcRn transgenic mice. The formats tested were CA170_01519.g57 Fab'PEG, CA170_01519.g57 IgG1, CA170_01519.g57 IgG4P, CA170_01519.g57 Fab'HSA, CA170_01519.g57 FabFv and CA170_01519.g57 Fab and the results and are shown in Figures 20, 21, 22, 23 and 24 respectively. The single doses of active compound were as shown in the Figures. In order to detect their effects on the clearance of human IgG (IVIG), the mice were injected with 500mg/kg human IVIG which was quantified by LCMSMS in serial plasma samples withdrawn from the tails of the mice at intervals. Blocking of hFcRn by each of the different antibody formats tested resulted in accelerated clearance of hIVIG and lower concentrations of total IgG were observed compared to control mice.

Anti-FcRn treatment enhances the clearance of hIgG in hFcRn transgenic mice

Humanised FcRn transgenic mice (B6.Cg-*Fcgrt*^{tm1Dcr} Tg(FCGRT)32Dcr/DcrJ, JAX Mice) were infused intravenously with 500mg/kg human IgG (Human IgI 10% Gamunex-c, Talecris Biotherapeutics). 24 hours later animals were dosed with vehicle control (PBS) or anti-FcRn intravenously as a single dose. Tail tip blood samples were taken at -24, 8, 24, 48, 72, 144 and 192 hours relative to anti-FcRn treatment. Serum levels of human IgG in the hFcRn mouse and

the pharmacokinetics of FcRn inhibitors were determined by LC-MS/MS. Data presented in figures 20 to 24 are mean ± SEM with 3-6 mice per treatment group.

Quantification of human IgG, endogenous cynomolgus IgG and FcRn inhibitors by LC-MS/MS

Human IgG, cynomolgus IgG and FcRn inhibitors (1519.g57 Fab'PEG, 1519.g57 IgG4P, 1519.g57 IgG1, 1519.g57 FabFv, 1519.g57 Fab and 1519.g57 Fab'HAS) were quantified using liquid chromatography tandem mass spectrometry (LC-MS/MS) analysis following tryptic digestion.

Quantitation was achieved by comparison to authentic standard material spiked at known concentrations into blank matrix, with spiked horse myoglobin used as the internal standard. Unique ("proteotypic") peptides for all analytes of interest investigated were selected and both samples and calibration samples were tryptically digested as outlined below.

In brief, tryptic digest of 5 µl serum samples was performed overnight using Sequencing Grade Modified Trypsin (Promega, Southampton, UK) following denaturation with acetonitrile / tris (2-carboxyethyl) phosphine and carbamido-methylation with iodoacetamide (all from Sigma-Aldrich, Poole, UK).

Analytes were separated using an Onyx Monolithic C18 column (100x4.6 mm, Phenomenex, Macclesfield, UK) with a gradient of 2 to 95 % (v/v) water/acetonitrile (0.1 % formic acid) delivered at 1.5 mL/min over 6 minutes.

The injection volume was 10 µL; all of the eluent was introduced into the mass spectrometer source.

The source temperature of the mass spectrometer was maintained at 600 °C and other source parameters (e.g. collision energy, declustering potential, curtain gas pressure etc.) were optimized to achieve maximum sensitivity for each peptides of interest. Selective transitions for each proteotypic peptide of interest were monitored.

Example 10: Crystallography and binding epitope.

The crystal structure of 1519g57 Fab' and deglycosylated human FcRn extracellular domain (alpha chain extracellular domain (SEQ ID NO:94) in association with beta2 microglobulin SEQ ID NO:95) was determined, with the FcRn oligsaccharide excluded in order to facilitate crystallization. 1519.g57 Fab' was reacted with 10-fold molar excess of N-ethyl maleimide to prevent formation of diFab' and any existing diFab' removed by SEC (S200 on Akta FPLC). Human FcRn extracellular domain was treated by PNGaseF to remove N-linked sugars. For this, the FcRn sample concentration was adjusted using PBS (pH7.4) to 5mg/ml and a total volume of 1ml. 200 units of PNGaseF (Roche) was added to this solution of human FcRn. This was incubated at 37°C for ~18 hours, following which the extent of deglycosylation was checked using SDS PAGE. Upon completion of the reaction the deglycosylated FcRn was buffer exchanged into 50mM Sodium Acetate, 125mM NaCl, pH6.0.

The complex was formed by incubation of a mixture of reagents (Fab':FcRn::1.2:1, w/w) at room temperature for 60minutes, and then purified using SEC (S200 using Akta FPLC). Screening was performed using the various conditions that were available from Qiagen (approximately 2000 conditions). The incubation and imaging was performed by Formulatrix

Rock Imager 1000 (for a total incubation period of 21 days). The result of screening is shown in Tables 9, 10 and 11.

Table 9 The result of crystallisation screening, showing the crystal used for X-ray analysis.

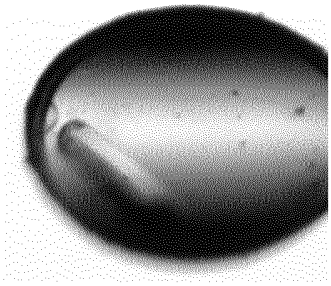
Crystallization experiment type	Sitting drop, vapour diffusion		
Crystallization condition	0.1M Sodium citrate pH 5.5, 11%PEG6000		
Protein concentration	10mg/ml	Drop volume/ratio	0.4ul Protein + 0.4ul Reservoir
Crystal growth time	8-21 days		
Cryoprotection	Crystals were harvested from the drop, transferred to cryoprotection buffer (70% reservoir + 30% ethylene glycol) and flash-frozen in liquid nitrogen (-180°C) within 10 seconds.		
Comments	 Picture of crystal in drop		Pictures of crystal frozen in the loop (red square is X-ray beam)

Table 10. Conditions for collection and processing of X-ray analysis data.

X-ray source	Diamond Light Source, Beamline I04				
Experiment Type	Single-wavelength		Wavelength	0.9795Å	
Processing Software	Mosflm/Scala				
Resolution Limits	35.00 – 2.90		Space group	$P3_2\,2\,1$	
Unit Cell parameters	a = 150.10 Å		b = 150.10 Å	c = 89.15 Å	
	α = 90.00 °		β = 90.00 °	γ = 120.00 °	
Completeness	99.9% (100.0%)		Multiplicity	6.7 (6.8)	
$I/\sigma(I)$	13.4 (4.8)		R_{merge}	9.2% (36.3%)	

Number of reflections	172724 (25602)	Number of unique reflections	25967 (3760)
Comments			

Note: Numbers in parenthesis refer to the outer resolution shell

Table 11 Structure determination and refinement.

Structure determination method	Molecular Replacement	Program(s) used	Phaser
Structure template	Structure FcRn receptor from PDB 3M17 and previously solved Fab-3DVN		
Refinement program	Refmac5	Resolution limits	30.00-2.9
R factor	23.2%	Free *R* factor	28.4%
Number of non-hydrogen atoms		- 6125 protein atoms - 2 Acetate ions (4 atoms each) - 27 waters in AU - 2 Cl^- ions - 2 Na^+ ions	
RMSD bond length	0.009Å	RMSD bond angle	1.338°
Ramachandran allowed	98.6%	Ramachandran outliers	1.4%
Comments	Rebuilt using CCP4/Coot.		

There was no obvious change in FcRn structure upon binding of 1519g57 Fab' (comparing this complex with published structures of FcRn). From the crystal structure it the secondary structure content was calculated to be: α-helix 9.4%; β-sheet 45.2%; 3-10 turn 2.5%.

The residues interacting with 1519g57 Fab'were all in the FcRn α chain (not β2M) and are indicated below in bold. The residues concerned encompass all but 1 of the residues critical for binding Fc. 1519g57 binds in a region that overlays the Fc-binding region, suggesting that blockade of FcRn by 1519g57 Fab' is by simple competition, the anti-FcRn being effective by virtue of its superior affinity.

AESHLSLLYH LTAVSSPAPG TPAFWVSGWL GPQQYLSYNS LRGEAEPCGA WVWENQVSWY WEKETTDLRI KEKLFLEAFK ALGGKGPYTL QGLLGCELG**P** DNTS**VPTAK**F ALNG**EEFMNF DLKQ**GTW**GGD WPE**ALAISQR WQQQDKAANK ELTFLLFSCP HRLREHLERG RGNLEWKEPP SMRLKARPSS PGFSVLTCSA FSFYPPELQL RFLRNGLAAG TGQGDFGPNS DGSFHASSSL TVKSGDEHHY CCIVQHAGLA QPLRVELESPAKSS

The FcRn α chain sequence, showing residues involved in interaction with 1519g57 Fab' (bold) and residues critical for interaction with Fc of IgG (underlined). All but 1 of the latter are included in the former.

Claims:

1. An anti-FcRn antibody or binding fragment thereof comprising a heavy chain or heavy chain fragment having a variable region, wherein said variable region comprises one, two or three CDRs independently selected from SEQ ID NO: 1, SEQ ID NO: 2 and SEQ ID NO: 3.
2. An anti-FcRn antibody or binding fragment thereof according to claim 1, wherein CDR H1 has the sequence given in SEQ ID NO: 1.
3. An anti-FcRn antibody or binding fragment thereof according to claim 1 or 2, wherein CDR H2 has the sequence given in SEQ ID NO: 2.
4. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 3, wherein CDR H3 has the sequence given in SEQ ID NO: 3.
5. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 4, wherein the antibody or binding fragment further comprises a light chain or fragment thereof having a variable region comprising one, two or three CDRs independently selected from SEQ ID NO: 4, SEQ ID NO: 5 and SEQ ID NO: 6.
6. An anti-FcRn antibody or binding fragment thereof according to claim 5, wherein CDR L1 has the sequence given in SEQ ID NO: 4.
7. An anti-FcRn antibody or binding fragment thereof according to claim 5 or 6, wherein CDR L2 has the sequence given in SEQ ID NO: 5.
8. An anti-FcRn antibody or binding fragment thereof according to any one of claims 5 to 7, wherein CDR L3 has the sequence given in SEQ ID NO: 6.
9. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 8, wherein the antibody is humanized.
10. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 9 having a heavy chain comprising the sequence given in SEQ ID NO:29 and a light chain comprising the sequence given in SEQ ID NO:15.
11. An anti-FcRn antibody or binding fragment thereof which binds human FcRn comprising a heavy chain, wherein the variable domain of the heavy chain comprises a sequence having at least 80% identity or similarity to the sequence given in SEQ ID NO:29 and wherein the variable domain of the light chain comprises a sequence having at least 80% identity or similarity to the sequence given in SEQ ID NO:15.
12. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 11, wherein the antibody is a scFv, Fv, Fab or Fab'fragment.
13. An anti-FcRn antibody Fab' fragment according to claim 12 having a heavy chain comprising the sequence given in SEQ ID NO:36 and a light chain comprising the sequence given in SEQ ID NO:22.
14. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 13, wherein the antibody or binding fragment is conjugated to a polymer for example selected from starch, albumin and polyethylene glycol.
15. An anti-FcRn antibody or binding fragment thereof according to claim 14, wherein the polymer is PEG, for example with a molecular weight in the range 5 to 50kDa.

16. An anti-FcRn antibody according to any one of claims 1 to 11, wherein the antibody is a full length antibody.
17. An anti-FcRn antibody according to claim 16 wherein the full length antibody is selected from the group consisting of an IgG1, IgG4 and IgG4P.
18. An anti-FcRn antibody according to claim 16 or claim 17 having a heavy chain comprising the sequence given in SEQ ID NO:72 or SEQ ID NO:87 or SEQ ID NO:43 and a light chain comprising the sequence given in SEQ ID NO:22.
19. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 11 wherein the antibody or binding fragment thereof is a Fab-dsFv having a heavy chain comprising the sequence given in SEQ ID NO:50 and a light chain comprising the sequence given in SEQ ID NO:46 or SEQ ID NO:78.
20. An anti-FcRn antibody or binding fragment thereof having a binding affinity for human FcRn of 100pM or less.
21. An anti-FcRn antibody or binding fragment thereof according to claim 20 wherein the binding affinity for human FcRn is 100pM or less when measured at pH6 and at pH7.4.
22. An anti-FcRn antibody or binding fragment thereof which binds to the same epitope of human FcRn as the antibody of claim 10.
23. An anti-FcRn antibody or binding fragment thereof which binds an epitope of human FcRn which comprises at least one amino acid selected from the group consisting of residues V105, P106, T107, A108 and K109 of SEQ ID NO:94 and at least one residue selected from the group consisting of P100, E115, E116, F117, M118, N119, F120, D121, L122, K123, Q124, G128, G129, D130, W131, P132 and E133 of SEQ ID NO:94.
24. An anti-FcRn antibody or binding fragment thereof which cross-blocks the binding of the antibody of claim 10 to human FcRn or is cross-blocked from binding human FcRn by the antibody of claim 10.
25. An anti-FcRn antibody or binding fragment thereof according to any one of claims 20 to 24 which is humanized or fully human.
26. An anti-FcRn antibody or binding fragment thereof according to any one of claims 22 to 25 which has a binding affinity for human FcRn of 100pM or less.
27. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 26 which binds human FcRn.
28. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 27 which blocks binding of human IgG to human FcRn.
29. An anti-FcRn antibody or binding fragment thereof according to any one of claims 1 to 28 which does not bind β2 microglobulin.
30. An assay for testing the ability of a test molecule such as an antibody molecule to block human FcRn activity and in particular the ability of human FcRn to recycle IgG, wherein the method comprises the steps of:
    a. coating onto a surface non-human mammalian cells recombinantly expressing human FcRn alpha chain and human β2 microglobulin (β2M),

b. contacting the cells under mildly acidic conditions such as about pH5.9 with a test antibody molecule and an IgG to be recycled by the cell for a period of time sufficient to allow binding of both the test antibody molecule and IgG to FcRn,
c. washing with a slightly acidic buffer, and
d. detecting the amount of IgG internalised and/or recycled by the cells.

31. The assay according to claim 30 wherein the the test antibody molecule is added before the IgG to be recycled and incubated for a period of time sufficient to allow binding of the test antibody molecule to FcRn before addition of the IgG to be recycled.
32. An isolated DNA sequence encoding the heavy and/or light chain(s) of an antibody according to any one of claims 1 to 29.
33. A cloning or expression vector comprising one or more DNA sequences according to claim 32.
34. A vector according to claim 33, wherein the vector comprises (i) the sequence given in SEQ ID NO:37 and the sequence given in SEQ ID NO:23 or (ii) the sequence given in SEQ ID NO:80 and the sequence given in SEQ ID NO:79 or (iii) the sequence given in SEQ ID NO:93 and the sequence given in SEQ ID NO:91.
35. A host cell comprising one or more cloning or expression vectors according to claim 33 or claim 34.
36. A process for the production of an antibody having binding specificity for human FcRn, comprising culturing the host cell of claim 35 and isolating the antibody.
37. A pharmaceutical composition comprising an anti-FcRn antibody or binding fragment thereof as defined in any one of claims 1 to 29 in combination with one or more of a pharmaceutically acceptable excipient, diluent or carrier.
38. A pharmaceutical composition according to claim 37, additionally comprising other active ingredients.
39. An antibody or binding fragment thereof as defined one in any one of claims 1 to 29 or a composition as defined in claim 37 or 38 for use in therapy.
40. An antibody or binding fragment thereof as defined in any one of claims 1 to 29 or a composition as defined in claim 37 or 38, for use in the treatment of an autoimmune disease, such as myasthenia gravis, Pemphigus vulgaris, Neuromyelitis optica, Guillain-Barré syndrome, lupus, and thrombotic thrombocytopenic purpura.
41. A method of treating a patient comprising administering a therapeutically effective amount of an antibody or binding fragment thereof as defined in any one of claims 1 to 29 or a composition as defined in claim 37 or claim 38.
42. A method according to claim 41, wherein the treatment is for an autoimmune disease such as myasthenia gravis, Pemphigus vulgaris, Neuromyelitis optica, Guillain-Barré syndrome, lupus, and thrombotic thrombocytopenic purpura.

FIGURE 1

CA170_1519 Ab sequences

CDRH1

GFTFSNYGMV SEQ ID NO: 1

CDRH2

YIDSDGDNTYYRDSVKG SEQ ID NO: 2

CDRH3

GIVRPFLY SEQ ID NO: 3

CDRL1

KSSQSLVGASGKTYLY SEQ ID NO: 4

CDRL2

LVSTLDS SEQ ID NO: 5

CDRL3

LQGTHFPHT SEQ ID NO: 6

Rat Ab 1519 VL region SEQ ID NO: 7

DVVMTQTPLS LSVALGQPAS ISCKSSQSLV GASGKTYLYW LFQRSGQSPK RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP HTFGAGTKLE LK

Rat Ab 1519 VL region SEQ ID NO: 8

gatgttgtga tgacccagac tccactgtct ttgtcggttg cccttggaca accagcctcc atctcttgca agtcaagtca gagcctcgta ggtgctagtg gaaagacata tttgtattgg ttatttcaga ggtccggcca gtctccaaag cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct cacacgtttg gagctgggac caagctggaa ttgaaa

Rat Ab 1519 VL region with signal sequence underlined and italicised SEQ ID NO: 9

MMSPAQFLFL LMLWIQGTSG DVVMTQTPLS LSVALGQPAS ISCKSSQSLV GASGKTYLYW LFQRSGQSPK RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP HTFGAGTKLE LK

FIGURE 1A

Rat Ab 1519 VL region with signal sequence underlined and italicised SEQ ID NO: 10

atgatgagtc ctgcccagtt cctgtttctg ctgatgctct ggattcaggg aaccagtggt gatgttgtga tgacccagac tccactgtct ttgtcggttg ccccttggaca accagcctcc atctcttgca agtcaagtca gagcctcgta ggtgctagtg gaaagacata tttgtattgg ttatttcaga ggtccggcca gtctccaaag cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct cacacgtttg gagctgggac caagctggaa ttgaaa

Rat Ab 1519 VH region SEQ ID NO: 11

EVPLVESGGG SVQPGRSMKL SCVVSGFTFS NYGMVWVRQA PKKGLEWVAY IDSDGDNTYY RDSVKGRFTI SRNNAKSTLY LQMDSLRSED TATYYCTTGI VRPFLYWGQG TTVTVS

Rat Ab 1519 VH region SEQ ID NO: 12

gaggtgccgc tggtggagtc tgggggcggc tcagtgcagc ctgggaggtc catgaaactc tcctgtgtag tctcaggatt cactttcagt aattatggca tggtctgggt ccgccaggct ccaaagaagg gtctggagtg ggtcgcatat attgattctg atggtgataa tacttactac cgagattccg tgaagggccg attcactatc tccagaaata atgcaaaaag cacctatat ttgcaaatgg acagtctgag gtctgaggac acggccactt attactgtac aacagggatt gtccggccct ttctctattg gggccaagga accacggtca ccgtctcg

Rat Ab 1519 VH region with signal sequence underlined and italicised SEQ ID NO: 13

*MDISLSLAFL VLFIKGVRC*E VPLVESGGGS VQPGRSMKLS CVVSGFTFSN YGMVWVRQAP KKGLEWVAYI DSDGDNTYYR DSVKGRFTIS RNNAKSTLYL QMDSLRSEDT ATYYCTTGIV RPFLYWGQGT TVTVS

Rat Ab 1519 VH region with signal sequence underlined and italicised SEQ ID NO: 14

*atggacatca gtctcagctt ggctttcctt gtccttttca taaaaggtgt ccggtgt*gag gtgccgctgg tggagtctgg gggcggctca gtgcagcctg ggaggtccat gaaactctcc tgtgtagtct caggattcac tttcagtaat tatggcatgg tctgggtccg ccaggctcca aagaagggtc tggagtgggt cgcatatatt gattctgatg gtgataatac ttactaccga gattccgtga agggccgatt cactatctcc agaaataatg caaaaagcac cctatatttg caaatggaca gtctgaggtc tgaggacacg gccacttatt actgtacaac agggattgtc cggcctttc tctattgggg ccaaggaacc acggtcaccg tctcg

FIGURE 1B

1519 gL20 V-region SEQ ID NO: 15
DIQMTQSPSS LSASVGDRVT ITCKSSQSLV GASGKTYLYW LFQKPGKAPK
RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI SSLQPEDFAT YYCLQGTHFP
HTFGQGTKLE IK

1519 gL20 V-region (*E. coli* expression) SEQ ID NO: 16
gatatccaga tgacccagag tccaagcagt ctctccgcca gcgtaggcga
tcgtgtgact attacctgta aaagctccca gtccctggtg ggtgcaagcg
gcaaaaccta cctgtactgg ctcttccaga aaccgggcaa agctccgaaa
cgcctgatct atctggtgtc taccctggat agcggtattc cgtctcgttt
ctccggtagc ggtagcggta ccgaattcac gctgaccatt agctccctcc
agccggagga ctttgctacc tattactgcc tccagggcac tcattttccg
cacactttcg gccagggtac caaactggaa atcaaa

1519 gL20 V-region (mammalian expression) SEQ ID NO: 17
gatatccaga tgacccagag cccatctagc ttatccgctt ccgttggtga
tcgcgtgaca attacgtgta agagctccca atctctcgtg ggtgcaagtg
gcaagaccta tctgtactgg ctctttcaga agcctggcaa ggcaccaaaa
cggctgatct atctggtgtc taccttgac tctgggatac cgtcacgatt
ttccggatct gggagcggaa ctgagttcac actcacgatt tcatcgctgc
aacccgagga ctttgctacc tactactgcc tgcaaggcac tcatttccct
cacactttcg gccaggggac aaaactcgaa atcaaa

1519 gL20 V-region with signal sequence underlined and italicized (*E. coli* expression) SEQ ID NO: 18
*MKKTAIAIAV ALAGFATVAQ A*DIQMTQSPS SLSASVGDRV TITCKSSQSL
VGASGKTYLY WLFQKPGKAP KRLIYLVSTL DSGIPSRFSG SGSGTEFTLT
ISSLQPEDFA TYYCLQGTHF PHTFGQGTKL EIK

1519 gL20 V-region with signal sequence underlined and italicized (*E. coli* expression) SEQ ID NO: 19
atgaaaaaga cagctatcgc aattgcagtg gccttggctg gtttcgctac
*cgtagcgcaa gct*gatatcc agatgaccca gagtccaagc agtctctccg
ccagcgtagg cgatcgtgtg actattacct gtaaaagctc ccagtccctg
gtgggtgcaa gcggcaaaac ctacctgtac tggctcttcc agaaaccggg
caaagctccg aaacgcctga tctatctggt gtctaccctg gatagcggta
ttccgtctcg tttctccggt agcggtagcg gtaccgaatt cacgctgacc
attagctccc tccagccgga ggactttgct acctattact gcctccaggg
cactcatttt ccgcacactt tcggccaggg taccaaactg gaaatcaaa

FIGURE 1C

1519 gL20 V-region with signal sequence underlined and italicized (mammalian expression)
SEQ ID NO: 20
MSVPTQVLGL LLLWLTDARC DIQMTQSPSS LSASVGDRVT ITCKSSQSLV
GASGKTYLYW LFQKPGKAPK RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI
SSLQPEDFAT YYCLQGTHFP HTFGQGTKLE IK

1519 gL20 V-region with signal sequence underlined and italicized (mammalian expression)
SEQ ID NO: 21
atgtctgtcc ccacccaagt cctcggactc ctgctactct ggcttacaga
tgccagatgc gatatccaga tgacccagag cccatctagc ttatccgctt
ccgttggtga tcgcgtgaca attacgtgta agagctccca atctctcgtg
ggtgcaagtg gcaagaccta tctgtactgg ctctttcaga agcctggcaa
ggcaccaaaa cggctgatct atctggtgtc tacccttgac tctgggatac
cgtcacgatt ttccggatct gggagcggaa ctgagttcac actcacgatt
tcatcgctgc aacccgagga ctttgctacc tactactgcc tgcaaggcac
tcatttccct cacactttcg gccaggggac aaaactcgaa atcaaa

1519 gL20 light chain (V + constant) SEQ ID NO: 22
DIQMTQSPSS LSASVGDRVT ITCKSSQSLV GASGKTYLYW LFQKPGKAPK
RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI SSLQPEDFAT YYCLQGTHFP
HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

1519 gL20 light chain (V + constant, *E. coli* expression) SEQ ID NO: 23
gatatccaga tgacccagag tccaagcagt ctctccgcca gcgtaggcga
tcgtgtgact attacctgta aaagctccca gtccctggtg ggtgcaagcg
gcaaaaccta cctgtactgg ctcttccaga aaccgggcaa agctccgaaa
cgcctgatct atctggtgtc taccctggat agcggtattc cgtctcgttt
ctccggtagc ggtagcggta ccgaattcac gctgaccatt agctccctcc
agccggagga ctttgctacc tattactgcc tccagggcac tcattttccg
cacactttcg gccagggtac caaactggaa atcaaacgta cggtagcggc
cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa
gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag
tgtcacagag caggacagca aggacagcac ctacagcctc agcagcaccc
tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
gtcacccatc agggcctgag ctcaccagta acaaaaagtt ttaatagagg ggagtgt

FIGURE 1D

1519 gL20 light chain (V + constant, mammalian expression) SEQ ID NO: 24

gatatccaga tgacccagag tccaagcagt ctctccgcca gcgtaggcga
tcgtgtgact attacctgta aaagctccca gtccctggtg ggtgcaagcg
gcaaaaccta cctgtactgg ctcttccaga aaccgggcaa agctccgaaa
cgcctgatct atctggtgtc taccctggat agcggtattc cgtctcgttt
ctccggtagc ggtagcggta ccgaattcac gctgaccatt agctccctcc
agccggagga ctttgctacc tattactgcc tccagggcac tcattttccg
cacactttcg gccagggtac caaactggaa atcaaacgta cggtagcggc
cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa
gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag
tgtcacagag caggacagca aggacagcac ctacagcctc agcagcaccc
tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt

1519 gL20 light chain with signal sequence underlined and italicized (*E. coli* expression)
SEQ ID NO: 25

*MKKTAIAIAV ALAGFATVAQ A*DIQMTQSPS SLSASVGDRV TITCKSSQSL
VGASGKTYLY WLFQKPGKAP KRLIYLVSTL DSGIPSRFSG SGSGTEFTLT
ISSLQPEDFA TYYCLQGTHF PHTFGQGTKL EIKRTVAAPS VFIFPPSDEQ
LKSGTASVVC LLNNFYPREA KVQWKVDNAL QSGNSQESVT EQDSKDSTYS
LSSTLTLSKA DYEKHKVYAC EVTHQGLSSP VTKSFNRGEC

1519 gL20 light chain with signal sequence underlined and italicized (*E. coli* expression)
SEQ ID NO: 26

atgaaaaaga cagctatcgc aattgcagtg gccttggctg gtttcgctac
*cgtagcgcaa gct*gatatcc agatgaccca gagtccaagc agtctctccg
ccagcgtagg cgatcgtgtg actattacct gtaaaagctc ccagtccctg
gtgggtgcaa gcggcaaaac ctacctgtac tggctcttcc agaaaccggg
caaagctccg aaacgcctga tctatctggt gtctaccctg gatagcggta
ttccgtctcg tttctccggt agcggtagcg gtaccgaatt cacgctgacc
attagctccc tccagccgga ggactttgct acctattact gcctccaggg
cactcatttt ccgcacactt tcggccaggg taccaaactg gaaatcaaac
gtacggtagc ggccccatct gtcttcatct tcccgccatc tgatgagcag
ttgaaatctg gaactgcctc tgttgtgtgc ctgctgaata acttctatcc
cagagaggcc aaagtacagt ggaaggtgga taacgccctc caatcgggta
actcccagga gagtgtcaca gagcaggaca gcaaggacag cacctacagc
ctcagcagca ccctgacgct gagcaaagca gactacgaga aacacaaagt
ctacgcctgc gaagtcaccc atcagggcct gagctcacca gtaacaaaaa
gttttaatag aggggagtgt

FIGURE 1E

1519 gL20 light chain with signal sequence underlined and italicized (mammalian expression) SEQ ID NO: 27

MSVPTQVLGL LLLWLTDARC DIQMTQSPSS LSASVGDRVT ITCKSSQSLV
GASGKTYLYW LFQKPGKAPK RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI
SSLQPEDFAT YYCLQGTHFP HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL
KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGEC

1519 gL20 light chain with signal sequence underlined and italicized (mammalian expression) SEQ ID NO: 28

atgtctgtcc ccacccaagt cctcggactc ctgctactct ggcttacaga tgccagatgc gatatccaga tgacccagag cccatctagc ttatccgctt
ccgttggtga tcgcgtgaca attacgtgta agagctccca atctctcgtg
ggtgcaagtg gcaagaccta tctgtactgg ctctttcaga agcctggcaa
ggcaccaaaa cggctgatct atctggtgtc tacccttgac tctgggatac
cgtcacgatt ttccggatct gggagcggaa ctgagttcac actcacgatt
tcatcgctgc aacccgagga ctttgctacc tactactgcc tgcaaggcac
tcatttccct cacactttcg gccaggggac aaaactcgaa atcaaacgta
cggtagcggc cccatctgtc ttcatcttcc cgccatctga tgagcagttg
aaatctggaa ctgcctctgt tgtgtgcctg ctgaataact tctatcccag
agaggccaaa gtacagtgga aggtggataa cgccctccaa tcgggtaact
cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc
agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta
cgcctgcgaa gtcacccatc agggcctgag ctcgcccgtc acaaagagct
tcaacagggg agagtgt

1519 gH20 V-region SEQ ID NO: 29

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI
VRPFLYWGQG TLVTVS

1519 gH20 V-region (*E. coli* expression) SEQ ID NO: 30

gaggttccgc tggtcgagtc tggaggcggg cttgtccagc ctggagggag
cctgcgtctc tcttgtgcag tatctggctt cacgttctcc aactacggta
tggtgtgggt tcgtcaggct ccaggtaaag gtctggaatg ggtggcgtat
attgactccg acggcgacaa cacctactat cgcgactctg tgaaaggtcg
cttcaccatt tcccgcgata acgccaaatc cagcctgtac ctgcagatga
acagcctgcg tgctgaagat actgcggtgt actattgcac cactggcatc
gtgcgtccgt ttctgtattg gggtcagggt accctcgtta ctgtctcg

FIGURE 1F (signal sequences underlined and italicized)

1519 gH20 V-region (mammalian expression) SEQ ID NO: 31
gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcg

1519 gH20 V-region (*E. coli* expression) SEQ ID NO: 32
*MKKTAIAIAV ALAGFATVAQ A*EVPLVESGG GLVQPGGSLR LSCAVSGFTF
SNYGMVWVRQ APGKGLEWVA YIDSDGDNTY YRDSVKGRFT ISRDNAKSSL
YLQMNSLRAE DTAVYYCTTG IVRPFLYWGQ GTLVTVS

1519 gH20 V-region (*E. coli* expression) SEQ ID NO: 33
atgaagaaga ctgctatagc aattgcagtg gcgctagctg gtttcgccac
*cgtggcgcaa gct*gaggttc cgctggtcga gtctggaggc gggcttgtcc
agcctggagg gagcctgcgt ctctcttgtg cagtatctgg cttcacgttc
tccaactacg gtatggtgtg ggttcgtcag gctccaggta aaggtctgga
atgggtggcg tatattgact ccgacggcga caacacctac tatcgcgact
ctgtgaaagg tcgcttcacc atttcccgcg ataacgccaa atccagcctg
tacctgcaga tgaacagcct gcgtgctgaa gatactgcgg tgtactattg
caccactggc atcgtgcgtc cgtttctgta ttggggtcag ggtaccctcg
ttactgtctc g

1519 gH20 V-region (mammalian expression) SEQ ID NO: 34
*MEWSWVFLFF LSVTTGVHS*E VPLVESGGGL VQPGGSLRLS CAVSGFTFSN
YGMVWVRQAP GKGLEWVAYI DSDGDNTYYR DSVKGRFTIS RDNAKSSLYL
QMNSLRAEDT AVYYCTTGIV RPFLYWGQGT LVTVS

1519 gH20 V-region with signal sequence underlined and italicized (mammalian expression)
SEQ ID NO: 35
atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt
*ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg
gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat
tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt
ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga
aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac
gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg tctcg

FIGURE 1G

1519gH20 Fab' heavy chain (V + human gamma-1 CH1 + hinge) SEQ ID NO: 36

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI
VRPFLYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC
NVNHKPSNTK VDKKVEPKSC DKTHTCAA

1519gH20 Fab' heavy chain (V + human gamma-1 CH1 + hinge, *E.coli* expression) SEQ ID NO: 37

gaggttccgc tggtcgagtc tggaggcggg cttgtccagc ctggagggag
cctgcgtctc tcttgtgcag tatctggctt cacgttctcc aactacggta
tggtgtgggt tcgtcaggct ccaggtaaag gtctggaatg ggtggcgtat
attgactccg acggcgacaa cacctactat cgcgactctg tgaaaggtcg
cttcaccatt tcccgcgata acgccaaatc cagcctgtac ctgcagatga
acagcctgcg tgctgaagat actgcggtgt actattgcac cactggcatc
gtgcgtccgt ttctgtattg gggtcagggt accctcgtta ctgtctcgag
cgcttctaca aagggcccat cggtcttccc cctggcaccc tcctccaaga
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtcgacaaga aagttgagcc
caaatcttgt gacaaaactc acacatgcgc cgcg

1519gH20 Fab' heavy chain (V + human gamma-1 CH1 + hinge, mammalian expression) SEQ ID NO: 38

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag
cgcttctaca aagggcccat cggtcttccc cctggcaccc tcctccaaga
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtcgacaaga aagttgagcc
caaatcttgt gacaaaactc acacatgcgc cgcg

FIGURE 1H

1519 gH20 Fab' heavy chain with signal sequence underlined and italicized (*E. coli* expression) SEQ ID NO: 39

*MKKTAIAIAV ALAGFATVAQ A*EVPLVESGG GLVQPGGSLR LSCAVSGFTF
SNYGMVWVRQ APGKGLEWVA YIDSDGDNTY YRDSVKGRFT ISRDNAKSSL
YLQMNSLRAE DTAVYYCTTG IVRPFLYWGQ GTLVTVSSAS TKGPSVFPLA
PSSKSTSGGT AALGCLVKDY FPEPVTVSWN SGALTSGVHT FPAVLQSSGL
YSLSSVVTVP SSSLGTQTYI CNVNHKPSNT KVDKKVEPKS CDKTHTCAA

1519 gH20 Fab' heavy chain with signal sequence underlined and italicized (*E. coli* expression) SEQ ID NO: 40

atgaagaaga ctgctatagc aattgcagtg gcgctagctg gtttcgccac
*cgtggcgcaa gct*gaggttc cgctggtcga gtctggaggc gggcttgtcc
agcctggagg gagcctgcgt ctctcttgtg cagtatctgg cttcacgttc
tccaactacg gtatggtgtg ggttcgtcag gctccaggta aaggtctgga
atgggtggcg tatattgact ccgacggcga caacacctac tatcgcgact
ctgtgaaagg tcgcttcacc atttcccgcg ataacgccaa atccagcctg
tacctgcaga tgaacagcct gcgtgctgaa gatactgcgg tgtactattg
caccactggc atcgtgcgtc cgtttctgta ttggggtcag ggtaccctcg
ttactgtctc gagcgcttct acaaagggcc catcggtctt ccccctggca
ccctcctcca agagcacctc tgggggcaca gcggccctgg gctgcctggt
caaggactac ttccccgaac cggtgacggt gtcgtggaac tcaggcgccc
tgaccagcgg cgtgcacacc ttcccggctg tcctacagtc ctcaggactc
tactccctca gcagcgtggt gaccgtgccc tccagcagct tgggcaccca
gacctacatc tgcaacgtga atcacaagcc cagcaacacc aaggtcgaca
agaaagttga gcccaaatct tgtgacaaaa ctcacacatg cgccgcg

1519 gH20 Fab' heavy chain with signal sequence underlined and italicized (mammalian expression) SEQ ID NO: 41

*MEWSWVFLFF LSVTTGVHS*E VPLVESGGGL VQPGGSLRLS CAVSGFTFSN
YGMVWVRQAP GKGLEWVAYI DSDGDNTYYR DSVKGRFTIS RDNAKSSLYL
QMNSLRAEDT AVYYCTTGIV RPFLYWGQGT LVTVSSASTK GPSVFPLAPS
SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCAA

FIGURE 1I

1519 gH20 Fab' heavy chain with signal sequence underlined and italicized (mammalian expression) SEQ ID NO: 42

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt
*ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg
gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat
tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt
ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga
aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac
gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg
tctcgagcgc ttctacaaag ggcccatcgg tcttcccccc ggcaccctcc
tccaagagca cctctggggg cacagcggcc ctgggctgcc tggtcaagga
ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc gccctgacca
gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta
catctgcaac gtgaatcaca agcccagcaa caccaaggtc gacaagaaag
ttgagcccaa atcttgtgac aaaactcaca catgcgccgc g

1519gH20 IgG4 heavy chain (V + human gamma-4P constant) SEQ ID NO: 43

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI
VRPFLYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC
NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI
SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV
SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP
SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS
FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK

FIGURE 1J

1519gH20 IgG4 heavy chain (V + human gamma-4P constant, exons underlined) SEQ ID NO: 44

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag
cgcttctaca aagggcccat ccgtcttccc cctggcgccc tgctccagga
gcacctccga gagcacagcc gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacgaagac ctacacctgc
aacgtagatc acaagcccag caacaccaag gtggacaaga gagttggtga
gaggccagca cagggaggga gggtgtctgc tggaagccag gctcagccct
cctgcctgga cgcaccccgg ctgtgcagcc ccagcccagg gcagcaaggc
atgccccatc tgtctcctca cccggaggcc tctgaccacc ccactcatgc
ccagggagag ggtcttctgg atttttccac caggctccgg gcagccacag
gctggatgcc cctaccccag gccctgcgca tacaggggca ggtgctgcgc
tcagacctgc caagagccat atccgggagg accctgcccc tgacctaagc
ccaccccaaa ggccaaactc tccactccct cagctcagac accttctctc
ctcccagatc tgagtaactc ccaatcttct ctctgcagag tccaaatatg
gtcccccatg cccaccatgc ccaggtaagc caacccaggc ctcgccctcc
agctcaaggc gggacaggtg ccctagagta gcctgcatcc agggacaggc
cccagccggg tgctgacgca tccacctcca tctcttcctc agcacctgag
ttcctggggg gaccatcagt cttcctgttc cccccaaaac ccaaggacac
tctcatgatc tcccggaccc ctgaggtcac gtgcgtggtg gtggacgtga
gccaggaaga ccccgaggtc cagttcaact ggtacgtgga tggcgtggag
gtgcataatg ccaagacaaa gccgcgggag gagcagttca acagcacgta
ccgtgtggtc agcgtcctca ccgtcctgca ccaggactgg ctgaacggca
aggagtacaa gtgcaaggtc tccaacaaag gcctcccgtc ctccatcgag
aaaaccatct ccaaagccaa aggtgggacc cacggggtgc gagggccaca
tggacagagg tcagctcggc ccaccctctg ccctgggagt gaccgctgtg
ccaacctctg tccctacagg gcagccccga gagccacagg tgtacaccct
gcccccatcc caggaggaga tgaccaagaa ccaggtcagc ctgacctgcc
tggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga
cggctccttc ttcctctaca gcaggctaac cgtggacaag agcaggtggc
aggaggggaa tgtcttctca tgctccgtga tgcatgaggc tctgcacaac
cactacacac agaagagcct ctccctgtct ctgggtaaa

FIGURE 1K

1519gH20 IgG4 heavy chain (V + human gamma-4P constant) with signal sequence underlined and italicised SEQ ID NO: 45

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt
*ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg
gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat
tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt
ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga
aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac
gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg
tctcgagcgc ttctacaaag ggcccatccg tcttcccccc ggcgccctgc
tccaggagca cctccgagag cacagccgcc ctgggctgcc tggtcaagga
ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc gccctgacca
gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cgaagaccta
cacctgcaac gtagatcaca agcccagcaa caccaaggtg gacaagagag
ttggtgagag gccagcacag ggagggaggg tgtctgctgg aagccaggct
cagccctcct gcctggacgc accccggctg tgcagcccca gcccagggca
gcaaggcatg ccccatctgt ctcctcaccc ggaggcctct gaccacccca
ctcatgccca gggagagggt cttctggatt tttccaccag gctccgggca
gccacaggct ggatgccccc accccaggcc ctgcgcatac aggggcaggt
gctgcgctca gacctgccaa gagccatatc cgggaggacc ctgcccctga
cctaagccca ccccaaaggc caaactctcc actccctcag ctcagacacc
ttctctcctc ccagatctga gtaactccca atcttctctc tgcagagtcc
aaatatggtc ccccatgccc accatgccca ggtaagccaa cccaggcctc
gccctccagc tcaaggcggg acaggtgccc tagagtagcc tgcatccagg
gacaggcccc agccgggtgc tgacgcatcc acctccatct cttcctcagc
acctgagttc ctgggggggac catcagtctt cctgttcccc ccaaaaccca
aggacactct catgatctcc cggacccctg aggtcacgtg cgtggtggtg
gacgtgagcc aggaagaccc cgaggtccag ttcaactggt acgtggatgg
cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagttcaaca
gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg
aacggcaagg agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc
catcgagaaa accatctcca aagccaaagg tgggacccac ggggtgcgag
ggccacatgg acagaggtca gctcggccca ccctctgccc tgggagtgac
cgctgtgcca acctctgtcc ctacagggca gccccgagag ccacaggtgt
acaccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga
gagcaatggg cagccggaga acaactacaa gaccacgcct cccgtgctgg
actccgacgg ctccttcttc ctctacagca ggctaaccgt ggacaagagc
aggtggcagg aggggaatgt cttctcatgc tccgtgatgc atgaggctct
gcacaaccac tacacacaga agagcctctc cctgtctctg ggtaaa

FIGURE 1L

1519gL20 FabFv light chain SEQ ID NO: 46

DIQMTQSPSS LSASVGDRVT ITCKSSQSLV GASGKTYLYW LFQKPGKAPK
RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI SSLQPEDFAT YYCLQGTHFP
HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGECS GGGGSGGGGS GGGGSDIQMT QSPSSVSASV
GDRVTITCQS SPSVWSNFLS WYQQKPGKAP KLLIYEASKL TSGVPSRFSG
SGSGTDFTLT ISSLQPEDFA TYYCGGGYSS ISDTTFGCGT KVEIKRT

1519gL20 FabFv light chain SEQ ID NO: 47

gatatccaga tgacccagag cccatctagc ttatccgctt ccgttggtga
tcgcgtgaca attacgtgta agagctccca atctctcgtg ggtgcaagtg
gcaagaccta tctgtactgg ctctttcaga agcctggcaa ggcaccaaaa
cggctgatct atctggtgtc taccttgac tctgggatac cgtcacgatt
ttccggatct gggagcggaa ctgagttcac actcacgatt tcatcgctgc
aacccgagga ctttgctacc tactactgcc tgcaaggcac tcatttccct
cacactttcg gccaggggac aaaactcgaa atcaaacgta cggtagcggc
cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa
gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag
tgtcacagag caggacagca aggacagcac ctacagcctg agcagcaccc
tgacgctgtc taaagcagac tacgagaaac acaaagtgta cgcctgcgaa
gtcacccatc agggcctgag ctcaccagta acaaaaagtt ttaatagagg
ggagtgtagc ggtggcggtg gcagtggtgg gggaggctcc ggaggtggcg
gttcagacat acaaatgacc cagagtcctt catcggtatc cgcgtccgtt
ggcgataggg tgactattac atgtcaaagc tctcctagcg tctggagcaa
ttttctatcc tggtatcaac agaaaccggg gaaggctcca aaacttctga
tttatgaagc ctcgaaactc accagtggag ttccgtcaag attcagtggc
tctggatcag ggacagactt cacgttgaca atcagttcgc tgcaaccaga
ggactttgcg acctactatt gtggtggagg ttacagtagc ataagtgata
cgacatttgg gtgcggtact aaggtggaaa tcaaacgtac c

1519gL20 FabFv light chain with signal sequence underlined & italicised SEQ ID NO: 48

MSVPTQVLGL LLLWLTDARC DIQMTQSPSS LSASVGDRVT ITCKSSQSLV
GASGKTYLYW LFQKPGKAPK RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI
SSLQPEDFAT YYCLQGTHFP HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL
KSGTASVVCL LNNFYPREAK VQWKVDNALQ SGNSQESVTE QDSKDSTYSL
SSTLTLSKAD YEKHKVYACE VTHQGLSSPV TKSFNRGECS GGGGSGGGGS
GGGGSDIQMT QSPSSVSASV GDRVTITCQS SPSVWSNFLS WYQQKPGKAP
KLLIYEASKL TSGVPSRFSG SGSGTDFTLT ISSLQPEDFA TYYCGGGYSS
ISDTTFGCGT KVEIKRT

FIGURE 1M

1519gL20 FabFv light chain with signal sequence underlined and italicised SEQ ID NO: 49

atgtctgtcc ccacccaagt cctcggactc ctgctactct ggcttacaga tgccagatgc gatatccaga tgacccagag cccatctagc ttatccgctt ccgttggtga tcgcgtgaca attacgtgta agagctccca atctctcgtg ggtgcaagtg gcaagaccta tctgtactgg ctctttcaga agcctggcaa ggcaccaaaa cggctgatct atctggtgtc tacccttgac tctgggatac cgtcacgatt ttccggatct gggagcggaa ctgagttcac actcacgatt tcatcgctgc aacccgagga ctttgctacc tactactgcc tgcaaggcac tcatttccct cacactttcg gccaggggac aaaactcgaa atcaaacgta cggtagcggc cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctg agcagcaccc tgacgctgtc taaagcagac tacgagaaac acaaagtgta cgcctgcgaa gtcacccatc agggcctgag ctcaccagta acaaaaagtt ttaatagagg ggagtgtagc ggtggcggtg gcagtggtgg gggaggctcc ggaggtggcg gttcagacat acaaatgacc cagagtcctt catcggtatc cgcgtccgtt ggcgataggg tgactattac atgtcaaagc tctcctagcg tctggagcaa ttttctatcc tggtatcaac agaaaccggg gaaggctcca aaacttctga tttatgaagc ctcgaaactc accagtggag ttccgtcaag attcagtggc tctggatcag ggacagactt cacgttgaca atcagttcgc tgcaaccaga ggactttgcg acctactatt gtggtggagg ttacagtagc ataagtgata cgacatttgg gtgcggtact aaggtggaaa tcaaacgtac c

1519gH20 FabFv heavy chain SEQ ID NO: 50

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI VRPFLYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC SGGGGSGGGG TGGGGSEVQL LESGGGLVQP GGSLRLSCAV SGIDLSNYAI NWVRQAPGKC LEWIGIIWAS GTTFYATWAK GRFTISRDNS KNTVYLQMNS LRAEDTAVYY CARTVPGYST APYFDLWGQG TLVTVSS

FIGURE 1N

1519gH20 FabFv heavy chain SEQ ID NO: 51

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag
cgcgtccaca aagggcccat cggtcttccc cctggcaccc tcctccaaga
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc
cccgaaccag tgacggtgtc gtggaactca ggtgccctga ccagcggcgt
tcacaccttc ccggctgtcc tacagtcttc aggactctac tccctgagca
gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtcgataaga aagttgagcc
caaatcttgt agtggaggtg ggggctcagg tggaggcggg accggtggag
gtggcagcga ggttcaactg cttgagtctg gaggaggcct agtccagcct
ggagggagcc tgcgtctctc ttgtgcagta agcggcatcg acctgagcaa
ttacgccatc aactgggtga gacaagctcc ggggaagtgt ttagaatgga
tcggtataat atgggccagt gggacgacct tttatgctac atgggcgaaa
ggaaggttta caattagccg ggacaatagc aaaaacaccg tgtatctcca
aatgaactcc ttgcgagcag aggacacggc ggtgtactat tgtgctcgca
ctgtcccagg ttatagcact gcaccctact tcgatctgtg gggacaaggg
accctggtga ctgtttcaag t

1519gH20 FabFv heavy chain with signal sequence underlined and italicised SEQ ID NO: 52

*MEWSWVFLFF LSVTTGVHS*E VPLVESGGGL VQPGGSLRLS CAVSGFTFSN
YGMVWVRQAP GKGLEWVAYI DSDGDNTYYR DSVKGRFTIS RDNAKSSLYL
QMNSLRAEDT AVYYCTTGIV RPFLYWGQGT LVTVSSASTK GPSVFPLAPS
SKSTSGGTAA LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS
LSSVVTVPSS SLGTQTYICN VNHKPSNTKV DKKVEPKSCS GGGGSGGGGT
GGGGSEVQLL ESGGGLVQPG GSLRLSCAVS GIDLSNYAIN WVRQAPGKCL
EWIGIIWASG TTFYATWAKG RFTISRDNSK NTVYLQMNSL RAEDTAVYYC
ARTVPGYSTA PYFDLWGQGT LVTVSS

FIGURE 1P

1519gH20 FabFv heavy chain with signal sequence underlined & italicised SEQ ID NO: 53

*atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg tctcgagcgc gtccacaaag ggcccatcgg tcttcccccc ggcaccctcc tccaagagca cctctggggg cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccagtga cggtgtcgtg gaactcaggt gccctgacca gcggcgttca caccttcccg gctgtcctac agtcttcagg actctactcc ctgagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac gtgaatcaca agcccagcaa caccaaggtc gataagaaag ttgagcccaa atcttgtagt ggaggtgggg gctcaggtgg aggcgggacc ggtggaggtg gcagcgaggt tcaactgctt gagtctggag gaggcctagt ccagcctgga gggagcctgc gtctctcttg tgcagtaagc ggcatcgacc tgagcaatta cgccatcaac tgggtgagac aagctccggg gaagtgttta gaatggatcg gtataatatg ggccagtggg acgacctttt atgctacatg ggcgaaagga aggtttacaa ttagccggga caatagcaaa aacaccgtgt atctccaaat gaactccttg cgagcagagg acacggcggt gtactattgt gctcgcactg tcccaggtta tagcactgca ccctacttcg atctgtgggg acaagggacc ctggtgactg tttcaagt

Human VK1 2-1-(1) A30 JK2 acceptor framework SEQ ID NO: 54

DIQMTQSPSS LSASVGDRVT ITCRASQGIR NDLGWYQQKP GKAPKRLIYA ASSLQSGVPS RFSGSGSGTE FTLTISSLQP EDFATYYCLQ HNSYPYTFGQ GTKLEIK

Human VK1 2-1-(1) A30 JK2 acceptor framework SEQ ID NO: 55

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca gggaaagccc ctaagcgcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct gaagattttg caacttatta ctgtctacag cataatagtt acccttacac ttttggccag gggaccaagc tggagatcaa a

FIGURE 1Q

Human VH3 1-3 3-07 JH4 acceptor framework SEQ ID NO: 56

EVQLVESGGG LVQPGGSLRL SCAASGFTFS SYWMSWVRQA PGKGLEWVAN
IKQDGSEKYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARYF
DYWGQGTLVT VS

Human VH3 1-3 3-07 JH4 acceptor framework SEQ ID NO: 57

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc
cctgagactc tcctgtgcag cctctggatt cacctttagt agctattgga
tgagctgggt ccgccaggct ccagggaagg ggctggagtg ggtggccaac
ataaagcaag atggaagtga gaaatactat gtggactctg tgaagggccg
attcaccatc tccagagaca acgccaagaa ctcactgtat ctgcaaatga
acagcctgag agccgaggac acggctgtgt attactgtgc gagatacttt
gactactggg gccagggaac cctggtcacc gtctcc

Rat Ab 1548 VL region SEQ ID NO: 58

DVVMTQTPLS LSVALGQPAS ISCKSSQSLV GASGKTYLYW LFQRSGQSPK
RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP
HTFGAGTKLE IK

Rat Ab 1548 VL region SEQ ID NO: 59

gatgttgtga tgacccagac tccactgtct ttgtcggttg cccttggaca
accagcctcc atctcttgca agtcaagtca gagcctcgta ggtgctagtg
gaaagacata tttgtattgg ttatttcaga ggtccggcca gtctccaaag
cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt
cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg
aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct
cacacgtttg gagctgggac caagctggaa ataaaa

Rat Ab 1548 VH region SEQ ID NO: 60

EVPLVESGGG SVQPGRSMKL SCVVSGFTFS NYGMVWVRQA PKKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRNNAKSTLY LQMDSLRSED TATYYCTTGI
VRPFLYWGQG VMVTVS

FIGURE 1R

Rat Ab 1548 VH region SEQ ID NO: 61

gaggtgccgc tggtggagtc tgggggcggc tcagtgcagc ctgggaggtc
catgaaactc tcctgtgtag tctcaggatt cactttcagt aattatggca
tggtctgggt ccgccaggct ccaaagaagg gtctggagtg ggtcgcatat
attgattctg atggtgataa tacttactac cgagattccg tgaagggccg
attcactatc tccagaaata atgcaaaaag caccctatat ttgcaaatgg
acagtctgag gtctgaggac acggccactt attactgtac aacagggatt
gtccggccct ttctctattg gggccaagga gtcatggtca cagtctcg

Rat Ab 1644 VL region SEQ ID NO: 62

DVVMTQTPLS LSVAIGQPAS ISCKSSQSLV GASGKTYLYW LFQRSGQSPK
RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP
HTFGAGTKLE LK

Rat Ab 1644 VL region SEQ ID NO: 63

gatgttgtga tgacccagac tccactgtct ttgtcggttg ccattggaca
accagcctcc atctcttgca agtcaagtca gagcctcgta ggtgctagtg
gaaagacata tttgtattgg ttatttcaga ggtccggcca gtctccaaag
cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt
cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg
aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct
cacacgtttg gagctgggac caagctggaa ctgaaa

Rat Ab 1644 VH region SEQ ID NO: 64

EVPLVESGGG SVQPGRSTKL SCVVSGFTFS NYGMVWVRQA PKKGLEWVAY
IGSDGDNIYY RDSVKGRFTI SRNNAKSTLY LQMDSLRSED TATYYCTTGI
VRPFLYWGQG TTVTVS

Rat Ab 1644 VH region SEQ ID NO: 65

gaggtgccgc tggtggagtc tgggggcggc tcagtgcagc ctgggaggtc
cacgaaactc tcctgtgtag tctcaggatt cactttcagt aactatggca
tggtctgggt ccgccaggct ccaaagaagg gtctggagtg ggtcgcatat
attggttctg atggtgataa tatttactac cgagattccg tgaagggtcg
attcactatc tccagaaata atgcaaaaag caccctatat ttgcaaatgg
acagtctgag gtctgaggac acggccactt attactgtac aacagggatt
gtccggccct ttctctactg gggccaagga accacggtca ccgtctcg

Figure 1S

Rat Ab 1496 VK region SEQ ID NO: 66

DVVMTQTPLS LSVALGQPAS ISCKSSQSLV GASGKTYLYW LFQRSGQSPK
RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP
HTFGAGTKLE LK

Rat Ab 1496 VK region SEQ ID NO: 67

gatgttgtga tgacccagac tccactgtct ttgtcggttg cccttggaca
accagcctcc atctcttgca agtcaagtca gagcctcgta ggtgctagtg
gaaagacata tttgtattgg ttatttcaga ggtccggcca gtctccaaag
cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt
cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg
aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct
cacacgtttg gagctgggac caagctggaa ctgaaa

Rat Ab 1496 VH region SEQ ID NO: 68

EVLLVESGGG SVQPGRSMKL SCVVSGFTFS NYGMVWVRQA PKKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRNNAKSTLY LQMDSLRSED TATYYCTTGI
VRPFLYWGQG TMVTVS

Rat Ab 1496 VH region SEQ ID NO: 69

gaggtgctgc tggtggagtc tgggggcggc tcagtgcagc ctgggaggtc
catgaaactc tcctgtgtag tctcaggatt cactttcagt aattatggca
tggtctgggt ccgccaggct ccaaagaagg gtctggagtg ggtcgcatat
attgattctg atggtgataa tacttactac cgagattccg tgaagggccg
attcactatc tccagaaata atgcaaaaag caccctatat ttgcaaatgg
acagtctgag gtctgaggac acggccactt attactgtac aacagggatt
gtccggccct ttctctattg gggccaagga accatggtca ccgtctcg

1519gH20 IgG1 heavy chain (V + human gamma-1 constant) SEQ ID NO:72

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY IDSDGDNTYY
RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI VRPFLYWGQG TLVTVSSAST
KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF PEPVTVSWNS GALTSGVHTF PAVLQSSGLY
SLSSVVTVPS SSLGTQTYIC NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV
FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK
NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG
NVFSCSVMHE ALHNHYTQKS LSLSPGK

Figure 1T

1519gH20 IgG1 heavy chain (V + human gamma-1 constant, exons underlined) SEQ ID NO:73

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag tttacgtctc
tcttgtgctg tgtctggctt caccttctcc aattacggaa tggtctgggt cagacaagca
cctggaaagg gtcttgaatg ggtggcctat attgactctg acggggacaa cacctactat
cgggattccg tgaaaggacg cttcacaatc tcccgagata acgccaagag ctcactgtac
ctgcagatga atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag cgcttctaca
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtcgacaaga aagttggtga gaggccagca
cagggaggga gggtgtctgc tggaagccag gctcagcgct cctgcctgga cgcatcccgg
ctatgcagcc ccagtccagg gcagcaaggc aggccccgtc tgcctcttca cccggaggcc
tctgcccgcc ccactcatgc tcagggagag ggtcttctgg ctttttcccc aggctctggg
caggcacagg ctaggtgccc ctaacccagg ccctgcacac aaaggggcag gtgctgggct
cagacctgcc aagagccata tccgggagga ccctgcccct gacctaagcc caccccaaag
gccaaactct ccactccctc agctcggaca ccttctctcc tcccagatct gagtaactcc
caatcttctc tctgcagagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc
aggtaagcca gcccaggcct cgccctccag ctcaaggcgg gacaggtgcc ctagagtagc
ctgcatccag ggacaggccc cagccgggtg ctgacacgtc cacctccatc tcttcctcag
cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc
tcatgatctc ccggacccct gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc
ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc aagacaaagc
cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc
aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc ctcccagccc
ccatcgagaa aaccatctcc aaagccaaag gtgggacccg tggggtgcga gggccacatg
gacagaggcc ggctcggccc accctctgcc ctgagagtga ccgctgtacc aacctctgtc
cctacagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggatgagctg
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag
aagagcctct ccctgtctcc gggtaaa

Figure 1U

1519gH20 IgG1 heavy chain (V + human gamma-1 constant) with signal sequence underlined and italicized SEQ ID NO:74

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt ccattctgag
gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg gaggaagttt acgtctctct
tgtgctgtgt ctggcttcac cttctccaat tacggaatgg tctgggtcag acaagcacct
ggaaagggtc ttgaatgggt ggcctatatt gactctgacg gggacaacac ctactatcgg
gattccgtga aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac gggaatcgtt
aggccttttc tgtactgggg acagggcacc ttggttactg tctcgagcgc ttctacaaag
ggcccatcgg tcttcccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc
ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc
gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac
gtgaatcaca agcccagcaa caccaaggtc gacaagaaag ttggtgagag gccagcacag
ggagggaggg tgtctgctgg aagccaggct cagcgctcct gcctggacgc atcccggcta
tgcagcccca gtccagggca gcaaggcagg ccccgtctgc ctcttcaccc ggaggcctct
gcccgcccca ctcatgctca gggagagggt cttctggctt tttccccagg ctctgggcag
gcacaggcta ggtgccccta acccaggccc tgcacacaaa ggggcaggtg ctgggctcag
acctgccaag agccatatcc gggaggaccc tgcccctgac ctaagcccac cccaaaggcc
aaactctcca ctccctcagc tcggacacct tctctcctcc cagatctgag taactcccaa
tcttctctct gcagagccca aatcttgtga caaaactcac acatgcccac cgtgcccagg
taagccagcc caggcctcgc cctccagctc aaggcgggac aggtgcccta gagtagcctg
catccaggga caggccccag ccgggtgctg acacgtccac ctccatctct tcctcagcac
ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag gacaccctca
tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac gaagaccctg
aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag acaaagccgc
gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg
actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagccccca
tcgagaaaac catctccaaa gccaaaggtg ggacccgtgg ggtgcgaggg ccacatggac
agaggccggc tcggcccacc ctctgccctg agagtgaccg ctgtaccaac ctctgtccct
acagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga tgagctgacc
aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg
gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag
gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
agcctctccc tgtctccgggtaaa

Figure 1V

1519 gL20 light chain (V + constant, mammalian expression alternative) SEQ ID NO: 75

gatatccaga tgacccagag cccatctagc ttatccgctt ccgttggtga
tcgcgtgaca attacgtgta agagctccca atctctcgtg ggtgcaagtg
gcaagaccta tctgtactgg ctctttcaga agcctggcaa ggcaccaaaa
cggctgatct atctggtgtc tacccttgac tctgggatac cgtcacgatt
ttccggatct gggagcggaa ctgagttcac actcacgatt tcatcgctgc
aacccgagga ctttgctacc tactactgcc tgcaaggcac tcatttccct
cacactttcg gccaggggac aaaactcgaa atcaaacgta cggtagcggc
cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa
gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag
tgtcacagag caggacagca aggacagcac ctacagcctc agcagcaccc
tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgt

1519gH20 Fab' heavy chain (V + human gamma-1 CH1 + hinge, mammalian expression one base change from SEQ ID NO: 38) SEQ ID NO: 76

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag
cgcttctaca aagggcccat cggtcttccc cctggcaccc tcctccaaga
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc
caaatcttgt gacaaaactc acacatgcgc cgcg

1519 gH20 Fab' heavy chain with signal sequence underlined and italicized (mammalian expression one base changed from SEQ ID NO: 42) SEQ ID NO: 77

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt
*ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg
gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat
tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt
ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga
aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac
gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg
tctcgagcgc ttctacaaag ggcccatcgg tcttcccccc ggcaccctcc
tccaagagca cctctggggg cacagcggcc ctgggctgcc tggtcaagga
ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc gccctgacca
gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta
catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag
ttgagcccaa atcttgtgac aaaactcaca catgcgccgc g

Figure 1W

1519gL20 FabFv light chain (alternative sequence to SEQ ID NO: 46) SEQ ID NO: 78

DIQMTQSPSS LSASVGDRVT ITCKSSQSLV GASGKTYLYW LFQKPGKAPK
RLIYLVSTLD SGIPSRFSGS GSGTEFTLTI SSLQPEDFAT YYCLQGTHFP
HTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGECG GGGSGGGGSG GGGSDIQMTQ SPSSVSASVG
DRVTITCQSS PSVWSNFLSW YQQKPGKAPK LLIYEASKLT SGVPSRFSGS
GSGTDFTLTI SSLQPEDFAT YYCGGGYSSI SDTTFGCGTK VEIKRT

1519gL20 FabFv light chain (alternative sequence to SEQ ID NO: 47) SEQ ID NO: 79

gacatccaga tgacccagtc cccctccagc ctgtccgcct ccgtgggcga
cagagtgacc atcacatgca agtcctccca gtccctggtc ggagcctccg
gcaagaccta cctgtactgg ctgttccaga agcccggcaa ggcccccaag
cggctgatct acctggtgtc taccctggac tccggcatcc cctcccggtt
ctccggctct ggctctggca ccgagttcac cctgaccatc tccagcctgc
agcccgagga cttcgccacc tactactgtc tgcaaggcac ccacttcccc
cacaccttcg gccagggcac caagctggaa atcaagcgga ccgtagcggc
cccatctgtc ttcatcttcc cgccatctga tgagcagttg aaatctggaa
ctgcctctgt tgtgtgcctg ctgaataact tctatcccag agaggccaaa
gtacagtgga aggtggataa cgccctccaa tcgggtaact cccaggagag
tgtcacagag caggacagca aggacagcac ctacagcctc agcagcaccc
tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa
gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg
agagtgtggt ggaggtggct ctggcggtgg tggctccgga ggcggaggaa
gcgacatcca gatgacccag agcccttcct ctgtaagcgc cagtgtcgga
gacagagtga ctattacctg ccaaagctcc ccttcagtct ggtccaattt
tctatcctgg tatcagcaaa agcccggaaa ggctcctaaa ttgctgatct
acgaagcaag caaactcacc agcggcgtgc ccagcaggtt cagcggcagt
gggtctggaa ctgactttac cctgacaatc tcctcactcc agcccgagga
cttcgccacc tattactgcg gtggaggtta cagtagcata agtgatacga
catttggatg cggcactaaa gtggaaatca agcgtacc

FIGURE 1X

1519gH20 FabFv heavy chain (alternative sequence to SEQ ID NO: 51) SEQ ID NO: 80

gaggtgcccc tggtggaatc tggcggcgga ctggtgcagc ctggcggctc
cctgagactg tcttgcgccg tgtccggctt caccttctcc aactacggca
tggtctgggt ccgacaggct cctggcaagg gactggaatg ggtggcctac
atcgactccg acggcgacaa cacctactac cgggactccg tgaagggccg
gttcaccatc tcccgggaca acgccaagtc ctccctgtac ctgcagatga
actccctgcg ggccgaggac accgccgtgt actactgcac caccggcatc
gtgcggccct ttctgtactg gggccagggc accctggtca ccgtgtcctc
tgcttctaca aagggcccat cggtcttccc cctggcaccc tcctccaaga
gcacctctgg gggcacagcg gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc tggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttgagcc
caaatcttgt tccggaggtg gcggttccgg aggtggcggt acaggtggcg
gtgggtccga agtccagctg cttgaatccg gaggcggact cgtgcagccc
ggaggcagtc ttcgcttgtc ctgcgctgta tctggaatcg acctgagcaa
ttacgccatc aactgggtga gacaggcacc tgggaaatgc ctcgaatgga
tcggcattat atgggctagt gggacgacct tttatgctac atgggcgaag
ggtagattca caatctcacg ggataatagt aagaacacag tgtacctgca
gatgaactcc ctgcgagcag aggataccgc cgtttactat tgtgctcgca
ctgtcccagg ttatagcact gcaccctact ttgatctgtg ggggcagggc
actctggtca ccgtctcgtc c

Figure 1Y (signal sequences underlined and italicised)

Rat Ab 1548 VL region (alternative sequence to SEQ ID NO: 58) SEQ ID NO: 81
DVVMTQTPLS LSVAIGQPAS ISSKSSQSLV GAGGKTYLYW LLQRSGQSPK
RLIYLVSTLD SGIPDRFSGS GAETDFTLKI RRVEADDLGV YYCLQGTHFP
HTFGAGTNLE IK

Rat Ab 1548 VL region (alternative sequence to SEQ ID NO: 59) SEQ ID NO: 82
gatgttgtga tgacccagac tccactgtct ttgtcggttg ccattggaca
accagcctcc atctcttcta agtcaagtca gagcctcgta ggtgctggtg
gaaagacata tttgtattgg ttattacaga ggtccggcca gtctccaaag
cgactaatct atctggtgtc cacactggac tctggaattc ctgataggtt
cagtggcagt ggagcagaga cagattttac tcttaaaatc cgcagagtgg
aagccgatga tttgggagtt tattactgct tgcaaggtac acattttcct
cacacgtttg gagctgggac caacctggaa ataaaa

Rat Ab 1548 VH region (alternative sequence to SEQ ID NO: 60) SEQ ID NO: 83
EVPLVESGGG SVQPGRSMKL SCVVSGFTFS NYGMVWVRQA PKKGLEWVAY
IGSDGDNTYY RDSVKGRFTI SRNNAKSTLY LQMDSLRSED TATYYCTTGI
VRPFLYWGQG VMVTVS

Rat Ab 1548 VH region (alternative sequence to SEQ IS NO: 61) SEQ ID NO: 84
gaggtgccgc tggtggagtc tgggggcggc tcagtgcagc ctgggaggtc
catgaaactc tcctgtgtag tctcaggatt cactttcagt aactatggca
tggtctgggt ccgccaggct ccaaagaagg gtctggagtg ggtcgcatat
attggttctg atggtgataa tacttactac cgagattccg tgaagggccg
attcactatc tccagaaata atgcaaaaag caccctatat ttgcaaatgg
acagtctgag gtctgaggac acggccactt attactgtac aacagggatt
gtccggccct ttctctactg gggccaagga gtcatggtca cagtctcg

Figure 1Z

1519gH20 IgG1 heavy chain (V + human gamma-1 constant, exons underlined one base change to SEQ ID NO: 71) SEQ ID NO: 85

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag tttacgtctc
tcttgtgctg tgtctggctt caccttctcc aattacggaa tggtctgggt cagacaagca
cctggaaagg gtcttgaatg ggtggcctat attgactctg acggggacaa cacctactat
cgggattccg tgaaaggacg cttcacaatc tcccgagata acgccaagag ctcactgtac
ctgcagatga atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag cgcttctaca
aagggcccat cggtcttccc cctggcaccc tcctccaaga gcacctctgg gggcacagcg
gccctgggct gcctggtcaa ggactacttc cccgaaccgg tgacggtgtc gtggaactca
ggcgccctga ccagcggcgt gcacaccttc ccggctgtcc tacagtcctc aggactctac
tccctcagca gcgtggtgac cgtgccctcc agcagcttgg gcacccagac ctacatctgc
aacgtgaatc acaagcccag caacaccaag gtggacaaga aagttggtga gaggccagca
cagggaggga gggtgtctgc tggaagccag gctcagcgct cctgcctgga cgcatcccgg
ctatgcagcc ccagtccagg gcagcaaggc aggccccgtc tgcctcttca cccggaggcc
tctgcccgcc ccactcatgc tcagggagag ggtcttctgg ctttttcccc aggctctggg
caggcacagg ctaggtgccc ctaacccagg ccctgcacac aaaggggcag gtgctgggct
cagacctgcc aagagccata tccgggagga ccctgcccct gacctaagcc caccccaaag
gccaaactct ccactccctc agctcggaca ccttctctcc tcccagatct gagtaactcc
caatcttctc tctgcagagc ccaaatcttg tgacaaaact cacacatgcc caccgtgccc
aggtaagcca gcccaggcct cgccctccag ctcaaggcgg gacaggtgcc ctagagtagc
ctgcatccag ggacaggccc cagccgggtg ctgacacgtc cacctccatc tcttcctcag
cacctgaact cctgggggga ccgtcagtct tcctcttccc cccaaaaccc aaggacaccc
tcatgatctc ccggaccccc gaggtcacat gcgtggtggt ggacgtgagc cacgaagacc
ctgaggtcaa gttcaactgg tacgtggacg gcgtggaggt gcataatgcc aagacaaagc
cgcgggagga gcagtacaac agcacgtacc gtgtggtcag cgtcctcacc gtcctgcacc
aggactggct gaatggcaag gagtacaagt gcaaggtctc caacaaagcc ctcccagccc
ccatcgagaa aaccatctcc aaagccaaag gtgggacccg tggggtgcga gggccacatg
gacagaggcc ggctcggccc accctctgcc ctgagagtga ccgctgtacc aacctctgtc
cctacagggc agccccgaga accacaggtg tacaccctgc ccccatcccg ggatgagctg
accaagaacc aggtcagcct gacctgcctg gtcaaaggct tctatcccag cgacatcgcc
gtggagtggg agagcaatgg gcagccggag aacaactaca agaccacgcc tcccgtgctg
gactccgacg gctccttctt cctctacagc aagctcaccg tggacaagag caggtggcag
caggggaacg tcttctcatg ctccgtgatg catgaggctc tgcacaacca ctacacgcag
aagagcctct ccctgtctcc gggtaaa

Figure 1AA

1519gH20 IgG1 heavy chain (V + human gamma-1 constant) with signal sequence underlined and italicized (one base change from SEQ ID NO:72) SEQ ID NO:86

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt ccattctgag
gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg gaggaagttt acgtctctct
tgtgctgtgt ctggcttcac cttctccaat tacggaatgg tctgggtcag acaagcacct
ggaaagggtc ttgaatgggt ggcctatatt gactctgacg gggacaacac ctactatcgg
gattccgtga aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac gggaatcgtt
aggccttttc tgtactgggg acagggcacc ttggttactg tctcgagcgc ttctacaaag
ggcccatcgg tcttccccct ggcaccctcc tccaagagca cctctggggg cacagcggcc
ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc
gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta catctgcaac
gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttggtgagag gccagcacag
ggagggaggg tgtctgctgg aagccaggct cagcgctcct gcctggacgc atcccggcta
tgcagcccca gtccagggca gcaaggcagg ccccgtctgc ctcttcaccc ggaggcctct
gcccgcccca ctcatgctca gggagagggt cttctggctt tttccccagg ctctgggcag
gcacaggcta ggtgccccta acccaggccc tgcacacaaa ggggcaggtg ctgggctcag
acctgccaag agccatatcc gggaggaccc tgcccctgac ctaagcccac cccaaaggcc
aaactctcca ctccctcagc tcggacacct tctctcctcc cagatctgag taactcccaa
tcttctctct gcagagccca aatcttgtga caaaactcac acatgcccac cgtgcccagg
taagccagcc caggcctcgc cctccagctc aaggcgggac aggtgcccta gagtagcctg
catccaggga caggccccag ccgggtgctg acacgtccac ctccatctct tcctcagcac
ctgaactcct gggggggaccg tcagtcttcc tcttcccccc aaaacccaag gacaccctca
tgatctcccg gacccctgag gtcacatgcg tggtggtgga cgtgagccac gaagaccctg
aggtcaagtt caactggtac gtggacggcg tggaggtgca taatgccaag acaaagccgc
gggaggagca gtacaacagc acgtaccgtg tggtcagcgt cctcaccgtc ctgcaccagg
actggctgaa tggcaaggag tacaagtgca aggtctccaa caaagccctc ccagcccca
tcgagaaaac catctccaaa gccaaaggtg ggacccgtgg ggtgcgaggg ccacatggac
agaggccggc tcggcccacc ctctgccctg agagtgaccg ctgtaccaac ctctgtccct
acagggcagc cccgagaacc acaggtgtac accctgcccc catcccggga tgagctgacc
aagaaccagg tcagcctgac ctgcctggtc aaaggcttct atcccagcga catcgccgtg
gagtgggaga gcaatgggca gccggagaac aactacaaga ccacgcctcc cgtgctggac
tccgacggct ccttcttcct ctacagcaag ctcaccgtgg acaagagcag gtggcagcag
gggaacgtct tctcatgctc cgtgatgcat gaggctctgc acaaccacta cacgcagaag
agcctctccc tgtctccgggtaaa

1519gH20 IgG4 heavy chain (V + human gamma-4 constant no P mutations) SEQ ID NO:87

EVPLVESGGG LVQPGGSLRL SCAVSGFTFS NYGMVWVRQA PGKGLEWVAY
IDSDGDNTYY RDSVKGRFTI SRDNAKSSLY LQMNSLRAED TAVYYCTTGI
VRPFLYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC
NVDHKPSNTK VDKRVESKYG PPCPSCPAPE FLGGPSVFLF PPKPKDTLMI
SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV
SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP
SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS
FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK

Figure 1BB

1519gH20 IgG4 heavy chain (V + human gamma-4 constant, exons underlined no P mutations) SEQ ID NO:88

gaggtaccac ttgtggaaag cggaggaggt cttgtgcagc ctggaggaag
tttacgtctc tcttgtgctg tgtctggctt caccttctcc aattacggaa
tggtctgggt cagacaagca cctggaaagg gtcttgaatg ggtggcctat
attgactctg acggggacaa cacctactat cgggattccg tgaaaggacg
cttcacaatc tcccgagata acgccaagag ctcactgtac ctgcagatga
atagcctgag agccgaggat actgccgtgt actattgcac aacgggaatc
gttaggcctt ttctgtactg gggacagggc accttggtta ctgtctcgag
cgcttctaca aagggcccat ccgtcttccc cctggcgccc tgctccagga
gcacctccga gagcacagcc gccctgggct gcctggtcaa ggactacttc
cccgaaccgg tgacggtgtc gtggaactca ggcgccctga ccagcggcgt
gcacaccttc ccggctgtcc tacagtcctc aggactctac tccctcagca
gcgtggtgac cgtgccctcc agcagcttgg gcacgaagac ctacacctgc
aacgtagatc acaagcccag caacaccaag gtggacaaga gagttggtga
gaggccagca cagggaggga gggtgtctgc tggaagccag gctcagccct
cctgcctgga cgcaccccgg ctgtgcagcc ccagcccagg gcagcaaggc
atgccccatc tgtctcctca cccggaggcc tctgaccacc ccactcatgc
ccagggagag ggtcttctgg atttttccac caggctccgg gcagccacag
gctggatgcc cctaccccag gccctgcgca tacaggggca ggtgctgcgc
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ccaccccaaa ggccaaactc tccactccct cagctcagac accttctctc
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gtcccccatg cccatcatgc ccaggtaagc caacccaggc ctcgccctcc
agctcaaggc gggacaggtg ccctagagta gcctgcatcc agggacaggc
cccagccggg tgctgacgca tccacctcca tctcttcctc agcacctgag
ttcctggggg gaccatcagt cttcctgttc cccccaaaac ccaaggacac
tctcatgatc tcccggaccc ctgaggtcac gtgcgtggtg gtggacgtga
gccaggaaga ccccgaggtc cagttcaact ggtacgtgga tggcgtggag
gtgcataatg ccaagacaaa gccgcgggag gagcagttca acagcacgta
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aggagtacaa gtgcaaggtc tccaacaaag gcctcccgtc ctccatcgag
aaaaccatct ccaaagccaa aggtgggacc cacggggtgc gagggccaca
tggacagagg tcagctcggc ccaccctctg ccctgggagt gaccgctgtg
ccaacctctg tccctacagg gcagccccga gagccacagg tgtacaccct
gcccccatcc caggaggaga tgaccaagaa ccaggtcagc ctgacctgcc
tggtcaaagg cttctacccc agcgacatcg ccgtggagtg ggagagcaat
gggcagccgg agaacaacta caagaccacg cctcccgtgc tggactccga
cggctccttc ttcctctaca gcaggctaac cgtggacaag agcaggtggc
aggaggggaa tgtcttctca tgctccgtga tgcatgaggc tctgcacaac
cactacacac agaagagcct ctccctgtct ctgggtaaa

Figure 1CC

1519gH20 IgG4 heavy chain (V + human gamma-4 constant) with signal sequence underlined and italicised– no P mutation SEQ ID NO:89

atggaatgga gctgggtctt tctcttcttc ctgtcagtaa ctacaggagt
*ccattct*gag gtaccacttg tggaaagcgg aggaggtctt gtgcagcctg
gaggaagttt acgtctctct tgtgctgtgt ctggcttcac cttctccaat
tacggaatgg tctgggtcag acaagcacct ggaaagggtc ttgaatgggt
ggcctatatt gactctgacg gggacaacac ctactatcgg gattccgtga
aaggacgctt cacaatctcc cgagataacg ccaagagctc actgtacctg
cagatgaata gcctgagagc cgaggatact gccgtgtact attgcacaac
gggaatcgtt aggccttttc tgtactgggg acagggcacc ttggttactg
tctcgagcgc ttctacaaag ggcccatccg tcttcccccc ggcgccctgc
tccaggagca cctccgagag cacagccgcc ctgggctgcc tggtcaagga
ctacttcccc gaaccggtga cggtgtcgtg gaactcaggc gccctgacca
gcggcgtgca caccttcccg gctgtcctac agtcctcagg actctactcc
ctcagcagcg tggtgaccgt gccctccagc agcttgggca cgaagaccta
cacctgcaac gtagatcaca agcccagcaa caccaaggtg gacaagagag
ttggtgagag gccagcacag ggagggaggg tgtctgctgg aagccaggct
cagccctcct gcctggacgc accccggctg tgcagcccca gcccagggca
gcaaggcatg ccccatctgt ctcctcaccc ggaggcctct gaccacccca
ctcatgccca gggagagggt cttctggatt tttccaccag gctccgggca
gccacaggct ggatgccccc accccaggcc ctgcgcatac aggggcaggt
gctgcgctca gacctgccaa gagccatatc cgggaggacc ctgcccctga
cctaagccca ccccaaaggc caaactctcc actccctcag ctcagacacc
ttctctcctc ccagatctga gtaactccca atcttctctc tgcagagtcc
aaatatggtc ccccatgccc atcatgccca ggtaagccaa cccaggcctc
gccctccagc tcaaggcggg acaggtgccc tagagtagcc tgcatccagg
gacaggcccc agccgggtgc tgacgcatcc acctccatct cttcctcagc
acctgagttc ctggggggac catcagtctt cctgttcccc ccaaaaccca
aggacactct catgatctcc cggacccctg aggtcacgtg cgtggtggtg
gacgtgagcc aggaagaccc cgaggtccag ttcaactggt acgtggatgg
cgtggaggtg cataatgcca agacaaagcc gcgggaggag cagttcaaca
gcacgtaccg tgtggtcagc gtcctcaccg tcctgcacca ggactggctg
aacggcaagg agtacaagtg caaggtctcc aacaaaggcc tcccgtcctc
catcgagaaa accatctcca aagccaaagg tgggacccac ggggtgcgag
ggccacatgg acagaggtca gctcggccca ccctctgccc tgggagtgac
cgctgtgcca acctctgtcc ctacagggca gccccgagag ccacaggtgt
acaccctgcc cccatcccag gaggagatga ccaagaacca ggtcagcctg
acctgcctgg tcaaaggctt ctaccccagc gacatcgccg tggagtggga
gagcaatggg cagccggaga acaactacaa gaccacgcct cccgtgctgg
actccgacgg ctccttcttc ctctacagca ggctaaccgt ggacaagagc
aggtggcagg aggggaatgt cttctcatgc tccgtgatgc atgaggctct
gcacaaccac tacacacaga agagcctctc cctgtctctg ggtaaa

Figure 1DD

1519 gL20 V-region (mammalian expression alternative to SEQ ID NO: 17) SEQ ID NO:90

gacatccaga tgacccagtc cccctccagc ctgtccgcct ccgtgggcga
cagagtgacc atcacatgca agtcctccca gtccctggtc ggagcctccg
gcaagaccta cctgtactgg ctgttccaga agcccggcaa ggcccccaag
cggctgatct acctggtgtc taccctggac tccggcatcc cctcccggtt
ctccggctct ggctctggca ccgagttcac cctgaccatc tccagcctgc
agcccgagga cttcgccacc tactactgtc tgcaaggcac ccacttcccc
cacaccttcg gccagggcac caagctggaa atcaag

1519 gL20 light chain (V + constant, mammalian expression alternative to SEQ ID NO: 24) SEQ ID NO:91

gacatccaga tgacccagtc cccctccagc ctgtccgcct ccgtgggcga
cagagtgacc atcacatgca agtcctccca gtccctggtc ggagcctccg
gcaagaccta cctgtactgg ctgttccaga agcccggcaa ggcccccaag
cggctgatct acctggtgtc taccctggac tccggcatcc cctcccggtt
ctccggctct ggctctggca ccgagttcac cctgaccatc tccagcctgc
agcccgagga cttcgccacc tactactgtc tgcaaggcac ccacttcccc
cacaccttcg gccagggcac caagctggaa atcaagcgga ccgtggccgc
tccctccgtg ttcatcttcc caccctccga cgagcagctg aagtccggca
ccgcctccgt cgtgtgcctg ctgaacaact tctacccccg cgaggccaag
gtgcagtgga aggtggacaa cgccctgcag tccggcaact cccaggaatc
cgtcaccgag caggactcca aggacagcac ctactccctg tcctccaccc
tgaccctgtc caaggccgac tacgagaagc acaaggtgta cgcctgcgaa
gtgacccacc agggcctgtc cagccccgtg accaagtcct tcaaccgggg
cgagtgc

Figure 1EE

1519 gH20 V-region (mammalian expression alternative to SEQ ID NO: 31) SEQ ID NO:92

gaggtgcccc tggtggaatc tggcggcgga ctggtgcagc ctggcggctc
cctgagactg tcttgcgccg tgtccggctt caccttctcc aactacggca
tggtctgggt ccgacaggct cctggcaagg gactggaatg ggtggcctac
atcgactccg acggcgacaa cacctactac cgggactccg tgaagggccg
gttcaccatc tcccgggaca acgccaagtc ctccctgtac ctgcagatga
actccctgcg ggccgaggac accgccgtgt actactgcac caccggcatc
gtgcggccct ttctgtactg gggccagggc accctggtca ccgtgtcc

Figure 1FF

1519gH20 IgG4 heavy chain (V + human gamma-4P constant alternative to SEQ ID NO: 44) SEQ ID NO:93

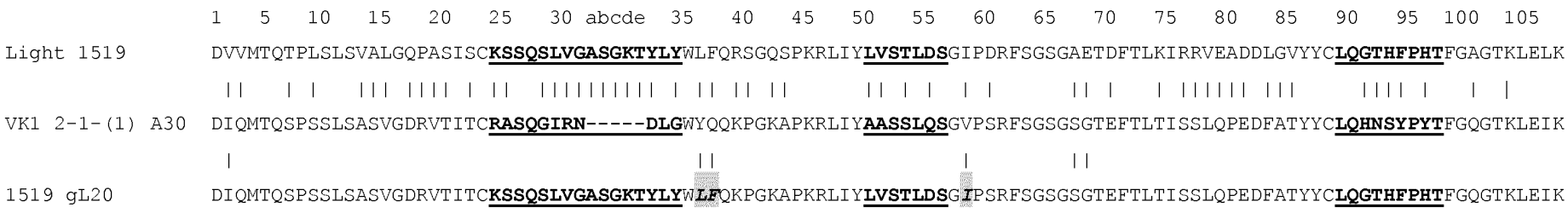
gaggtgcccc tggtggaatc tggcggcgga ctggtgcagc ctggcggctc
cctgagactg tcttgcgccg tgtccggctt caccttctcc aactacggca
tggtctgggt ccgacaggct cctggcaagg gactggaatg ggtggcctac
atcgactccg acggcgacaa cacctactac cgggactccg tgaagggccg
gttcaccatc tcccgggaca acgccaagtc ctccctgtac ctgcagatga
actccctgcg ggccgaggac accgccgtgt actactgcac caccggcatc
gtgcggccct ttctgtactg gggccagggc accctggtca ccgtgtcctc
tgcctccacc aagggcccct ccgtgttccc tctggccccc tgctcccggt
ccacctccga gtctaccgcc gctctgggct gcctggtcaa ggactacttc
cccgagcccg tgacagtgtc ctggaactct ggcgccctga cctccggcgt
gcacaccttc cctgccgtgc tgcagtcctc cggcctgtac tccctgtcct
ccgtcgtgac cgtgccctcc tccagcctgg gcaccaagac ctacacctgt
aacgtggacc acaagccctc caacaccaag gtggacaagc gggtggaatc
taagtacggc cctccctgcc ccccctgccc tgcccctgaa tttctgggcg
gaccttccgt gttcctgttc cccccaaagc ccaaggacac cctgatgatc
tcccggaccc ccgaagtgac ctgcgtggtg gtggacgtgt cccaggaaga
tcccgaggtc cagttcaatt ggtacgtgga cggcgtggaa gtgcacaatg
ccaagaccaa gcccagagag gaacagttca actccaccta ccgggtggtg
tccgtgctga ccgtgctgca ccaggactgg ctgaacggca aagagtacaa
gtgcaaggtg tccaacaagg gcctgccctc cagcatcgaa aagaccatct
ccaaggccaa gggccagccc cgcgagcccc aggtgtacac cctgcccccc
agccaggaag agatgaccaa gaaccaggtg tccctgacct gtctggtcaa
gggcttctac ccctccgaca ttgccgtgga atgggagtcc aacggccagc
ccgagaacaa ctacaagacc acccccccctg tgctggacag cgacggctcc
ttcttcctgt actctcggct gaccgtggac aagtcccggt ggcaggaagg
caacgtcttc tcctgctccg tgatgcacga ggccctgcac aaccactaca
cccagaagtc cctgtccctg agcctgggca ag

Human β2M (SEQ ID NO:95)

IQKTPQIQVYSRHPPENGKPNFLNCYVSQFHPPQIEIELLKNGKKIPNIEMSDLSFSKDWSFYILAHTEFTPTETDVYA
CRVKHVTLKEPKTVTWDRDM

FIGURE 2A

LIGHT CHAIN Graft 1519



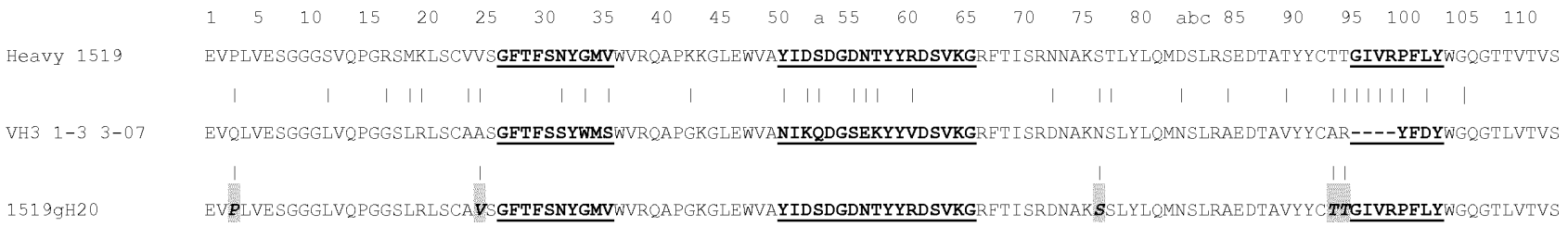
Legend

1519 = Rat variable light chain sequence
1519 gL20 = Humanized graft of 1519 variable light chain using VK1 2-1-(1) A30 human germline as the acceptor framework.

CDRs are shown in bold/underlined
Donor residues are shown in bold/italic and are highlighted: L36, F37 and I58

FIGURE 2B

HEAVY CHAIN Graft 1519



Legend

1519 = Rat variable heavy chain sequence
1519gH20 = Humanized graft of 1519 variable heavy chain using VH3 1-3 3-07 human germline as the acceptor framework.

CDRs are shown in bold/underlined
Donor residues are shown in bold/italic and are highlighted: P3, V24, S76, T93 and T94

FIGURE 3A CA170_01519.g57 Fab' binding on MDCK II clone 34 cells in acidic and neutral pH.

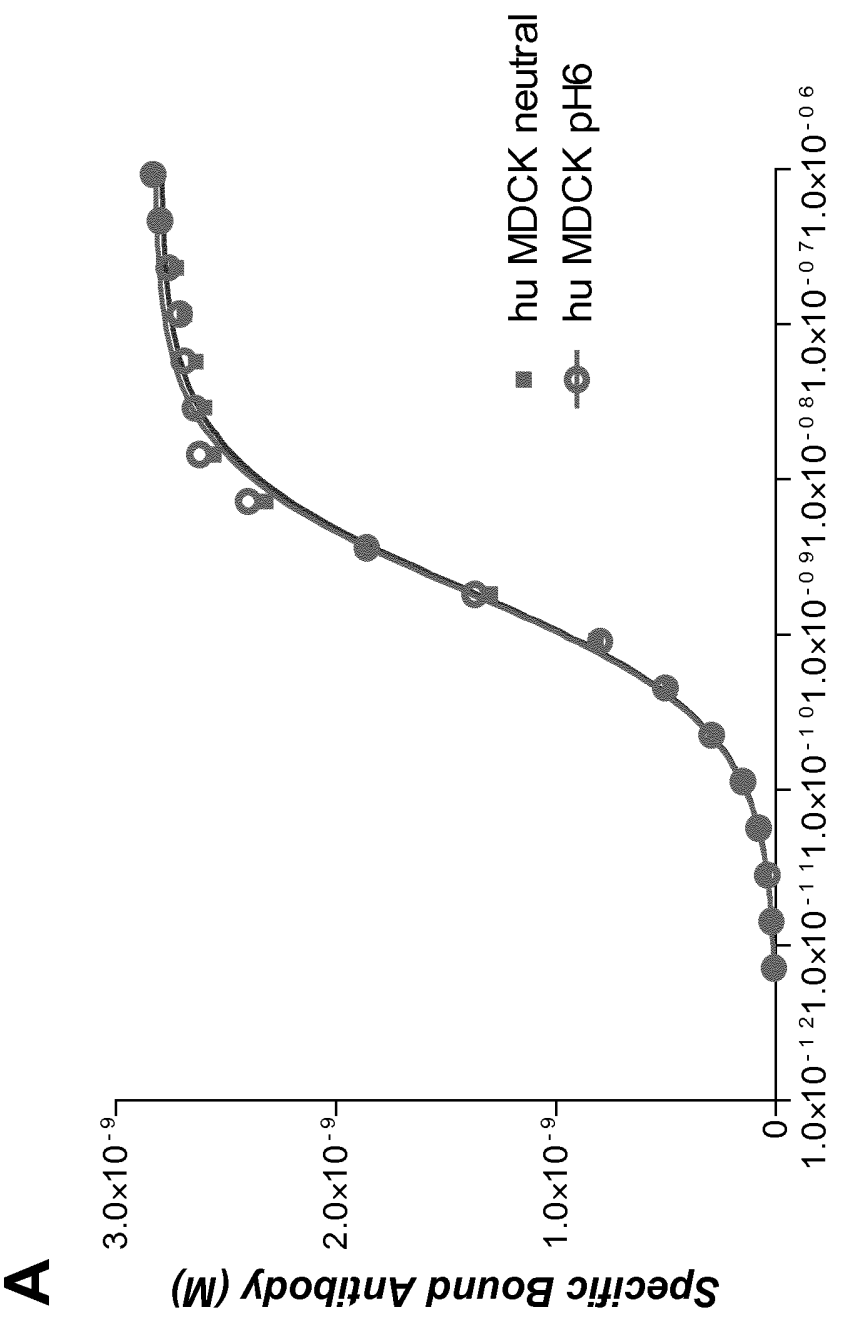


FIGURE 3B CA170_01519.g57 Fab'PEG binding on MDCK II clone 34 cells in acidic and neutral pH.

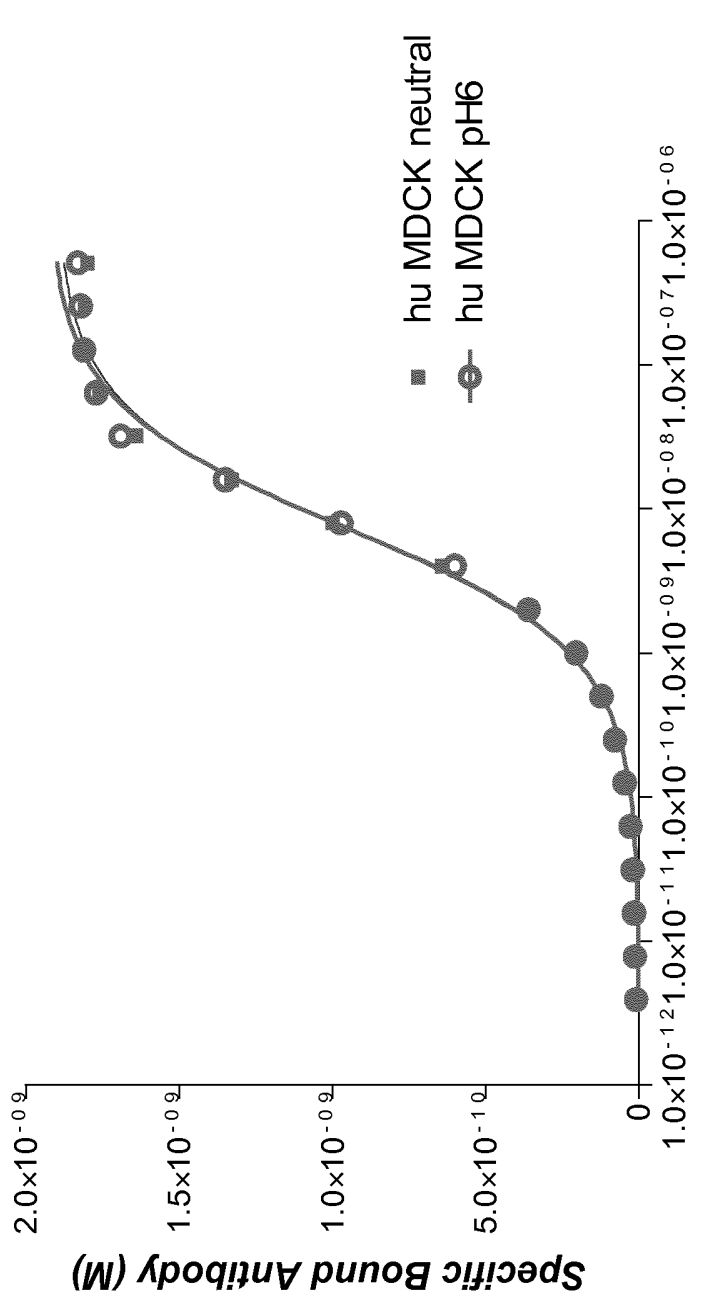
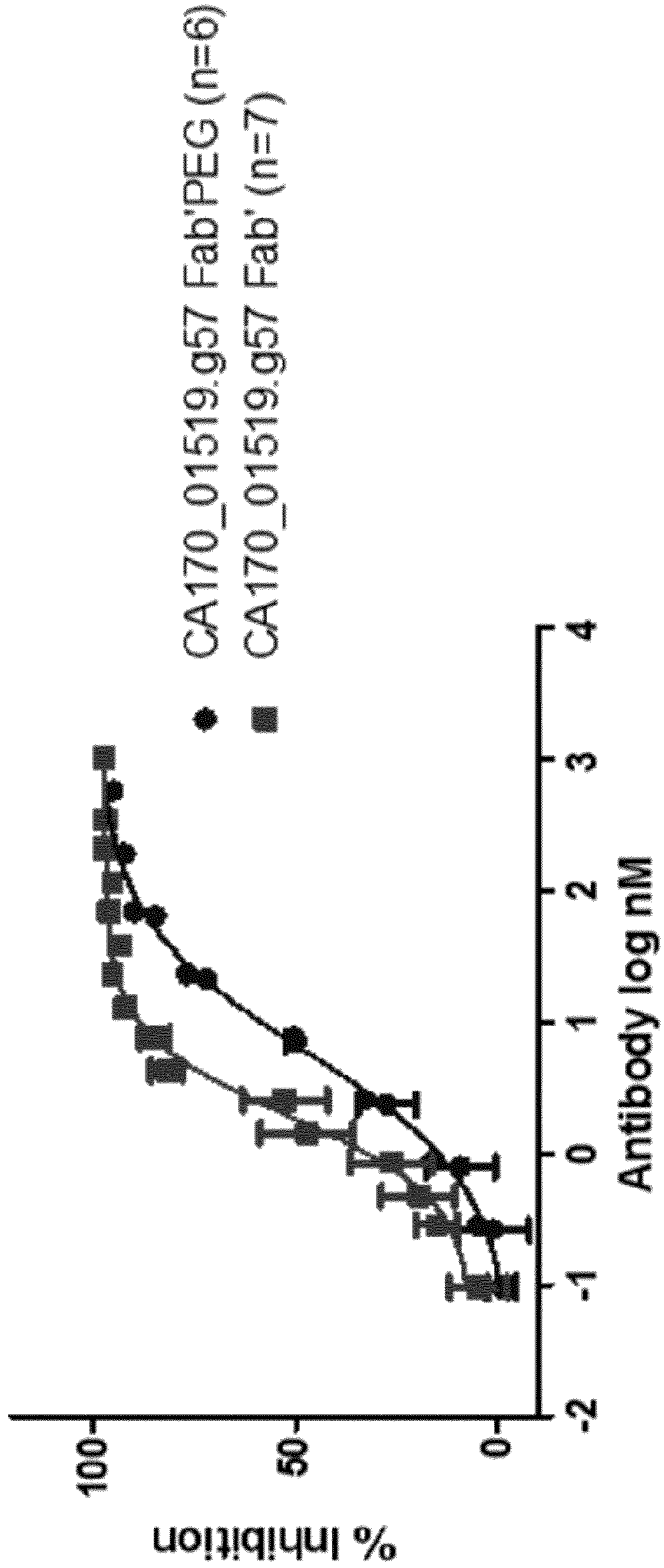


FIGURE 4 CA170_01519.g57 inhibits IgG recycling in MDCK II clone 34 cells



	1519.g57 Fab'PEG (n=6)	1519.g57 Fab' (n=7)
EC50	6.034	1.937
95% CI (nM)	4.614 to 7.891	1.426 to 2.632

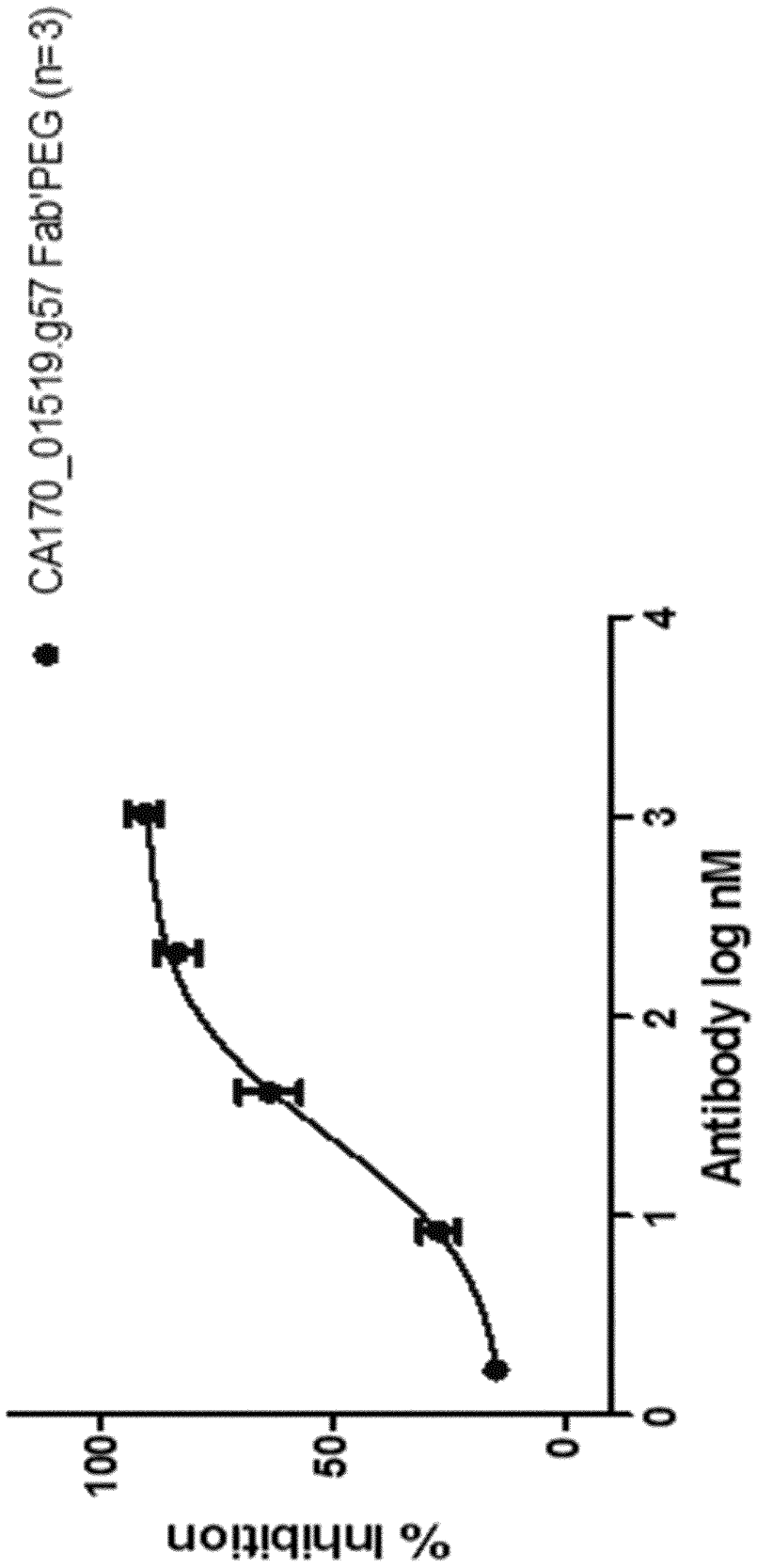


FIGURE 5 CA170_01519.g57 Fab'PEG inhibits apical to basolateral IgG transcytosis in MDCK II clone 34 cells

FIGURE 6A- CA170_01519.g57 Fab' binding on cynomoglus MDCK II (cm) cells in acidic and neutral pH

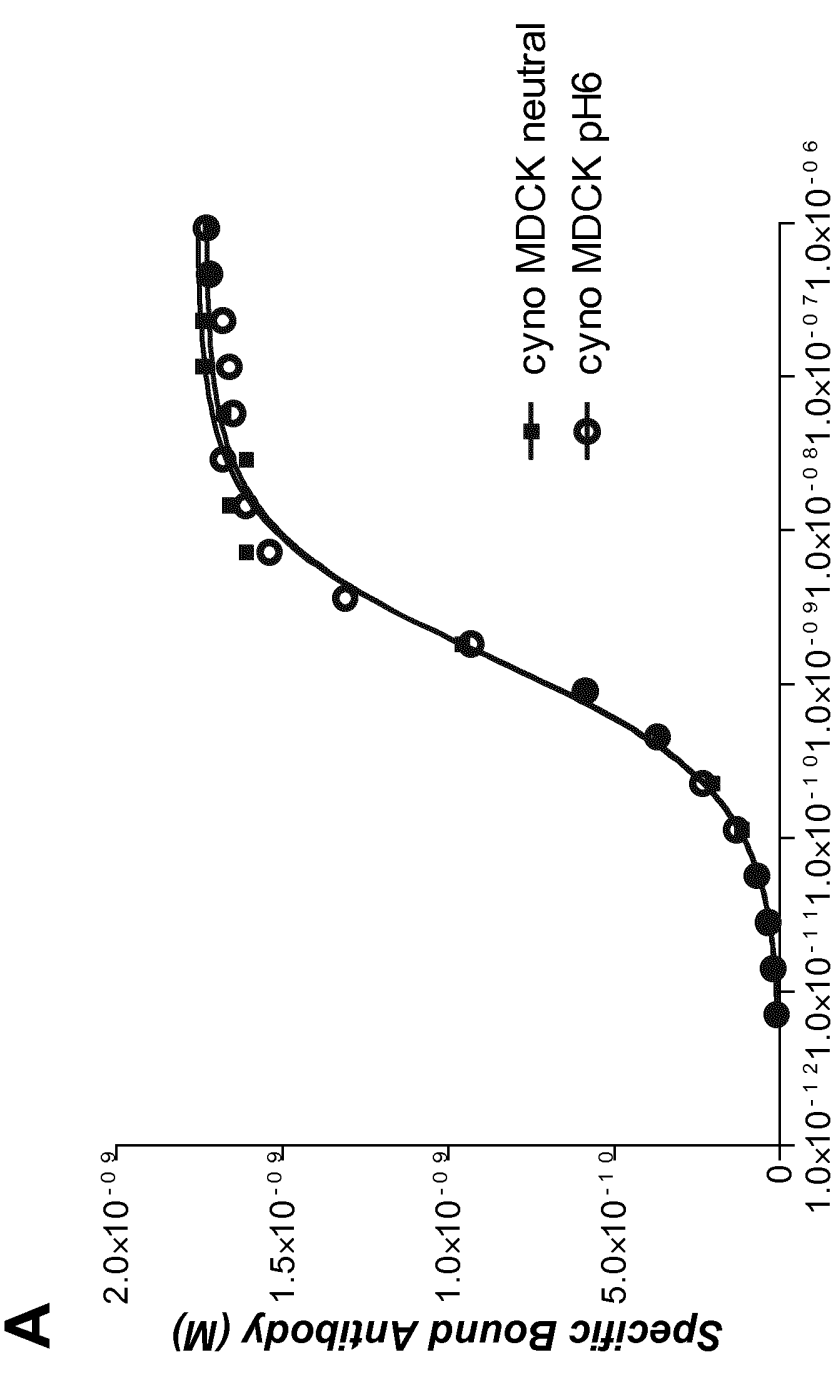


FIGURE 6B - CA170_01519.g57 Fab'PEG binding on cynomoglus MDCK II (cm) cells in acidic and neutral pH

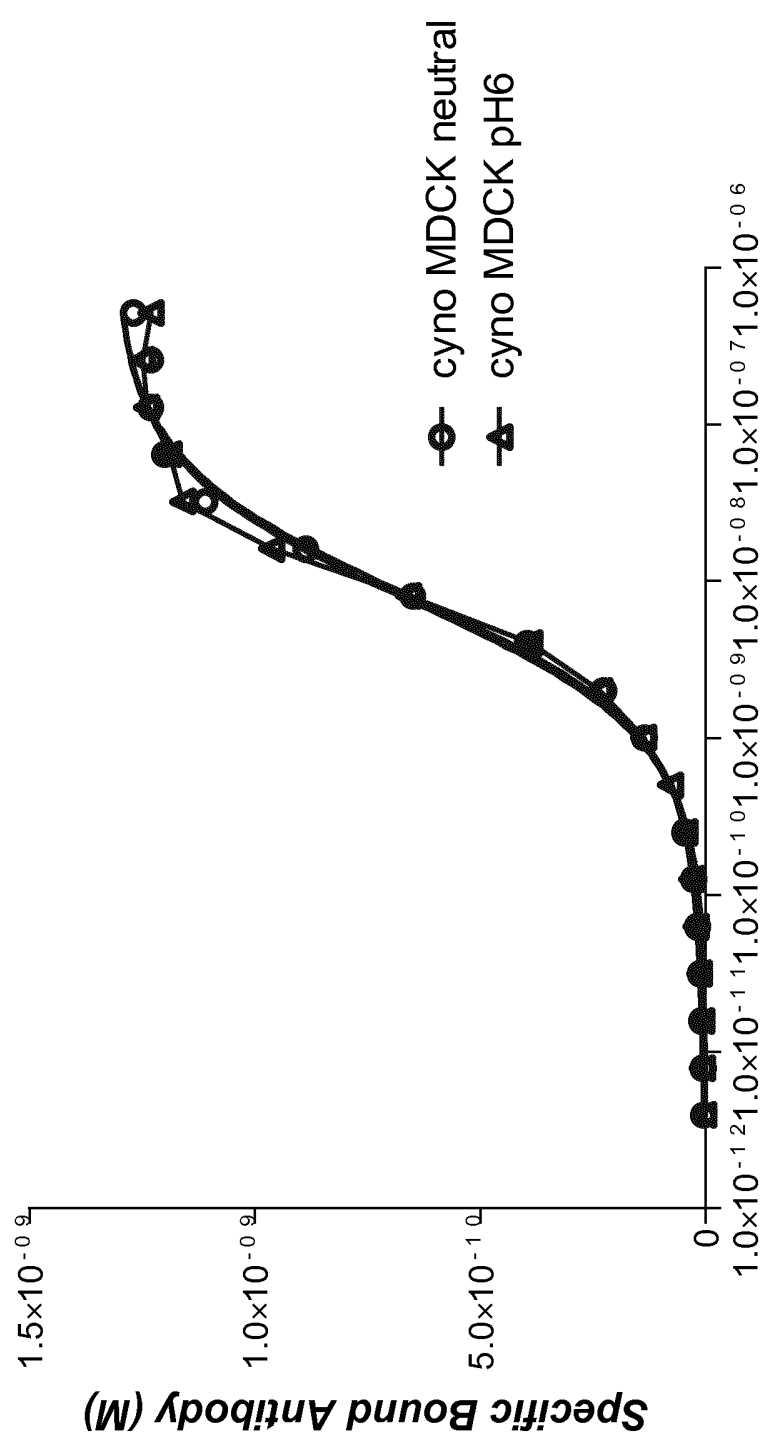


FIGURE 7 CA170_01519.g57 inhibits IgG recycling in human and cynomoglus MDCK II clone 34 cells and MDCK II (cm) cells.

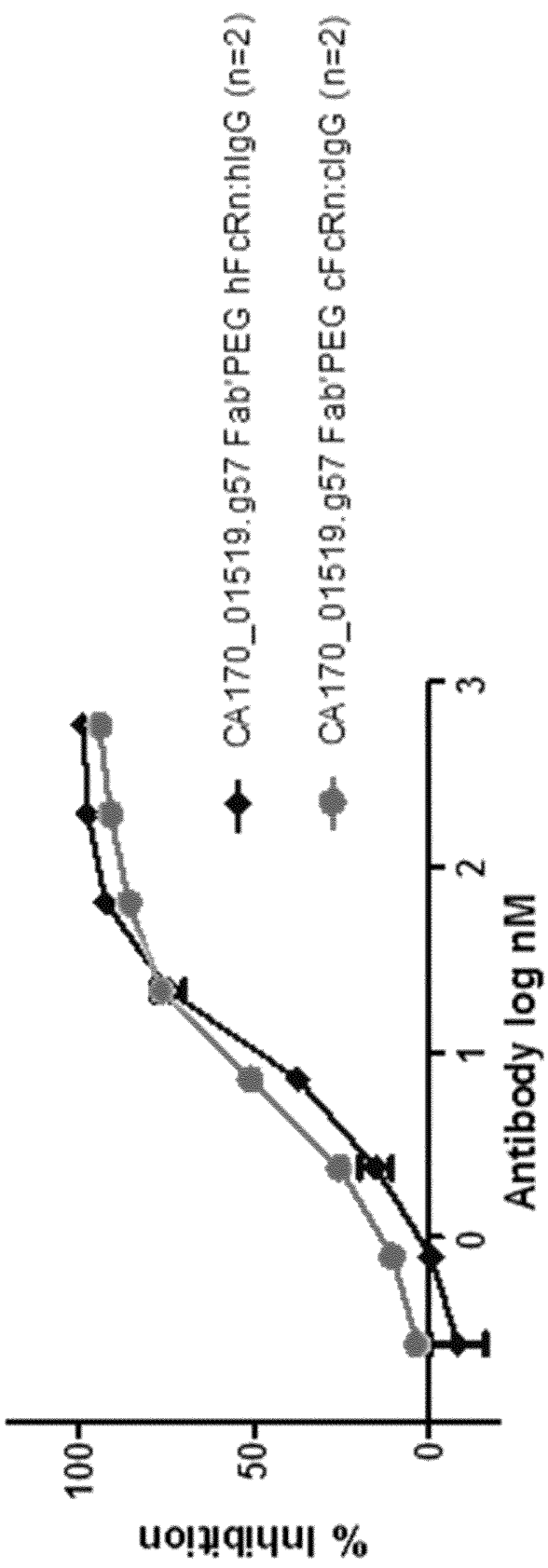


FIGURE 8 Cynomoglus Monkey- single dose of 1519 Fab'PEG on Plasma IgG levels

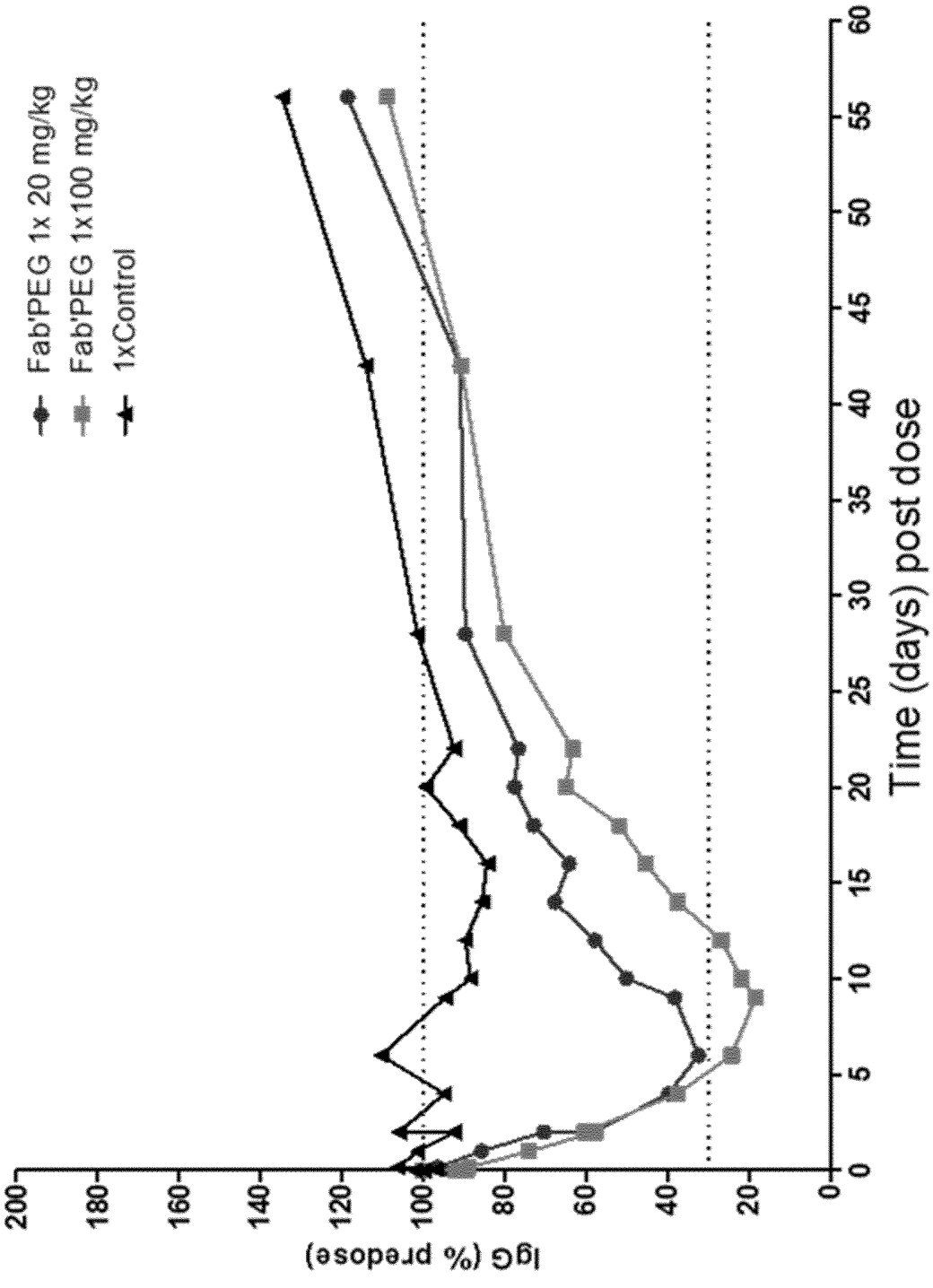
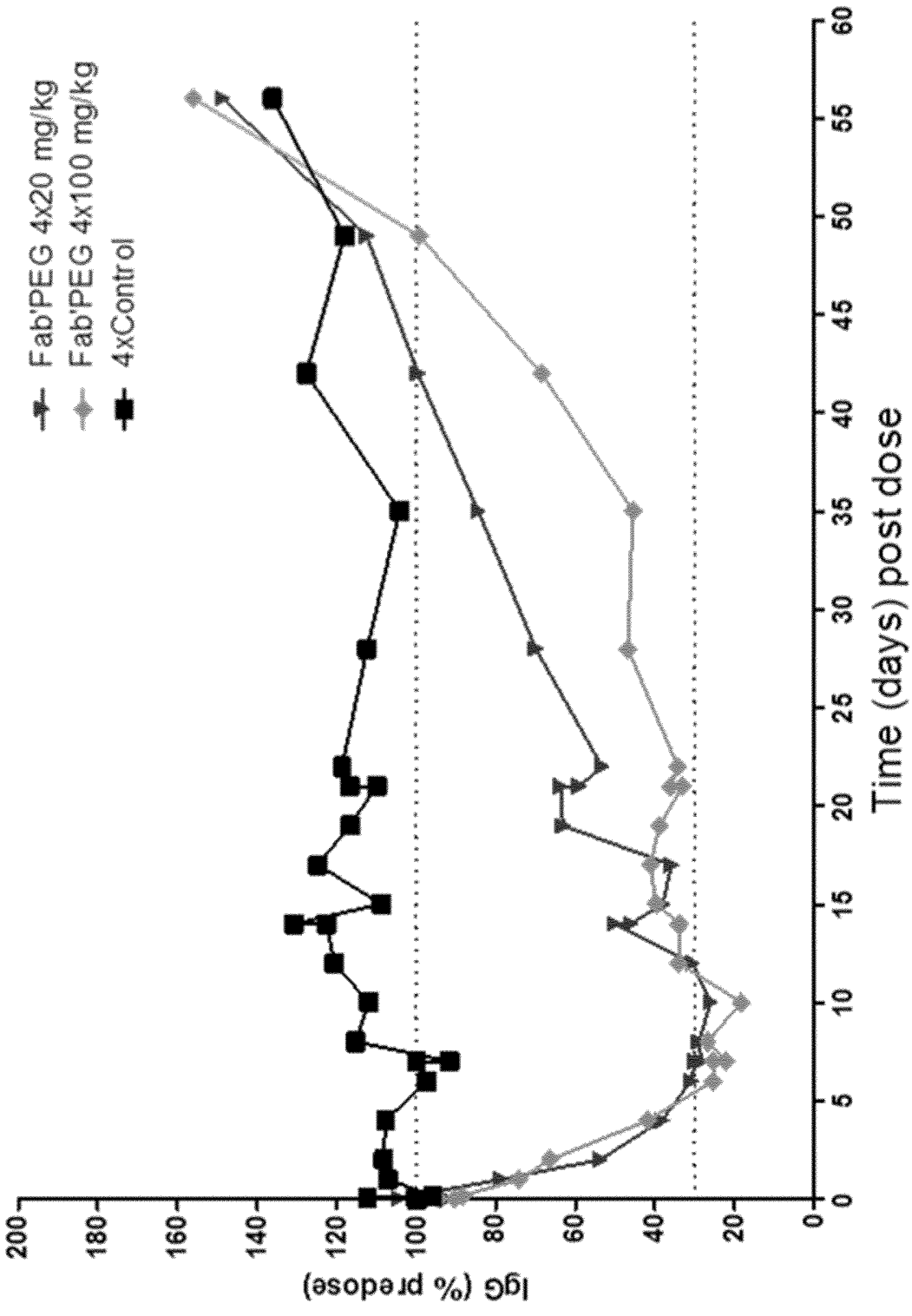


FIGURE 9 Cynomoglus Monkey 4 weekly doses of 1519 Fab'PEG on Plasma IgG Levels



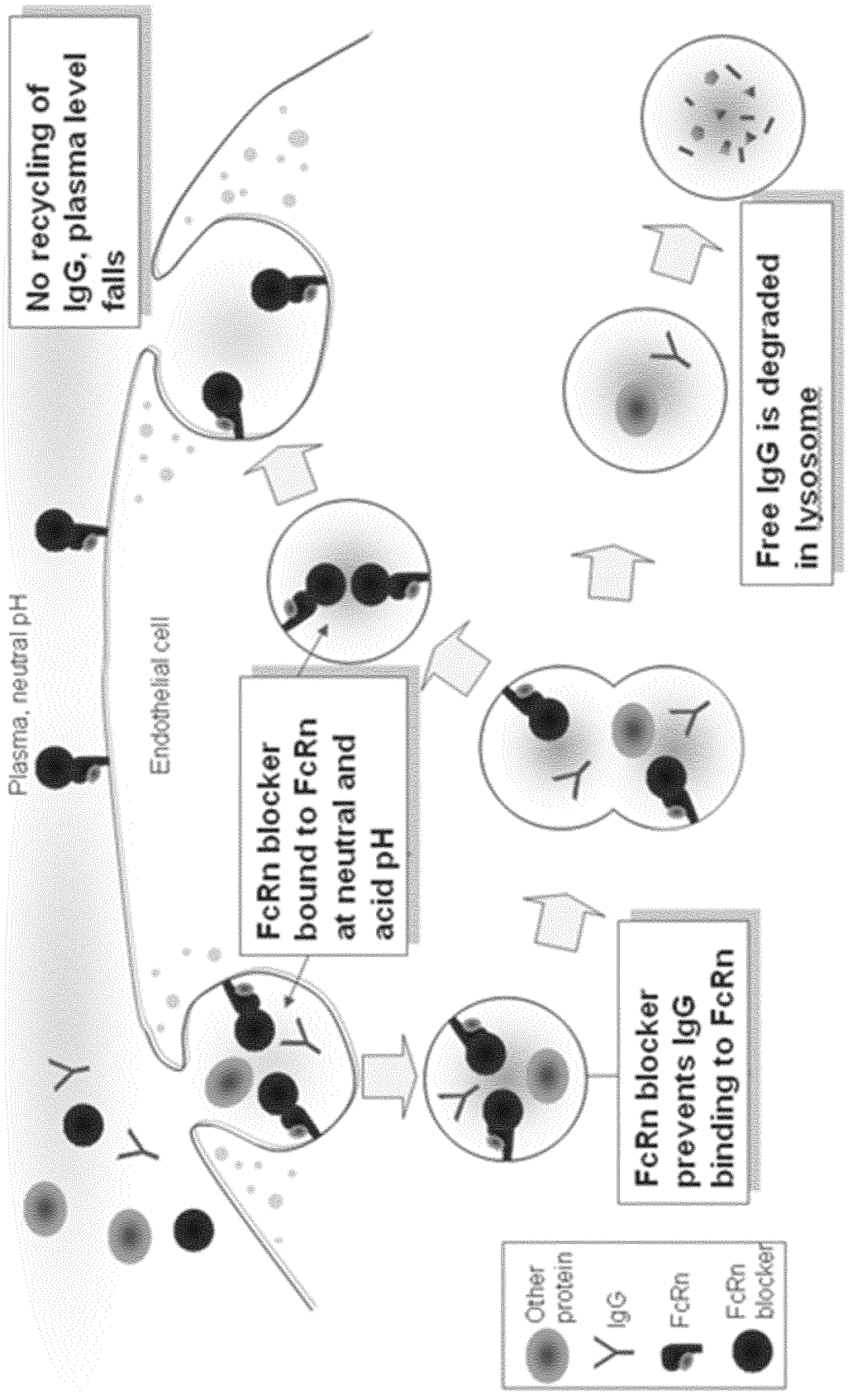

No recycling of IgG, plasma level falls
Plasma, neutral pH
Endothelial cell
FcRn blocker bound to FcRn at neutral and acid pH
FcRn blocker prevents IgG binding to FcRn
Free IgG is degraded in lysosome
Other protein
IgG
FcRn
FcRn blocker

Figure 10

Figure 11 Flow Cytometry based human IgG blocking assay using purified gamma 1 IgG Antibodies

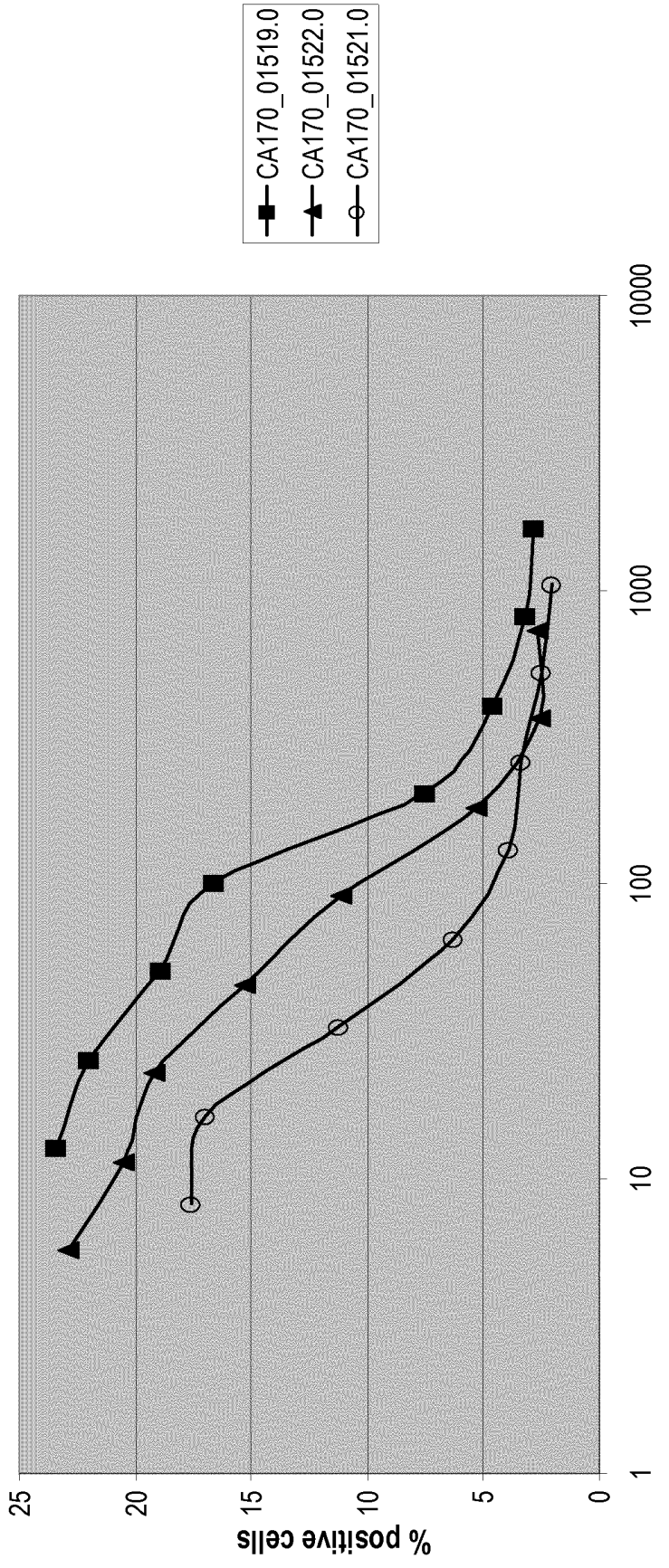


FIGURE 12 **Fab'PEG single/intermittent IV doses in Normal Cyno (4 animals n: 4-7) -1519 Fab'PEG 20mg/Kg days 1 and 67 IgG pharmacodynamics**

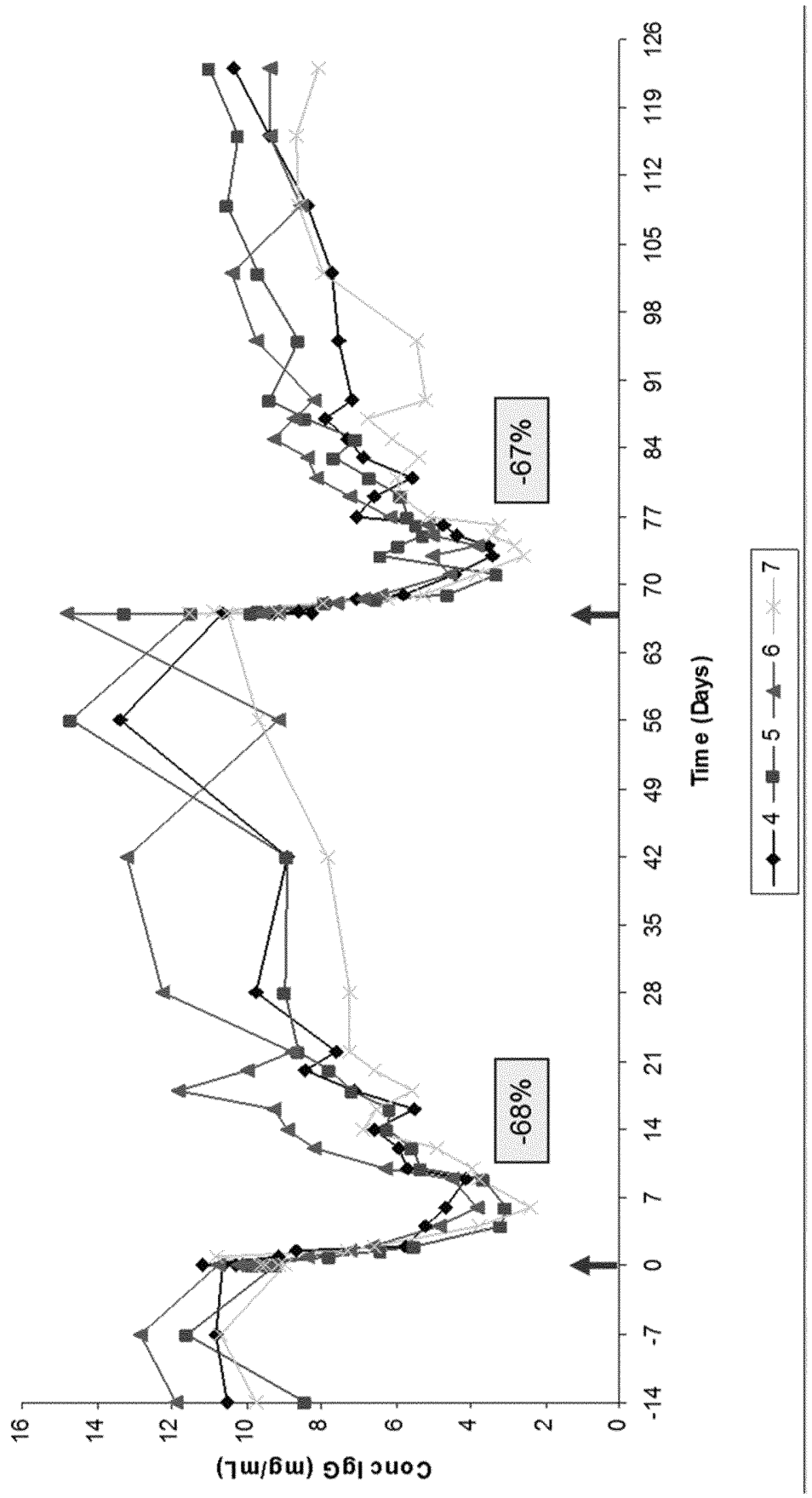


FIGURE 13 Fab'PEG: repeat IV doses in normal cyno- 4x 20 or 100 mg/Kg (top and bottom respectively) per week IgG pharmacodynamics (individual animals)

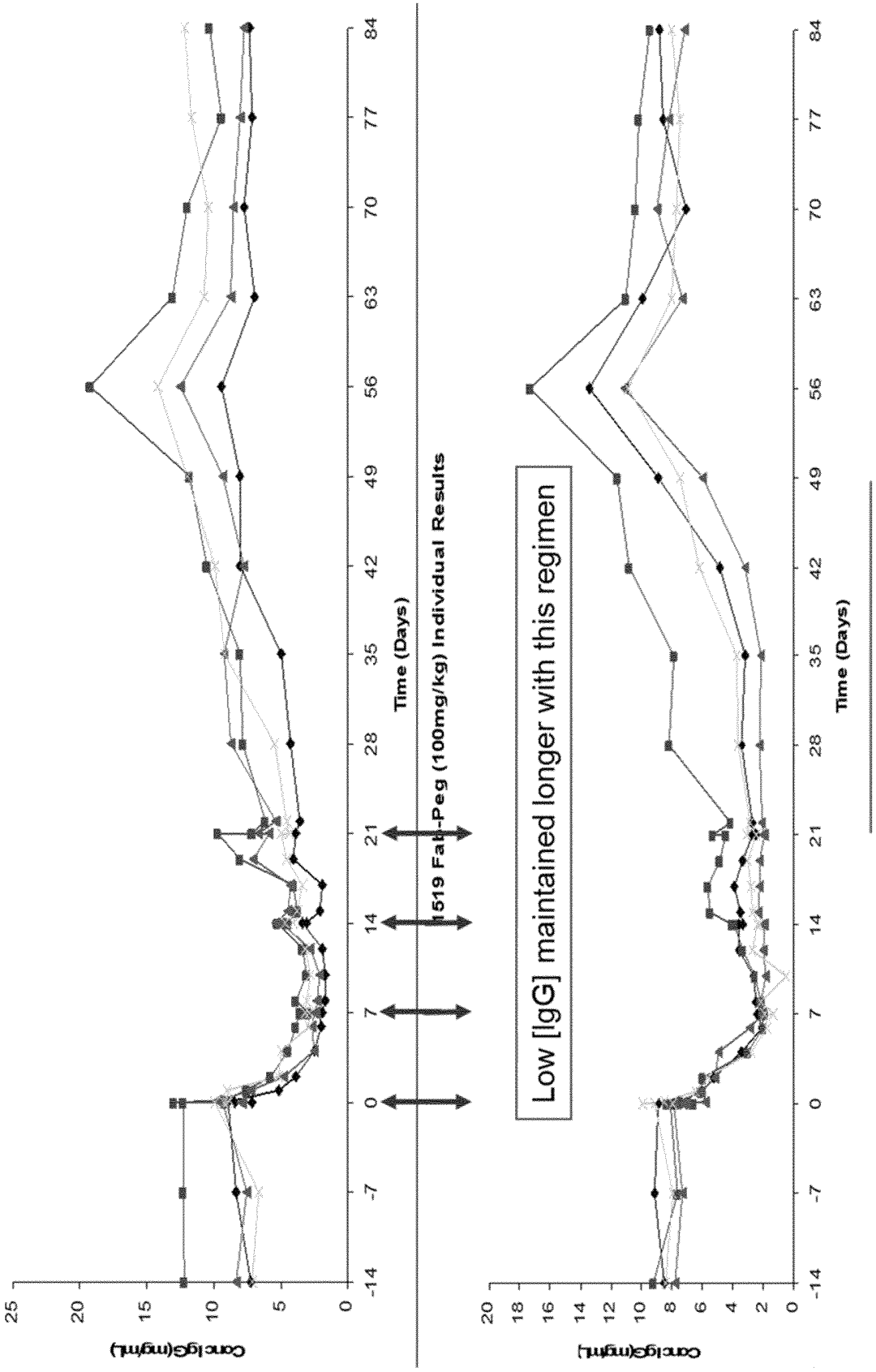


FIGURE 14 Fab'PEG single/intermittent IV doses in normal cyno 20 mg/Kg and 100 mg/Kg days 1 and 67 IgG Pharmacodynamics

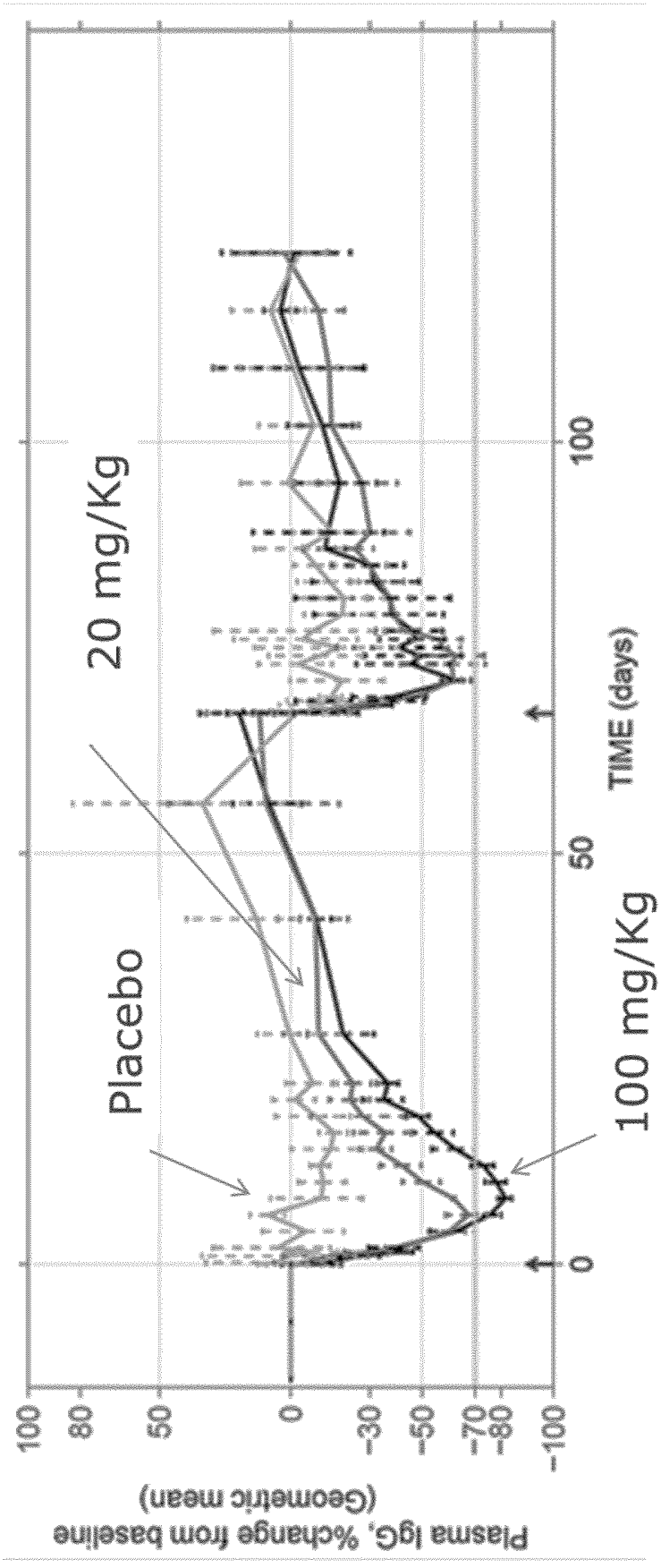


Figure 15 Change in plasma IgG levels in 4 cynomolgus monkeys after 2 IV doses of 20mg/Kg 1519.g57 Fab'PEG

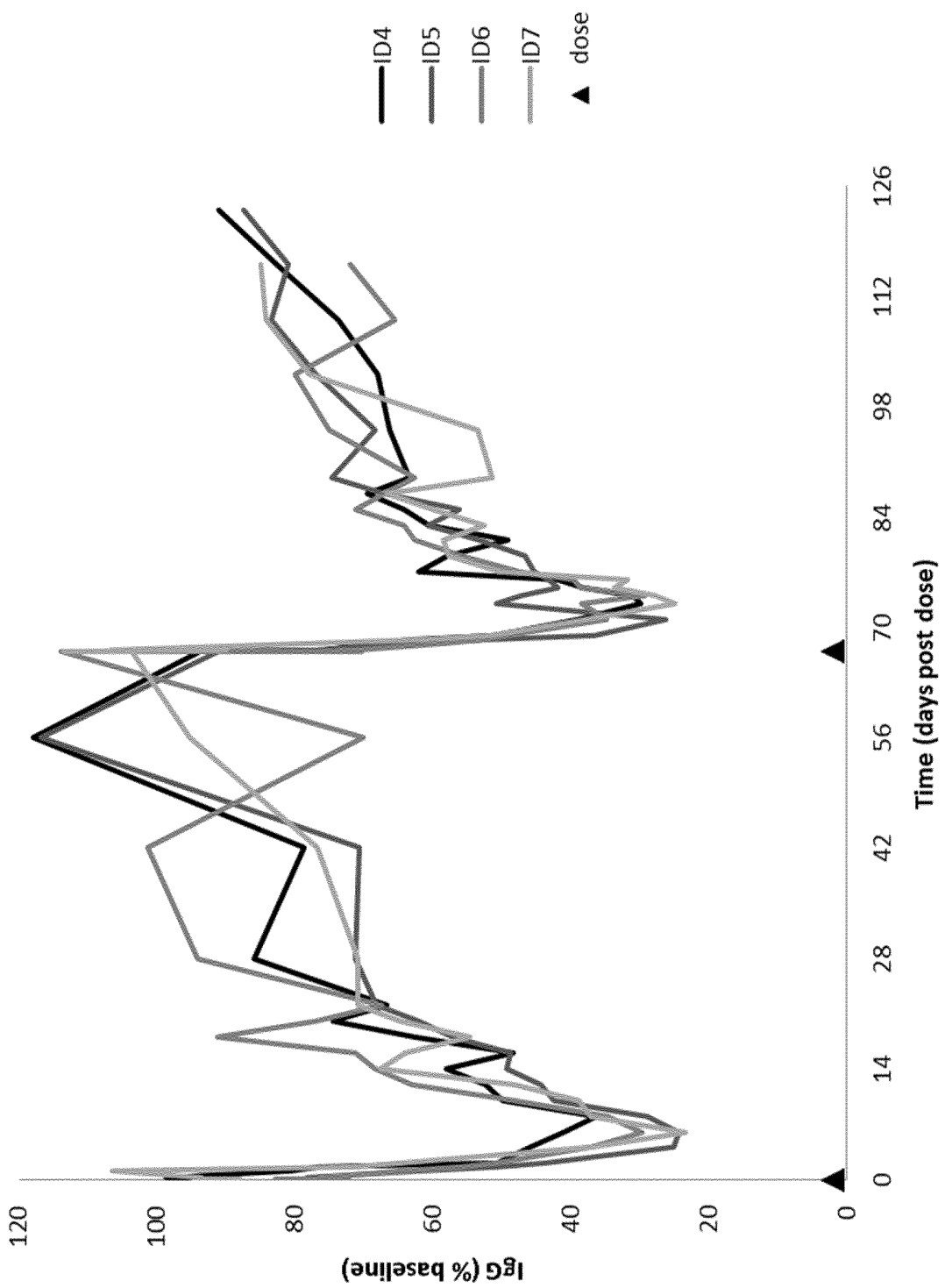


Figure 16 Change in plasma IgG levels in 4 cynomolgus monkeys receiving 10 IV doses of 20mg/Kg 1519.g57 Fab'PEG every 3 days

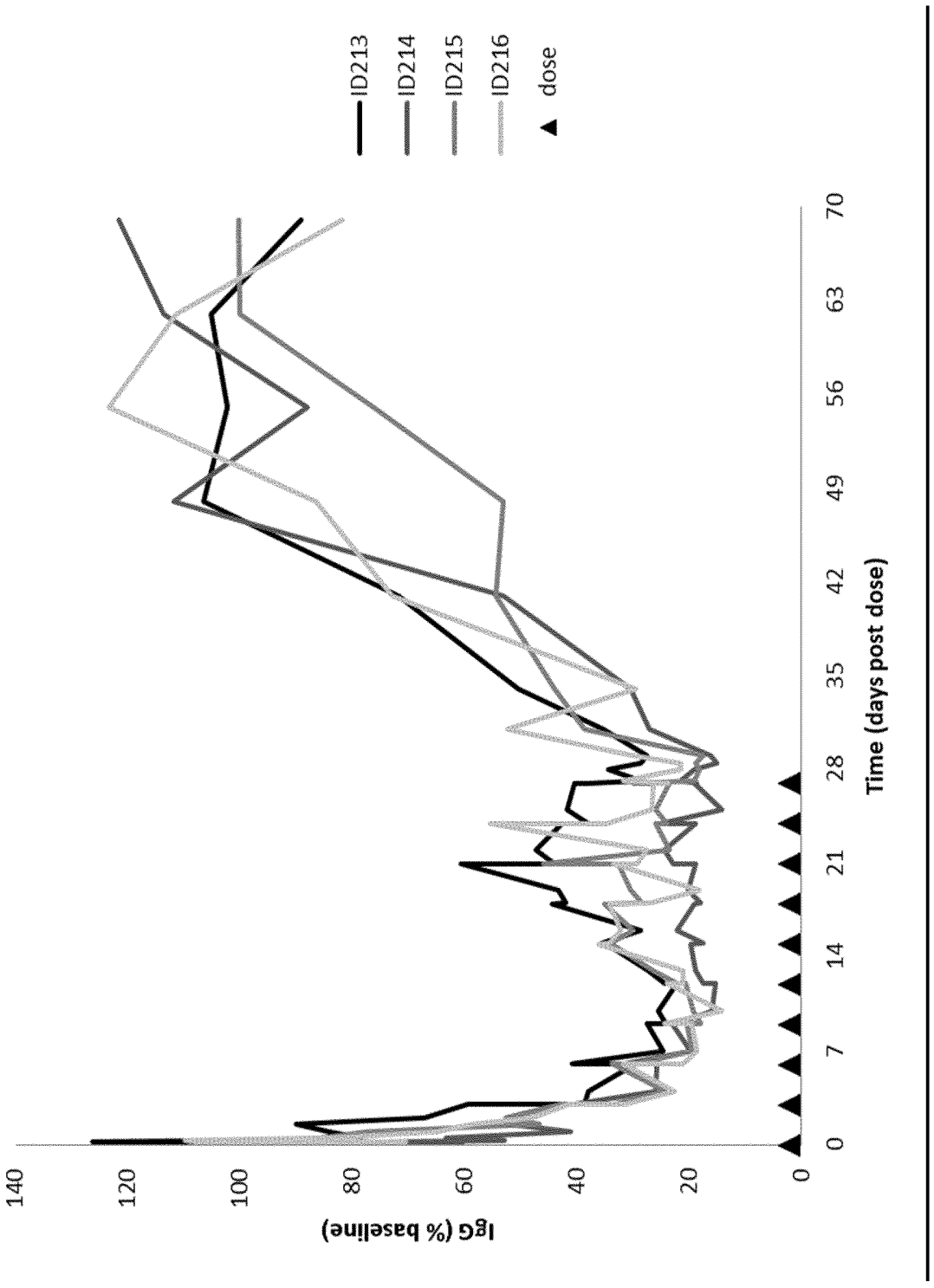


Figure 17 Change in plasma IgG levels in 4 cynomolgus monkeys after 2 IV doses of 30 mg/Kg 1519.g57 IgG4P i.v

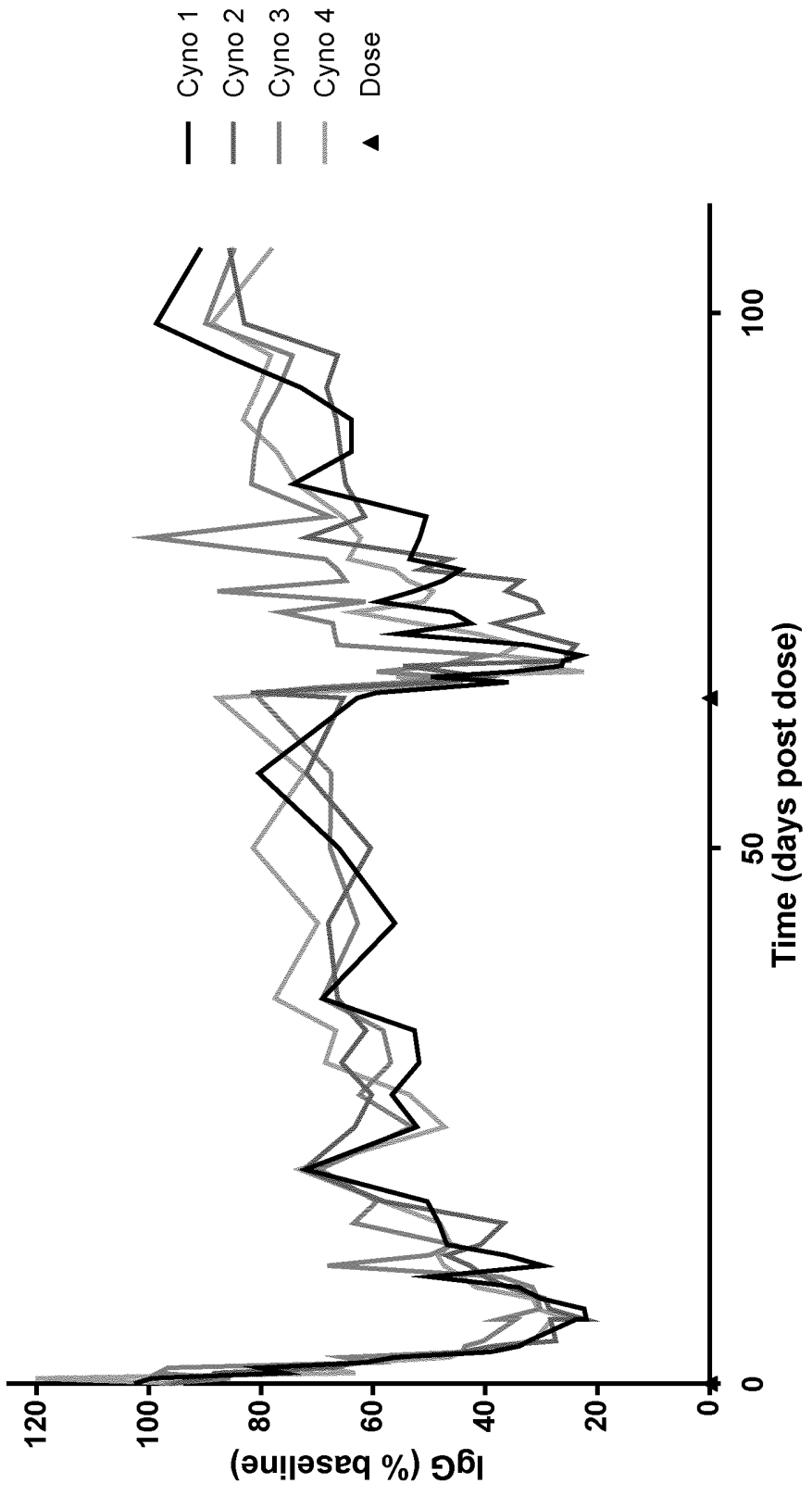


Figure 18 Change in plasma IgG levels in cynomolgus monkeys treated with 30 mg/Kg 1519.g57 IgG4P on day 0 followed by 5mg/Kg 1519.g57 IgG4P daily for 41 days

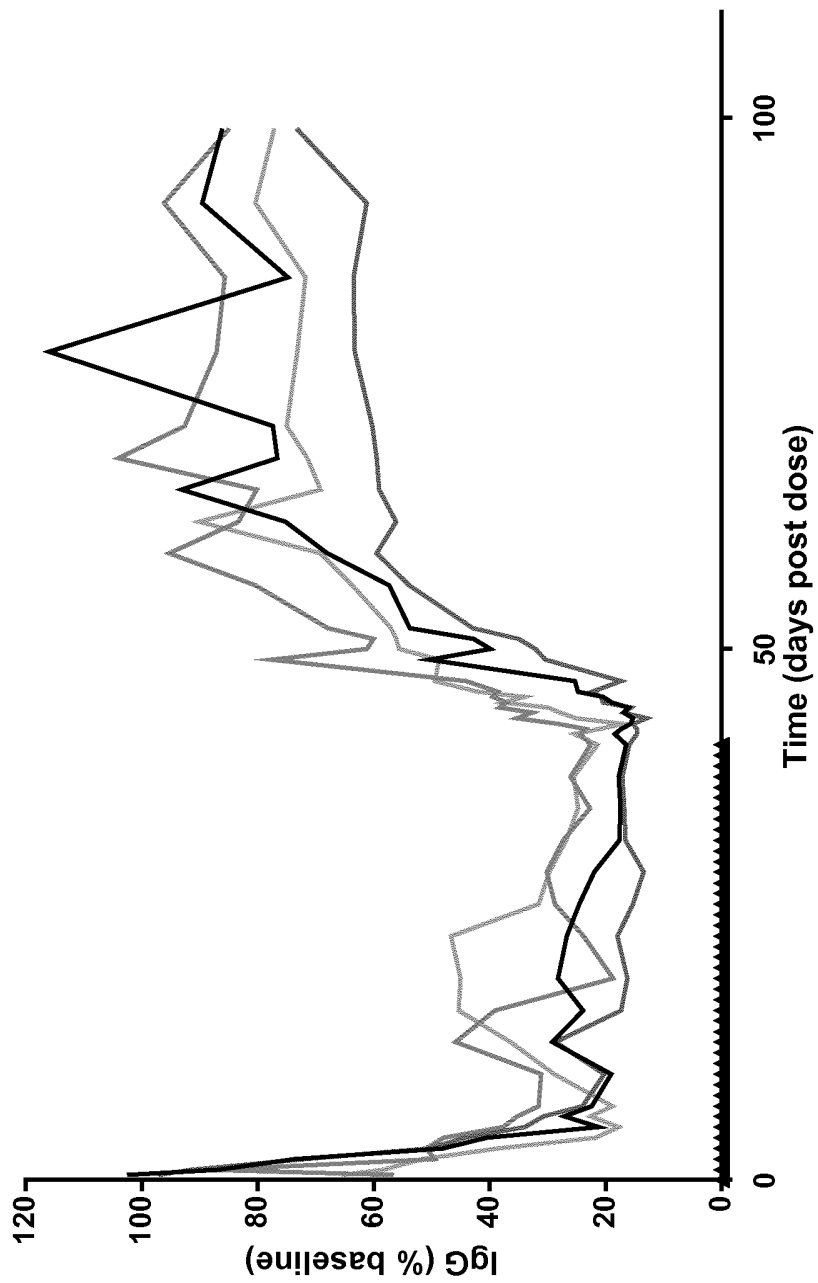


Figure 19 Change in plasma IgG levels in 4 cynomolgus monkeys receiving 42 daily doses of vehicle

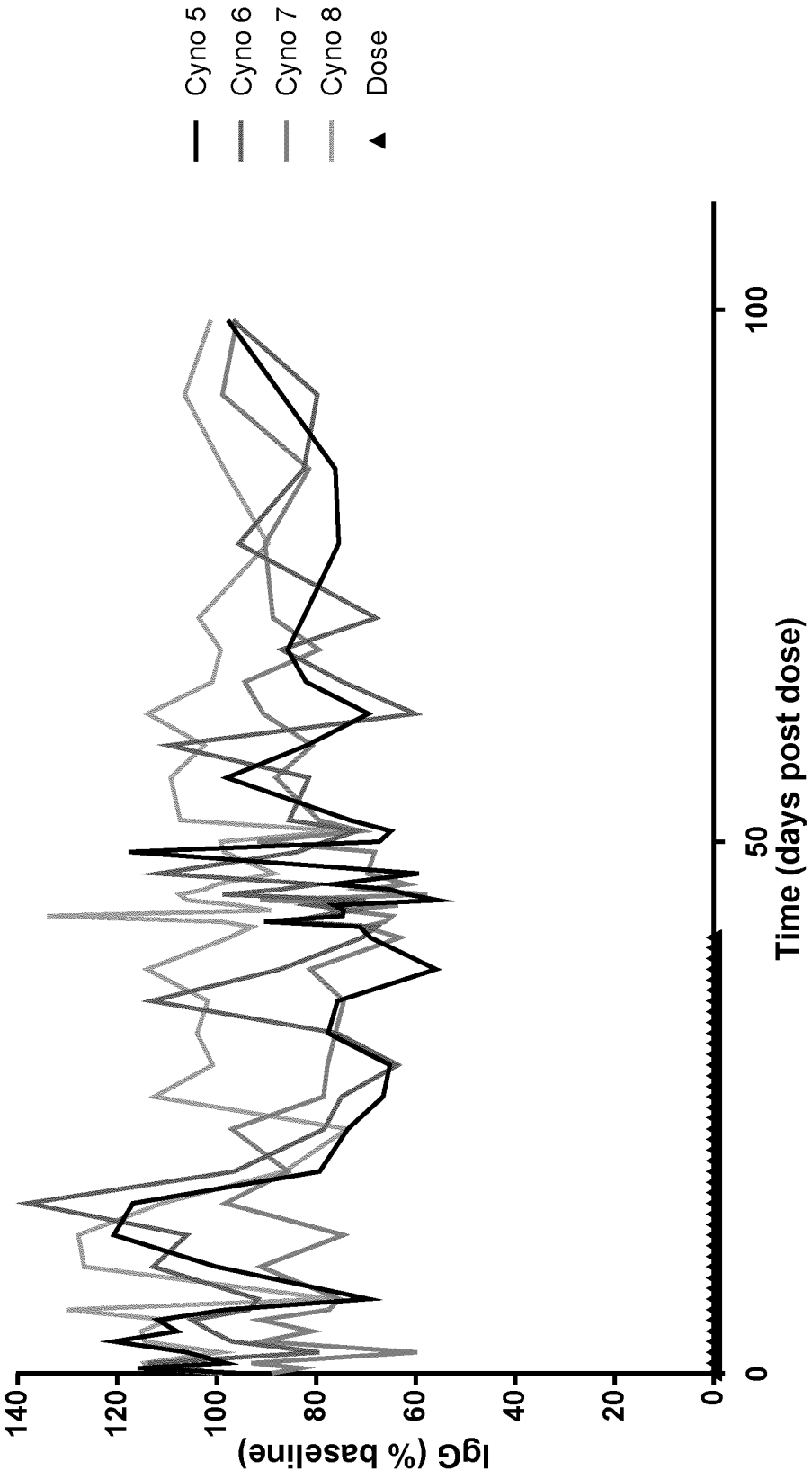


Figure 20 Increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'PEG or PBS IV

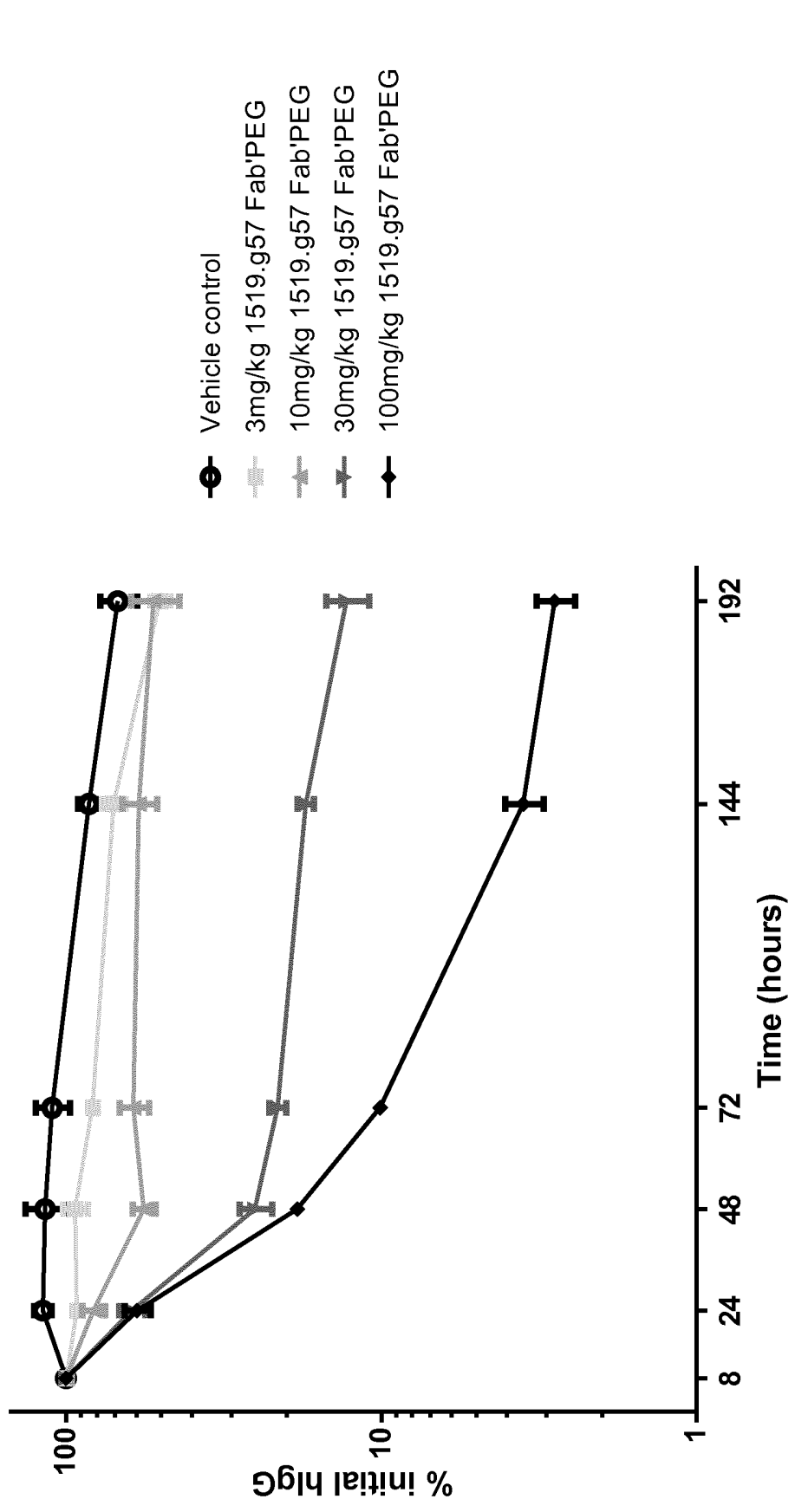


Figure 21 Increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 IgG1 or IgG4 or PBS IV

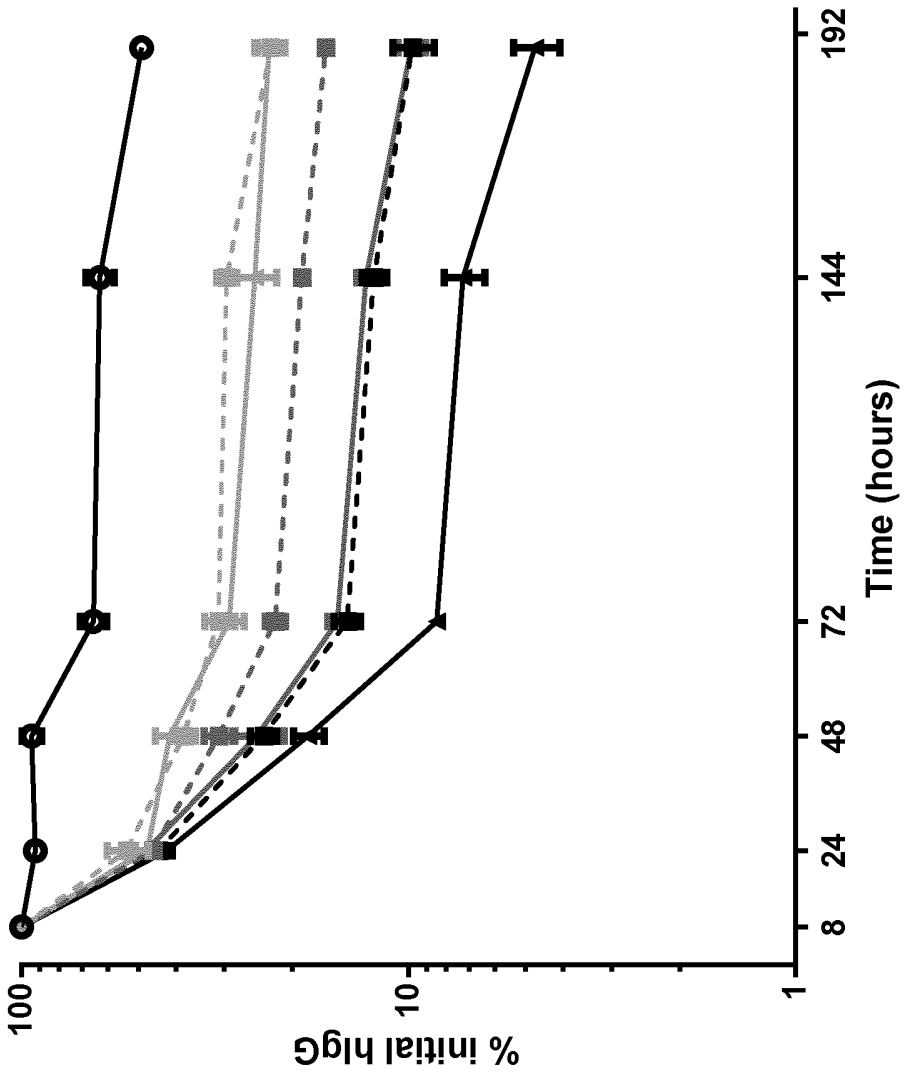


Figure 22 Increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab'-human serum albumin or PBS IV

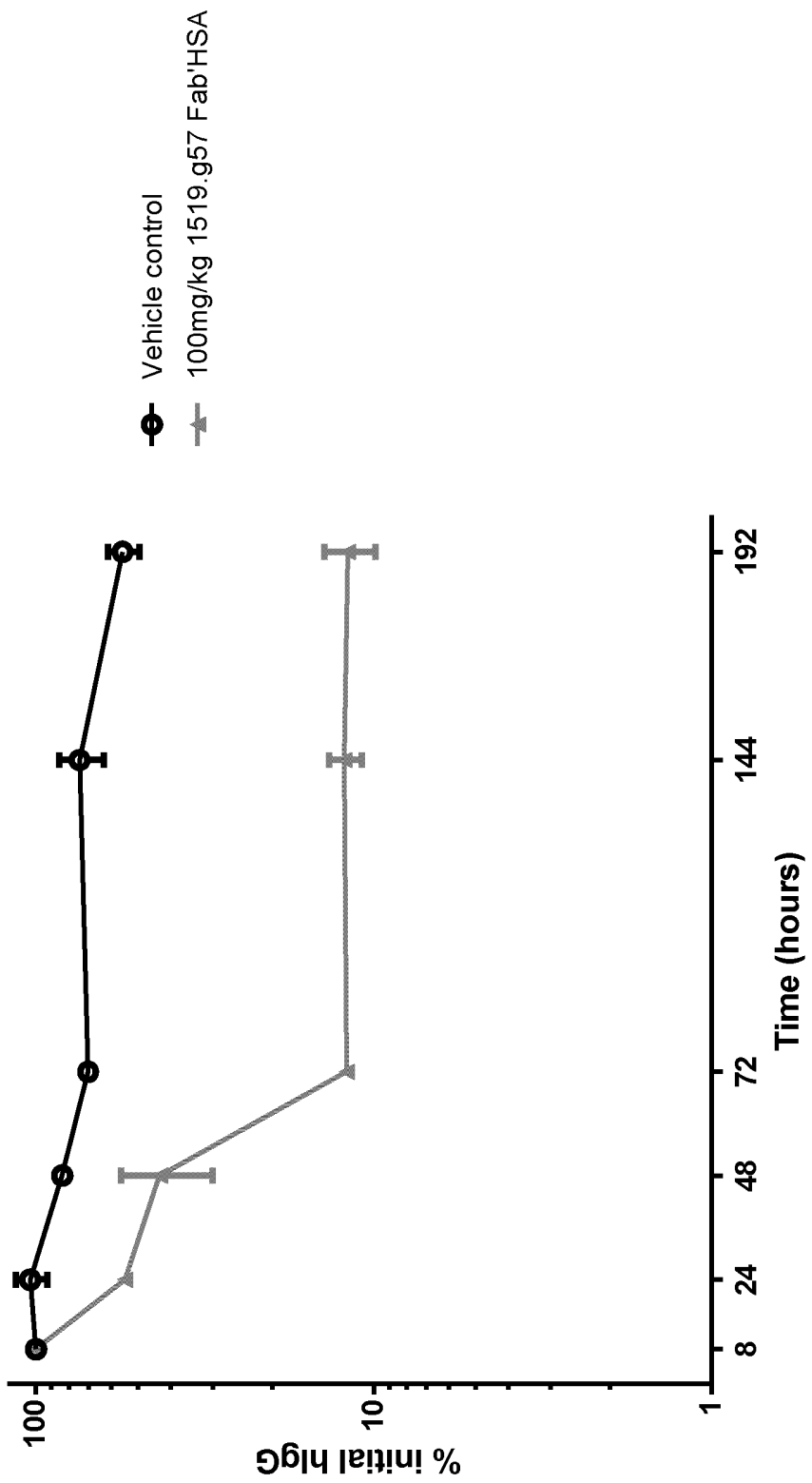


Figure 23 Increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 FabFv or PBS IV

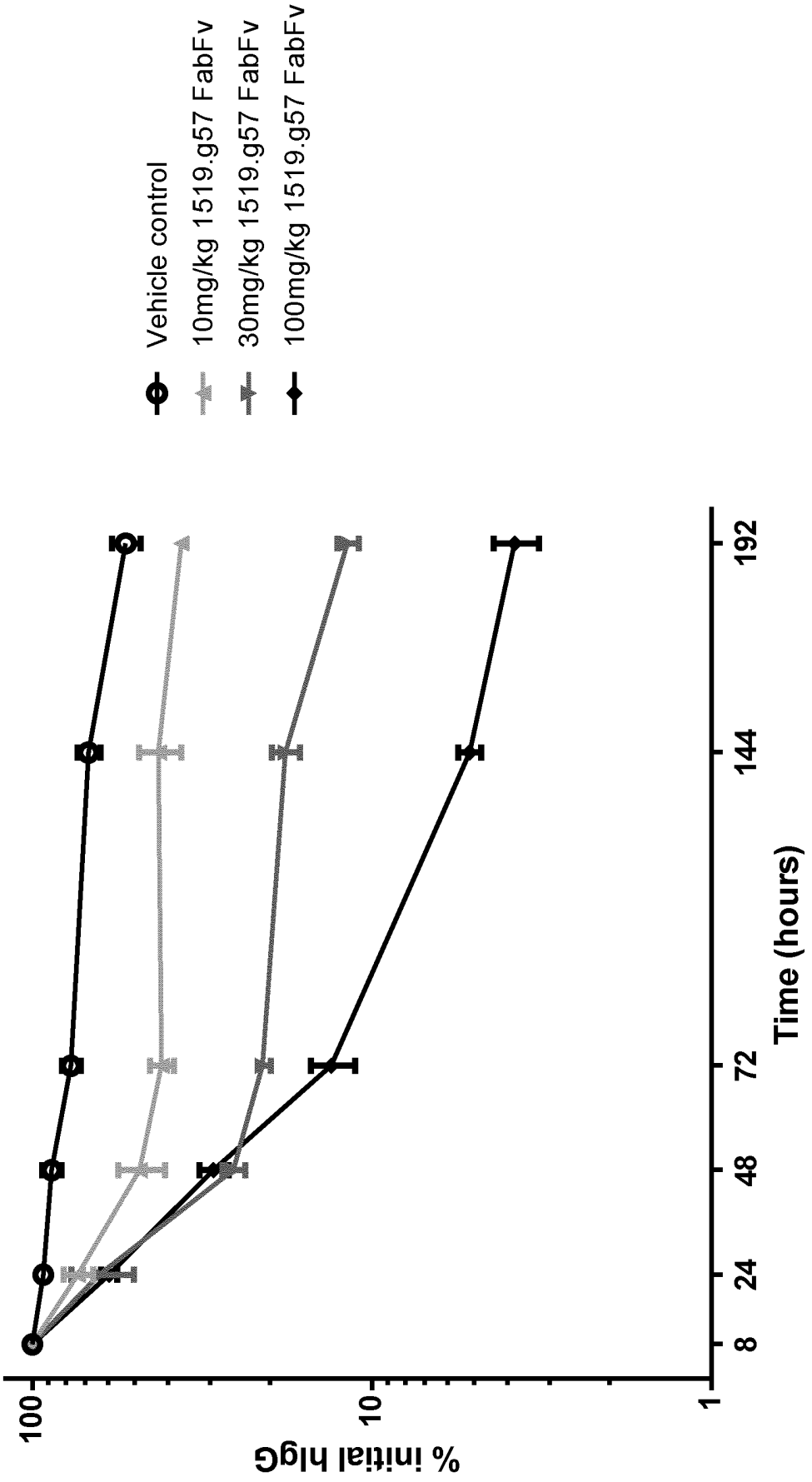


Figure 24 Increased clearance of IV hIgG in plasma of hFcRn transgenic mice treated with CA170_01519.g57 Fab or Fab'PEG or PBS IV

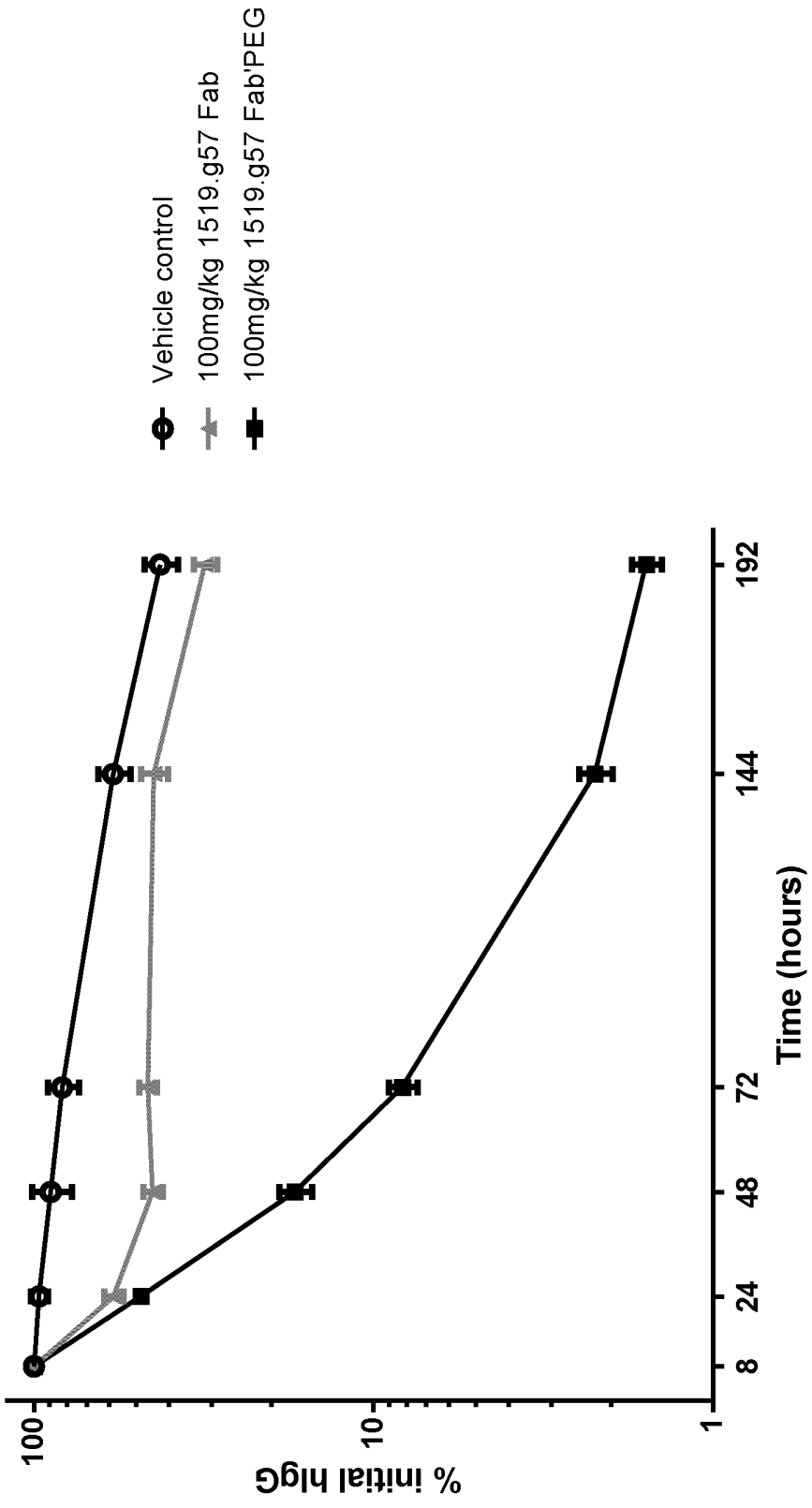
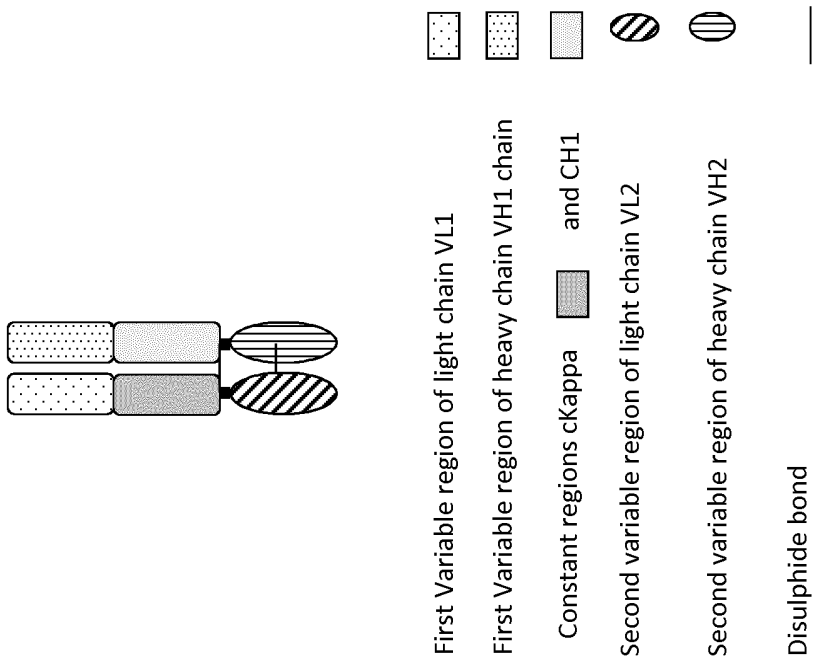


Figure 25


First Variable region of light chain VL1
First Variable region of heavy chain VH1 chain
Constant regions cKappa and CH1
Second variable region of light chain VL2
Second variable region of heavy chain VH2
Disulphide bond

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/059802

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 G01N33/53
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2007/092507 A1 (BALTHASAR JOSEPH P [US] ET AL) 26 April 2007 (2007-04-26) the whole document in particular, examples 12-15.	1-29, 32-42
Y	WO 2005/013912 A2 (UNIV NEW YORK STATE RES FOUND [US]; BALTHASAR JOSEPH P [US]; HANSEN RY) 17 February 2005 (2005-02-17) the whole document	1-29, 32-42
Y	WO 2009/080764 A2 (ABYLNX N V [BE]; HOOGENBOOM HENDRICUS RENERUS JACOBUS MATTHEUS [NL]; D) 2 July 2009 (2009-07-02) the whole document page 86 - page 104	1-29, 32-42

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 December 2013	02/01/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Pérez-Mato, Isabel

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/059802

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHRISTIANSON GREGORY J ET AL: "Monoclonal antibodies directed against human FcRn and their applications", MABS, vol. 4, no. 2, March 2012 (2012-03), pages 208-216, XP002700027, ISSN: 1942-0862 the whole document	1-29, 32-42
Y	GETMAN KATE E ET AL: "Pharmacokinetic effects of 4C9, an anti-FcRn antibody, in rats: implications for the use of FcRn inhibitors for the treatment of humoral autoimmune and alloimmune conditions", JOURNAL OF PHARMACEUTICAL SCIENCES, AMERICAN PHARMACEUTICAL ASSOCIATION, WASHINGTON, US, vol. 94, no. 4, 1 April 2005 (2005-04-01), pages 718-729, XP002417287, ISSN: 0022-3549, DOI: 10.1002/JPS.20297 the whole document	1-29, 32-42
Y	WARK K L ET AL: "Latest technologies for the enhancement of antibody affinity", ADVANCED DRUG DELIVERY REVIEWS, ELSEVIER BV, AMSTERDAM, NL, vol. 58, no. 5-6, 7 August 2006 (2006-08-07), pages 657-670, XP024892147, ISSN: 0169-409X, DOI: 10.1016/J.ADDR.2006.01.025 [retrieved on 2006-08-07] the whole document	10-29, 32-42
Y	WO 2006/106323 A1 (UCB SA [BE]; LAWSON ALASTAIR DAVID GRIFFITH [GB]) 12 October 2006 (2006-10-12) the whole document	10-29, 32-42
Y	E. P. ALTSHULER ET AL: "Generation of recombinant antibodies and means for increasing their affinity", BIOCHEMISTRY (MOSCOW), vol. 75, no. 13, 1 December 2010 (2010-12-01), pages 1584-1605, XP055069538, ISSN: 0006-2979, DOI: 10.1134/S0006297910130067 the whole document	10-29, 32-42

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/059802

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHOWDHURY P S ET AL: "IMPROVING ANTIBODY AFFINITY BY MIMICKING SOMATIC HYPERMUTATION IN VITRO", NATURE BIOTECHNOLOGY, NATURE PUBLISHING GROUP, NEW YORK, NY, US, vol. 17, 1 June 1999 (1999-06-01), pages 568-572, XP000918985, ISSN: 1087-0156, DOI: 10.1038/9872 the whole document -----	10-29, 32-42

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2013/059802

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-29, 32-42

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-29, 32-42

directed to anti-FcRn antibodies having certain sequences (or a certain KD), nucleic acids encoding these, vectors comprising said nucleic acids, host cells comprising said vectors, methods to produce the antibodies using said cells, pharmaceutical compositions comprising the antibodies and medical uses of said antibodies.

---

2. claims: 30, 31

directed to an assay for testing the ability of a test molecule such as an antibody to block human FcRn activity and in particular to recycle IgG comprising coating non-human mammalian cells expressing human FcRn alpha chain and human beta2 microglobulin onto a surface, contacting the cells with a test antibody and an IgG to be recycled allowing binding of both the test antibody and the IgG to FcRn, washing with an acidic buffer and detecting the amount of IgG internalised and/or recycled by the cells.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2013/059802

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2007092507 A1	26-04-2007	NONE	
WO 2005013912 A2	17-02-2005	CA 2534973 A1	17-02-2005
		EP 1660128 A2	31-05-2006
		JP 2007501847 A	01-02-2007
		US 2005079169 A1	14-04-2005
		WO 2005013912 A2	17-02-2005
WO 2009080764 A2	02-07-2009	NONE	
WO 2006106323 A1	12-10-2006	EP 1866337 A1	19-12-2007
		ES 2388177 T3	10-10-2012
		US 2009075398 A1	19-03-2009
		WO 2006106323 A1	12-10-2006

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names (Rec. INN): List 45

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–73) and Recommended (1–35) International Nonproprietary Names can be found in *Cumulative List No. 9, 1996.*

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMENDÉES (DCI Rec): Liste 45

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisises par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–73) et recommandées (1–35) dans la *Liste récapitulative No. 9, 1996.*

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS (DCI Rec.): Lista 45

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–73) y Recomendadas (1–35) se encuentran reunidas en *Cumulative List No. 9, 1996.*

Latin, English, French, Spanish:

Recommended INN	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula empírica; Fórmula desarrollada*

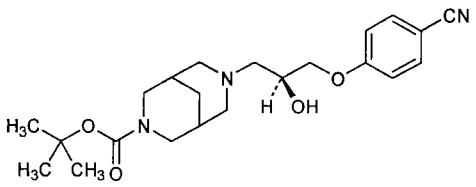
adekalantum

adekalant — *tert*-butyl 7-[(*S*)-3-(*p*-cyanophenoxy)-2-hydroxypropyl]-3,7-diazabicyclo [3.3.1] nonane-3-carboxylate

adékalant — 7-[(2*S*)-3-(4-cyanophénoxy)-2-hydroxypropyl]-3,7-diazabicyclo[3.3.1] nonane-3-carboxylate de 1,1-diméthyéthyle

adekalant — 7-[(*S*)-3-(*p*-cianofenoxi)-2-hidroxipropil]-3,7-diazabiciclo[3.3.1]nonano-3-carboxilato de *terc*-butilo

$C_{22}H_{31}N_3O_4$



alemtuzumabum

alemtuzumab — immunoglobulin G 1 (human-rat monoclonal CAMPATH-1H γ1-chain anti-human antigen CD52), disulfide with human-rat monoclonal CAMPATH-1H light chain, dimer

alemtuzumab — immunoglobuline G1 anti-(antigène CD52 humain) (chaîne γ1 de l'anticorps monoclonal de rat CAMPATH-1H humanisé), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de rat CAMPATH-1H humanisé

alemtuzumab — inmunoglobulina G 1 anti-(antígeno humano CD52) (cadena γ1 del anticuerpo monoclonal hombre-rata CAMPATH-1H), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-rata CAMPATH-1H

aliskirenum

aliskiren

(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoyl-2-methylpropyl)-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxypropoxy)benzyl]-8-methylnonanamide

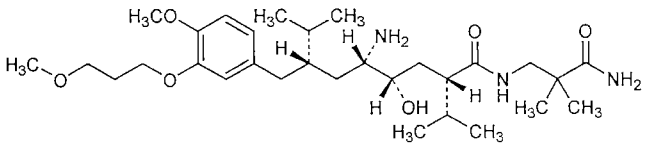
aliskirène

(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(3-amino-2,2-diméthyl-3-oxopropyl)-4-hydroxy-7-[4-méthoxy-3-(3-méthoxypropoxy)benzyl]-8-méthyl-2-(1-méthyléthyl)=nonanamide

aliskireno

(2*S*,4*S*,5*S*,7*S*)-5-amino-*N*-(2-carbamoil-2-metilpropil)-4-hidroxi-2-isopropil-7-[4-metoxi-3-(3-metoxipropoxi)bencil]-8-metilnonanamida

$C_{30}H_{53}N_3O_6$



amiloxatum

amiloxate

isopentyl *p*-methoxycinnamate

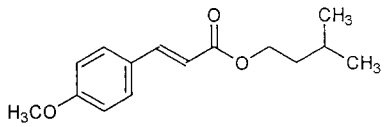
amiloxate

(*E*)-3-(4-méthoxyphényl)prop-2-énoate de 3-méthylbutyle

amiloxato

p-metoxicinamato de isopentilo

$C_{15}H_{20}O_3$



bevacizumabum

bevacizumab

immunoglobulin G 1 (human-mouse monoclonal rhuMAb-VEGF γ-chain anti-human vascular endothelial growth factor), disulfide with human-mouse monoclonal rhuMAb-VEGF light chain, dimer

bévacizumab

immunoglobuline G1 anti-(facteur de croissance de l'endothélium vasculaire humain) (chaîne γ1 de l'anticorps monoclonal de souris rhuMAb-VEGF humanisé), dimère du disulfure avec la chaîne légère de l'anticorps monoclonal de souris rhuMAb-VEGF humanisé

bevacizumab

inmunoglobulina G 1 anti-(factor de crecimiento del endotelio vascular humano) (cadena γ1 del anticuerpo monoclonal hombre ratón rhuMAb-VEGF), dímero del disulfuro con la cadena ligera del anticuerpo monoclonal hombre-ratón rhuMAb-VEGF

$C_{6638}H_{10160}N_{1720}O_{2108}S_{44}$

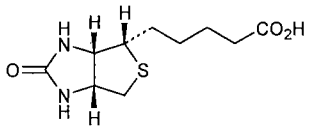
biotinum

biotin — 5-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]pentanoic acid

biotine — acide 5-[(3a*S*,4*S*,6a*R*)-2-oxohexahydro-1*H*-thiéno[3,4-*d*]imidazol-4-yl]pentanoïque

biotina — ácido 5-[(3a*S*,4*S*,6a*R*)-2-oxohexahidro-1*H*-tieno[3,4-*d*]imidazol-4-il]pentanoico

$C_{10}H_{16}N_2O_3S$



bivatuzumabum

bivatuzumab — immunoglobulin G 1 (human-mouse monoclonal BIWA4 γ1-chain anti-human antigen CD44v8), disulfide with human-mouse monoclonal BIWA4 κ-chain, dimer

bivatuzumab — immunoglobuline G1 anti-(antigène CD44v8 humain) (chaîne γ1 de l'anticorps monoclonal de souris BIWA4 humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris BIWA4 humanisé

bivatuzumab — inmunoglobulina G 1 anti-(antigeno humano CD44v8) cadena γ1 del anticuerpo monoclonal hombre-ratón BIWA4), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón BIWA4

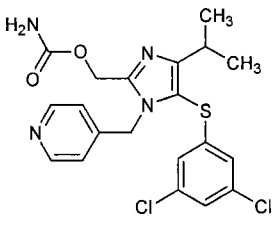
capravirinum

capravirine — 5-[(3,5-dichlorophenyl)thio]-4-isopropyl-1-(4-pyridylmethyl)imidazole-2-methanol carbamate (ester)

capravirine — carbamate de [5-[(3,5-dichlorophényl)sulfanyl]-4-(1-méthyléthyl)-1-(pyridin-4-ylméthyl)-1*H*-imidazol-2-yl]méthyle

capravirina — carbamato (éster)de 5-[(3,5-diclorofenil)tio]-4-isopropil-1-(4-piridilmetil) imidazol-2-metanol

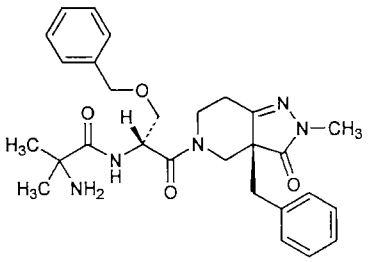
$C_{20}H_{20}Cl_2N_4O_2S$



capromorelinum

capromorelin	2-amino-*N*-[(1*R*)-1-[[(3a*R*)-3a-benzyl-2,3,3a,4,6,7-hexahydro-2-methyl-3-oxo-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]carbonyl]-2-(benzyloxy)ethyl]-2-methylpropionamide
capromoréline	2-amino-*N*-[(1*R*)-2-[(3a*R*)-3a-benzyl-2-méthyl-3-oxo-2,3,3a,4,6,7-hexahydro-5*H*-pyrazolo[4,3-*c*]pyridin-5-yl]-1-[(benzyloxy)méthyl]-2-oxoéthyl]-2-méthylpropanamide
capromorelina	2-amino-*N*-[(1*R*)-1-[[(3a*R*)-3a-bencil-2,3,3a,4,6,7-hexahidro-2-metil-3-oxo-5*H*-pirazolo[4,3-*c*]piridin-5-il]carbonil]-2-(benciloxi)etil]-2-metilpropionamida

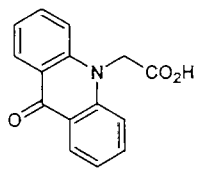
$C_{28}H_{35}N_5O_4$



cridanimodum

cridanimod	9-oxo-10-acridanacetic acid
cridanimod	acide (9-oxoacridin-10(9*H*)-yl)acétique
cridanimod	ácido 9-oxo-10-acridanacético

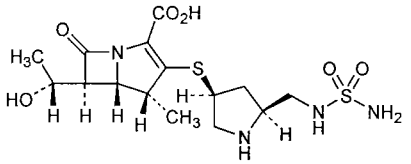
$C_{15}H_{11}NO_3$



doripenemum

doripenem	(+)-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-3-[[(3*S*,5*S*)-5-[(sulfamoylamino)methyl]-3-pyrrolidinyl]thio]-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid
doripénem	(+)-acide (4*R*,5*S*,6*S*)-6-[(1*R*)-1-hydroxyéthyl]-4-méthyl-7-oxo-3-[[(3*S*,5*S*)-5-[(aminosulfonylamino)méthyl]pyrrolidin-3-yl]sulfanyl]-1-azabicyclo[3.2.0]hept-2-ène-2-carboxylique
doripenem	ácido (+)-(4*R*,5*S*,6*S*)-6-[(1*R*)-1-hidroxietil]-4-metil-7-oxo-3-[[(3*S*,5*S*)-5-[(sulfamoilamino)metil]-3-pirrolidinil]tio]-1-azabicyclo[3.2.0]hept-2-eno-2-carboxílico

$C_{15}H_{24}N_4O_6S_2$



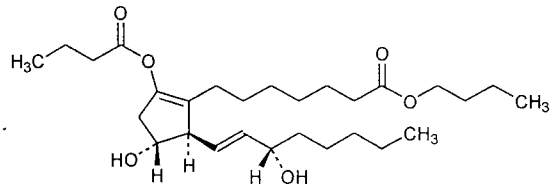
ecraprostum

ecraprost — butyl (*4R,5R*)-2,4-dihydroxy-5-[(1*E*,3*S*)-3-hydroxy-1-octenyl]-1-cyclopentene-1-heptanoate, 2-butyrate

écraprost — 7-[(*4R,5R*)-2-(butanoyloxy)-4-hydroxy-5-[(1*E*,3*S*)-3-hydroxyoct-1-ényl]cyclopent-1-ényl]heptanoate de butyle

ecraprost — 2-butirato de (*4R,5R*)-2,4-dihidroxi-5-[(1*E*,3*S*)-3-hidroxi-1-octenil]-1-ciclopenteno-1-heptanoato de butilo

$C_{28}H_{48}O_6$



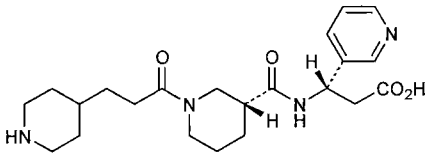
elarofibanum

elarofiban — (*S*)-β-[(*R*)-1-[3-(4-piperidyl)propionyl]nipecotamido]-3-pyridinepropionic acid

élarofiban — acide (3*S*)-3-[[[(3*R*)-1-[3-(pipéridin-4-yl)propanoyl]piperidin-3-yl]carbonyl]amino]-3-(pyridin-3-yl)propanoïque

elarofibán — ácido (*S*)-β-[(*R*)-1-[3-(4-piperidil)propionil]nipecotamido]-3-piridinapropiónico

$C_{22}H_{32}N_4O_4$

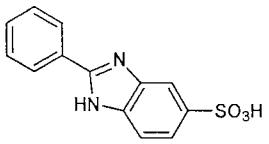


ensulizolum
ensulizole — 2-phenyl-5-benzimidazolesulfonic acid

ensulizole — acide 2-phényl-1*H*-benzimidazole-5-sulfonique

ensulizol — ácido 2-fenil-5-bencimidazolsulfónico

$C_{13}H_{10}N_2O_3S$

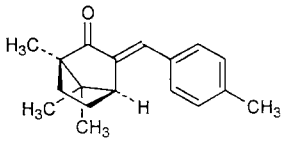


enzacamenum
enzacamene — (±)-3-(*p*-methylbenzylidene)camphor

enzacamène — (*E*)-(1*RS*,4*SR*)-1,7,7-triméthyl-3-(4-méthylbenzylidène)bicyclo[2.2.1]=heptan-2-one

enzacameno — 1,7,7-trimetil-3-(4-metilbencilideno)biciclo[2.2.1]heptan-2-ona

$C_{18}H_{22}O$



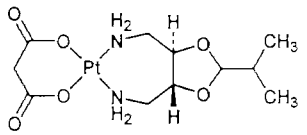
and enantiomer
et énantiomère
y enantiómero

eptaplatinum
eptaplatin — *cis*-[(4*R*,5*R*)-2-isopropyl-1,3-dioxolane-4,5-bis(methylamine)-*N*,*N*′][malonato(2-)-*O*,*O*′]platinum

eptaplatine — (*SP*-4-2)-[[(4*R*,5*R*)-2-(1-méthyléthyl)-1,3-dioxolane-4,5-diyl]bis(méthanamine)-*N*,*N*′][propanedioato(2-)-*O*,*O*′]platine

eptaplatino — *cis*-[(4*R*,5*R*)-2-isopropil-1,3-dioxolano-4,5-bis(metilamina)-*N*,*N*′][malonato=(2-)-*O*,*O*′]platino

$C_{11}H_{20}N_2O_6Pt$



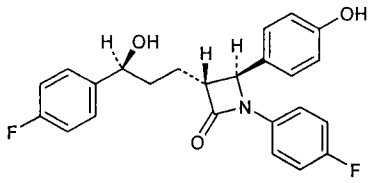
ezetimibum

ezetimibe — (3*R*,4*S*)-1-(*p*-fluorophenyl)-3-[(3*S*)-3-(*p*-fluorophenyl)-3-hydroxypropyl]-4-(*p*-hydroxyphenyl)-2-azetidinone

ézétimibe — (3*R*,4*S*)-1-(4-fluorophényl)-3-[(3*S*)-3-(4-fluorophényl)-3-hydroxypropyl]-4-(4-hydroxyphényl)azétidin-2-one

ezetimiba — (3*R*,4*S*)-1-(*p*-fluorofenil)-3-[(3*S*)-3-(*p*-fluorofenil)-3-hidroxipropil]-4-(*p*-hidroxifenil)-2-azetidinona

$C_{24}H_{21}F_2NO_3$



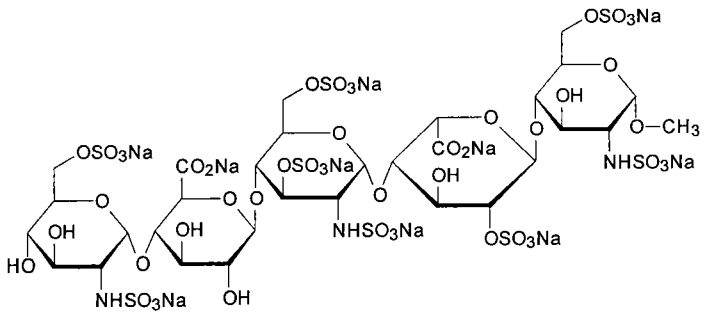
fondaparinuxum natricum

fondaparinux sodium — methyl *O*-2-deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-*O*-β-D-glucopyranuronosyl-(1→4)-*O*-2-deoxy-3,6-di-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-*O*-2-*O*-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopyranoside, decasodium salt

fondaparinux sodique — *O*-6-*O*-sulfo-2-(sulfoamino)-2-désoxy-α-D-glucopyranosyl-(1→4)-*O*-β-D-glucopyranuronosyl-(1→4)-*O*-3,6-di-*O*-sulfo-2-(sulfoamino)-2-désoxy-α-D-glucopyranosyl-(1→4)-*O*-2-*O*-sulfo-α-L-idopyranuronosyl-(1→4)-6-*O*-sulfo-2-(sulfoamino)-2-désoxy-α-D-glucopyranoside de méthyle décasodique

fondaparinux sódico — sal decasódica del *O*-2-desoxi-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopiranosil-(1→4)-*O*-β-D-glucopiranuronosil-(1→4)-*O*-2-desoxi-3,6-di-*O*-sulfo-2-(sulfoamino)-α-D-glucopiranosil-(1→4)-*O*-2-*O*-sulfo-α-L-idopirauronosil-(1→4)-2-desoxi-6-*O*-sulfo-2-(sulfoamino)-α-D-glucopiranósido de metilo

$C_{31}H_{43}N_3Na_{10}O_{49}S_8$



fosamprenavirum

fosamprenavir

(3*S*)-tetrahydro-3-furyl [(αS)-α-[(1R)-1-hydroxy-2-(N^1-isobutylsulfanilamido)= ethyl] phenethyl]carbamate, dihydrogen phosphate (ester)

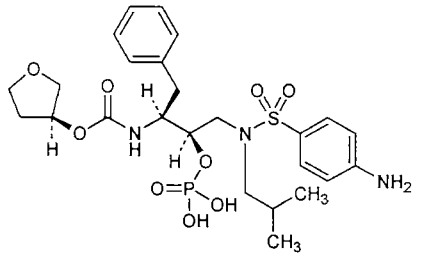
fosamprénavir

dihydrogénophosphate de (1R,2S)-1-[[[(4-aminophényl)sulfonyl](2-méthyl= propyl)amino]méthyl]-3-phényl-2-[[[[(3S)-tétrahydrofuran-3-yl]oxy]= carbonyl]amino] propyle

fosamprenavir

dihidrógenofosfato (éster) de [(αS)-α-[(1R)-1-hidroxi-2-(*N*^{1}-isobutilsulfanil= amido)etil]fenetil]carbamato de(3*S*)-tetrahidro-3-furilo

$C_{25}H_{36}N_3O_9PS$



fosfluconazolum

fosfluconazole

2,4-difluoro-α,α-bis(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol, dihydrogen phosphate (ester)

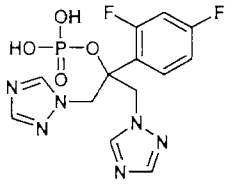
fosfluconazole

dihydrogénophosphate de 1-(2,4-difluorophényl)-2-(1*H*-1,2,4-triazol-1-yl)-1-(1*H*-1,2,4-triazol-1-ylméthyl)éthyle

fosfluconazol

dihidrógenofosfato (éster) de 2,4-difluoro-α,α-bis(1*H*-1,2,4-triazol-1-ilmetil) bencilo

$C_{13}H_{13}F_2N_6O_4P$



fosvesetum

fosveset

N-[2-[bis(carboxymethyl)amino]ethyl]-*N*-[(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine, 4,4-diphenylcyclohexyl hydrogen phosphate (ester)

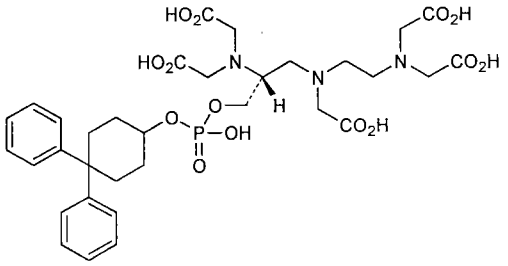
fosvéset

acide 2,2'-[[(1*R*)-1-[[[2-[bis(carboxyméthyl)amino]éthyl](carboxyméthyl)= amino] méthyl]-2-[[[(4,4-diphénylcyclohexyl)oxy]hydroxyphosphoryl]= oxy]éthyl]imino] diacétique

fosveset

4,4-difenilciclohexilhidrógenofosfato (éster) de *N*-[2-[bis(carboximetil)= amino]etil]-*N*-[(*R*)-2-[bis(carboximetil)amino]-3-hidroxipropil]glicina

$C_{33}H_{44}N_3O_{14}P$



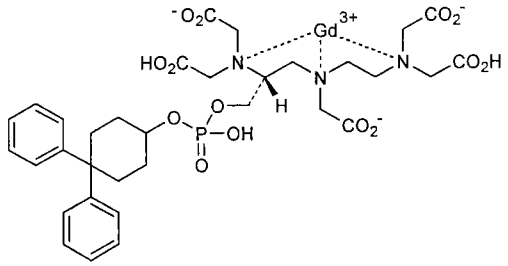
gadofosvesetum

gadofosveset — trihydrogen [*N*-[2-[bis(carboxymethyl)amino]ethyl]-*N*-[(*R*)-2-[bis(carboxymethyl)amino]-3-hydroxypropyl]glycine 4,4-diphenylcyclohexyl hydrogen phosphato(6-)]gadolinate(3-)

gadofosvéset — trihydrogéno[2,2'-[[(1*R*)-1-[[[2-[bis[(carboxy-κ-*O*)méthyl]amino-κ-*N*]éthyl]=[carboxy-κ-*O*)méthyl]amino-κ-*N*]méthyl]-2-[[[(4,4-diphénylcyclohexyl)oxy]=hydroxyphosphoryl]oxy]éthyl]imino-κ-*N*]diacétato(6-)-κ-*O*-κ-*O*']gadolinate(3-)

gadofosveset — [4,4-difenilciclohexilhidrógenofosfato de (6-)*N*-[2-[bis(carboximetil)amino]=etil]-*N*-[(*R*)-2-[bis(carboximetil)amino]-3-hidroxipropil]glicina]gadolinato(3-) de trihidrógeno

$C_{33}H_{41}GdN_3O_{14}P$



gemtuzumabum

gemtuzumab — immunoglobulin G 4 (human-mouse monoclonal hP67.6 γ4-chain anti-human antigen CD 33), disulfide with human-mouse monoclonal hP67.6 κ-chain, dimer

gemtuzumab — immunoglobuline G 4 anti-(antigène CD 33 humain) (chaîne γ4 de l'anticorps monoclonal de souris hP67.6 humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris hP67.6 humanisé

gemtuzumab — inmunoglobulina G 4 anti-(antigeno humano CD 33) (cadena γ4 del anticuerpo monoclonal hP67.6 hombre-ratón), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hP67.6 hombre-ratón

idraparinuxum natricum

idraparinux sodium

methyl *O*-2,3,4-tri-*O*-methyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside nonasodium

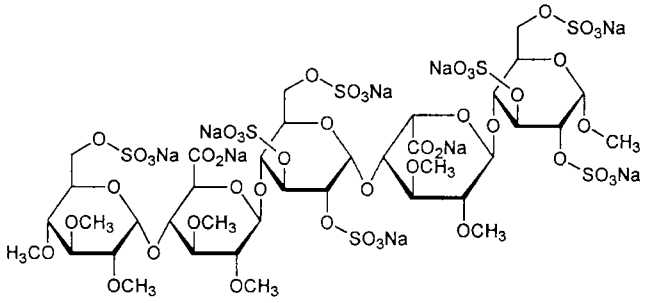
idraparinux sodique

O-2,3,4-tri-*O*-méthyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-méthyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-méthyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside de méthyle nonasodique

idraparinux sódico

O-2,3,4-tri-*O*-metil-6-*O*-sulfo-α-D-glucopiranosil-(1→4)-*O*-2,3-di-*O*-metil-β-D-glucopiranuronosil-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopiranosil-(1→4)-*O*-2,3-di-*O*-metil-α-L-idopiranuronosil-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopiranósido de metilo nonasódico

$C_{38}H_{55}Na_9O_{49}S_7$



isatoribinum

isatoribine

5-amino-3-(β-D-ribofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione

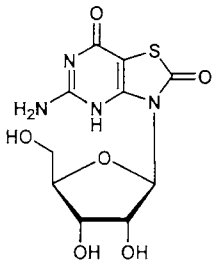
isatoribine

5-amino-3-(β-D-ribofuranosyl)thiazolo[4,5-*d*]pyrimidine-2,7(3*H*,6*H*)-dione

isatoribina

5-amino-3-β-D-ribofuranosiltiazolo[4,5-*d*]pirimidina-2,7(3*H*,6*H*)-diona

$C_{10}H_{12}N_4O_6S$



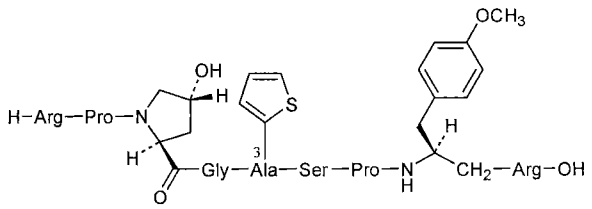
labradimilum

labradimil — N^2-[(*S*)-2-[L-arginyl-L-prolyl-*trans*-4-hydroxy-L-prolylglycyl-3-(2-thienyl)-L-alanyl-L-seryl-L-prolinamido]-3-(*p*-methoxyphenyl)propyl]-L-arginine

labradimil — N^2-[(2*S*)-2-[[L-arginyl-L-prolyl-[(4*R*)-4-hydroxy-L-prolyl]-glycyl-[3-(thiophén-2-yl]-L-alanyl]-L-seryl-L-prolyl]amino]-3-(4-méthoxyphényl)propyl]-L-arginine

labradimil — N^2-[(*S*)-2-[L-arginil-L-prolil-*trans*-4-hidroxi-L-prolilglicil-3-(2-tienil)-L-alanil-L-seril-L-prolinamido]-3-(*p*-metoxifenil)propil]-L-arginina

$C_{49}H_{75}N_{15}O_{12}S$



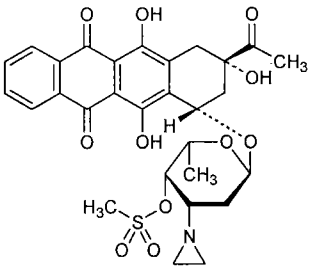
ladirubicinum

ladirubicin — (1*S*,3*S*)-3-acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-6,11-dioxo-1-naphthacenyl 3-(1-aziridinyl)-2,3,6-trideoxy-4-*O*-(methylsulfonyl)-α-L-*lyxo*-hexopyranoside

ladirubicine — (7*S*,9*S*)-9-acétyl-7-[[3-(aziridin-1-yl)-4-*O*-(méthylsulfonyl)-2,3,6-tridésoxy-α-L-*lyxo*-hexopyranosyl]oxy]-6,9,11-trihydroxy-7,8,9,10-tétrahydrotétracène-5,12-dione

ladirubicina — (1*S*,3*S*)-3-acetil-1,2,3,4,6,11-hexahidro-3,5,12-trihidroxi-6,11-dioxo-1-naftacenil 3-(1-aziridinil)-2,3,6-tridesoxi-4-*O*-(metilsulfonil)-α-L-*lixo*-hexopiranósido

$C_{29}H_{31}NO_{11}S$

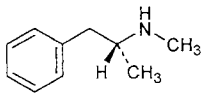


lerdelimumabum

lerdelimumab	immunoglobulin G4, anti-(human transforming growth factor b2) (human monocloal CAT-152 γ 4-chain), disulfide with human monoclonal CAT-152 λ-chain, dimer
lérdelimumab	immunoglobuline G4, anti-(facteur de croissance transformant humain b2) (chaine γ 4 de l'anticorps monoclonal humain CAT-152), dimère du disulfure avec la chaîne λ de l'anticorps monoclonal humain CAT-152
lerdelimumab	inmunoglobulina G4, anti-(factor b2 de crecimiento transformador humano)(cadena γ 4 del anticuerpo monoclonal humano CAT-152), dimero del disulfuro con la cadena λ del anticuerpo monoclonal humano CAT-152

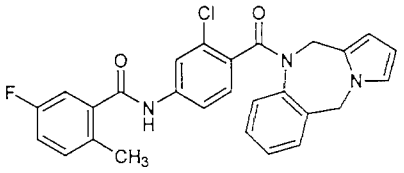
levmetamfetaminum

levmetamfetamine	(-)-(*R*)-*N*,α-dimethylphenethylamine
levmétamfétamine	(-)-(2*R*)-*N*-méthyl-1-phénylpropan-2-amine
levmetanfetamina	(-)-(*R*)-*N*,α-dimetilfenetilamina
	$C_{10}H_{15}N$



lixivaptanum

lixivaptan	3'-chloro-5-fluoro-4'-(5*H*-pyrrolo[2,1-*c*][1.4]benzodiazepin-10(11*H*)-ylcarbonyl)-*o*-toluanilide
lixivaptan	*N*-[3-chloro-4-[(5*H*-pyrrolo[2,1-*c*][1,4]benzodiazépin-10(11*H*)-yl)carbonyl]phényl]-5-fluoro-2-méthylbenzamide
lixivaptán	3'-cloro-5-fluoro-4'-(5*H*-pirrolo[2,1-*c*][1,4]benzodiazepin-10(11*H*)-ilcarbonil)-*o*-toluanilida
	$C_{27}H_{21}ClFN_3O_2$



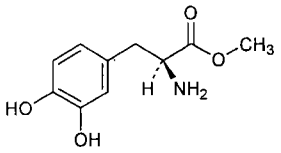
melevodopum

melevodopa (-)-3,4-dihydroxy-L-phenylalanine, methyl ester

mélévodopa (-)-(2*S*)-2-amino-3-(3,4-dihydroxyphényl)propanoate de méthyle

melevodopa éster metílico de (-)-3,4-dihidroxi-L-fenilalanina

$C_{10}H_{13}NO_4$



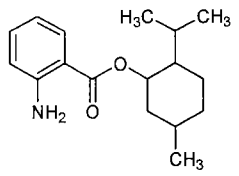
meradimatum

meradimate *p*-menth-3-yl anthranilate

méradimate 2-aminobenzoate de 5-méthyl-2-(1-méthyléthyl)cyclohexyle

meradimato antranilato de *p*-ment-3-ilo

$C_{17}H_{25}NO_2$



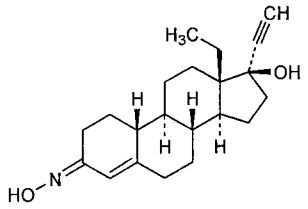
norelgestrominum

norelgestromin 13-ethyl-17-hydroxy-18,19-dinor-17α-pregn-4-en-20-yn-3-one oxime

norelgestromine 13-éthyl-17-hydroxy-18,19-dinor-17α-prégn-4-én-20-yn-3-one oxime

norelgestromina 13-etil-17-hidroxi-18,19-dinor-17α-pregn-4-en-20-in-3-ona oxima

$C_{21}H_{29}NO_2$



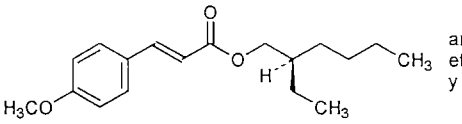
octinoxatum

octinoxate — 2-ethylhexyl *p*-methoxycinnamate

octinoxate — (*E*)-3-(4-méthoxyphényl)prop-2-énoate de (2*RS*)-2-éthylhexyle

octinoxato — *p*-metoxicinamato de 2-etilhexilo

$C_{18}H_{26}O_3$



and enantiomer
et énantiomère
y enantiómero

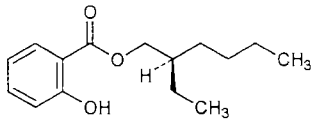
octisalatum

octisalate — 2-ethylhexyl salicylate

octisalate — 2-hydroxybenzoate de (2*RS*)-2-éthylhexyle

octisalato — salicilato de 2-etilhexilo

$C_{15}H_{22}O_3$



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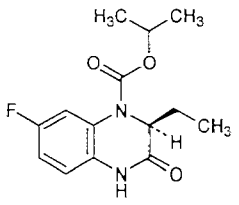
opaviralinum

opaviraline — isopropyl (*S*)-2-ethyl-7-fluoro-3,4-dihydro-3-oxo-1(2*H*)-quinoxalinecarboxylate

opaviraline — (2*S*)-2-éthyl-7-fluoro-3-oxo-3,4-dihydroquinoxaline-1(2*H*)-carboxylate de 1-méthyléthyle

opaviralina — (*S*)-2-etil-7-fluoro-3,4-dihidro-3-oxo-1(2*H*)-quinoxalinacarboxilato de isopropilo

$C_{14}H_{17}FN_2O_3$



opebacanum

opebacan — 132-L-alanine-1-193-bactericidal/permeability-increasing protein (human)

opébacan — [132-L-alanine]-1-193-protéine humaine augmentant la perméabilité et à action bactéricide

opebacán — 132-L-alanina-1-193-proteína(humana) bactericida/incrementadora de la permeabilidad

VNPGVVVRIS QKGLDYASQQ GTAALQKELK RIKIPDYSDS
FKIKHLGKGH YSFYSMDIRE FQLPSSQISM VPNVGLKFSI
SNANIKISGK WKAQKRFLKM SGNFDLSIEG MSISADLKLG
SNPTSGKPTI TASSCSSHIN SVHVHISKSK VGWLIQLFHK
KIESALRNKM NSQVCEKVTN SVSSELQPYF QTL

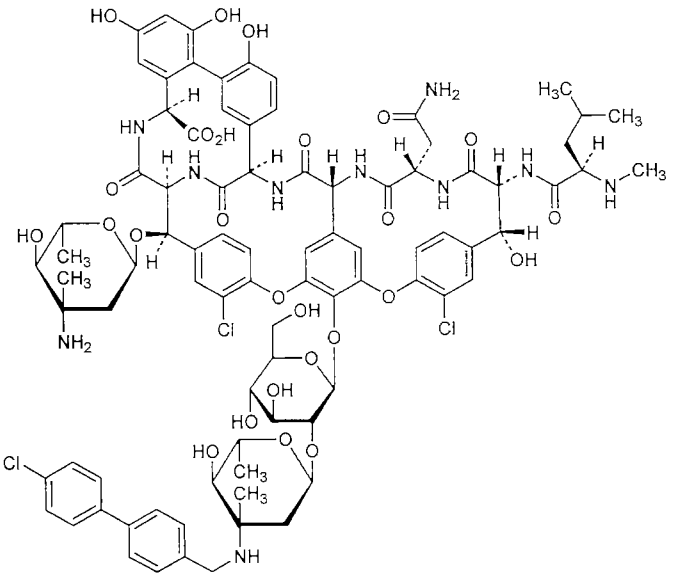
oritavancinum

oritavancin — (4″*R*)-22-*O*-(3-amino-2,3,6-trideoxy-3-*C*-methyl-α-L-*arabino*-hexopyranosyl)-$N^{3''}$-[*p*-(*p*-chlorophenyl)benzyl]vancomycin

oritavancine — acide (3*S*,6*R*,7*R*,22*R*,23*S*,26*S*,36*R*,38a*R*)-22-(3-amino-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyloxy)-3-(2-amino-2-oxoéthyl)-10,19-dichloro-44-[[2-*O*-[3-[[(4′-chlorobiphényl-4-yl)méthyl]amino]-3-*C*-méthyl-2,3,6-tridésoxy-α-L-*arabino*-hexopyranosyl]-β-D-glucopyranosyl]oxy]-7,28,30,32-tétrahydroxy-6-[[(2*R*)-4-méthyl-2-(méthylamino) pentanoyl]amino]-2,5,24,38,39-pentaoxo-2,3,4,5,6,7,23,24,25,26,36,37,38,38a-tétradécahydro-8,11:18,21-diéthéno-23,36-(iminométhano)-22*H*-13,16:31,35-diméthéno-1*H*,13*H*-[1,6,9]oxadiazacyclohexadécino [4,5-*m*][10,2,16] benzoxadiazacyclotétracosène-26-carboxylique

oritavancina — (4′*R*)-22-*O*-(3-amino-2,3,6-tridesoxi-3-*C*-metil-α-L-*arabino*-hexopiranosil)-$N^{3''}$-[*p*-(*p*-clorofenil)bencil]vancomicina

$C_{86}H_{97}Cl_3N_{10}O_{26}$



ozogamicinum
ozogamicin

methyl (1*R*,4*Z*,8*S*,13*E*)-13-[2-[[2-[[[*p*-(3-carbamoylpropoxy)-α-methylbenzylidene]hydrazino]carbonyl]-1,1-dimethylethyl]dithio]ethylidene]-8-[[4,6-dideoxy-4-[[[2,6-dideoxy-4-*S*-[4-[(6-deoxy-3-*O*-methyl-α-L-mannopyranosyl) oxy]-3-iodo-5,6-dimethoxy-*o*-toluoyl]-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]-2-*O*-[2,4-dideoxy-4-(*N*-ethylacetamido)-3-*O*-methyl-α-L-*threo*-pentopyranosyl]-β-D-glucopyranosyl]oxy]-1-hydroxy-11-oxobicyclo[7.3.1]trideca-4,9-diene-2,6-diyne-10-carbamate

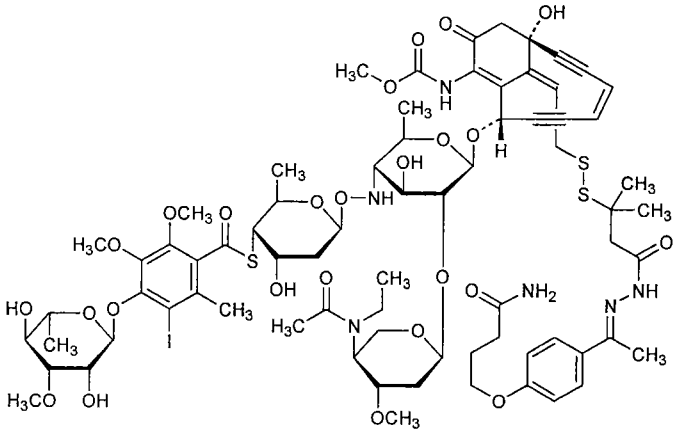
ozogamicine

[(1*R*,4*Z*,8*S*,13*E*)-8-[[2-*O*-[4-(acétyléthylamino)-3-*O*-méthyl-2,4-didésoxy-α-L-*thréo*-pentopyranosyl]-4-[[[4-*S*-[3-iodo-5,6-diméthoxy-2-méthyl-4-[(3-*O*-méthyl-6-désoxy-α-L-mannopyranosyl)oxy]benzoyl]-2,6-didésoxy-4-thio-β-D-*ribo*-hexopyranosyl]oxy]amino]-4,6-didésoxy-β-D-glucopyranosyl]oxy]-13-[2-[[3-[[1-[4-(4-amino-4-oxobutoxy)phényl]éthylidène]hydrazino]-1,1-diméthyl-3-oxopropyl]disulfanyl]éthylidène]-1-hydroxy-11-oxobicyclo[7.3.1] tridéca-4,9-diène-2,6-diyn-10-yl]carbamate de méthyle

ozogamicina

(1*R*,4*Z*,8*S*,13*E*)-13-[2-[[2-[[[*p*-(3-carbamoilpropoxi)-α-metilbencilideno] hidrazino]carbonil]-1,1-dimetiletil]ditio]etilideno]-8-[[4,6-didesoxi-4-[[[2,6-didesoxi-4-*S*-[4-[(6-desoxi-3-*O*-metil-α-L-manopiranosil)oxi]-3-iodo-5,6-dimetoxi-*o*-toluoil]-4-tio-β-D-*ribo*-hexopiranosil]oxi]amino]-2-*O*-[2,4-didesoxi-4-(*N*-etilacetamido)-3-*O*-metil-α-L-*treo*-pentopiranosil]-β-D-glucopiranosil] oxi]-1-hidroxi-11-oxobiciclo[7.3.1]trideca-4,9-dieno-2,6-diina-10-carbamato de metilo

$C_{73}H_{97}IN_6O_{25}S_3$



paliperidonum

paliperidone

(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidino]ethyl]-6,7,8,9-tetrahydro-9-hydroxy-2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

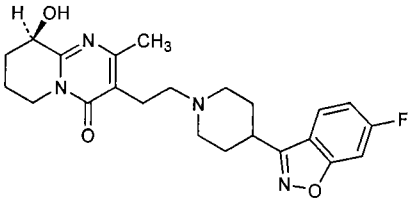
palipéridone

(9*RS*)-3-[2-[4-(6-fluoro-1,2-bensisoxazol-3-yl)pipéridin-1-yl]éthyl]-9-hydroxy-2-méthyl-6,7,8,9-tétrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one

paliperidona

(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-il)piperidino]etil]-6,7,8,9-tetrahidro-9-hidroxi-2-metil-4*H*-pirido[1,2-*a*]pirimidin-4-ona

$C_{23}H_{27}FN_4O_3$



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pitavastatinum

pitavastatin

(3*R*,5*S*,6*E*)-7-[2-cyclopropyl-4-(*p*-fluorophenyl)-3-quinolyl]-3,5-dihydroxy-6-heptenoic acid

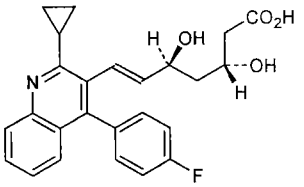
pitavastatine

acide (6*E*)-(3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophényl)quinoléin-3-yl]-3,5-dihydroxyhept-6-énoïque

pitavastatina

ácido (3*R*,5*S*,6*E*)-7-[2-ciclopropil-4-(*p*-fluorofenil)-3-quinolil]-3,5-dihidroxi-6-heptenoico

$C_{25}H_{24}FNO_4$



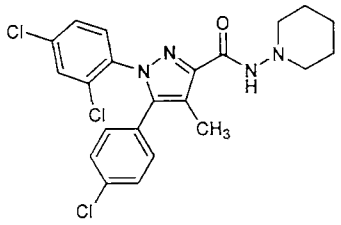
rimonabantum

rimonabant — 5-(*p*-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-*N*-piperidinopyrazole-3-carboxamide

rimonabant — 5-(4-chlorophényl)-1-(2,4-dichlorophényl)-4-méthyl-*N*-(pipéridin-1-yl)-1*H*-pyrazole-3-carboxamide

rimonabant — 5-(*p*-clorofenil)-1-(2,4-diclorofenil)-4-metil-*N*-piperidinopirazol-3-carboxamida

$C_{22}H_{21}Cl_3N_4O$



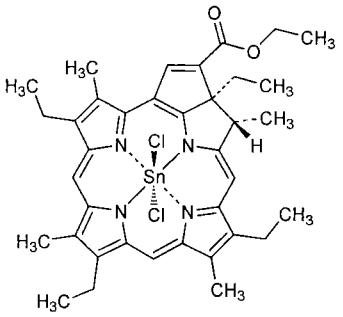
rostaporfinum

rostaporfin — (*OC*-6-13)-dichloro[ethyl (18*RS*, 19*SR*)-3,4,20,21-tetradehydro-4,9,14,19-tetraethyl-18,19-dihydro-3,8,13,18-tetramethyl-20-phorbinecarboxylato (2-)-N^{23},N^{24},N^{25},N^{26}]tin

rostaporfine — (*OC*-6-13)-dichloro[(2*RS*,3*SR*)-2,7,12,17-tétraéthyl-3,8,13,18-tétraméthyl-2,3-dihydrocyclopenta[*a*,*t*]porphyrine-2^1-carboxylato(3-)-N^{21},N^{22},N^{23},N^{24}] stannate(2-) d'éthyle

rostaporfina — (*OC*-6-13)-dicloro[(18*RS*, 19*SR*)-3,4,20,21-tetradeshidro-4,9,14,19-tetraetil-18,19-dihidro-3,8,13,18-tetrametil-20-forbinacarboxilato de etilo (2-)-N^{23},N^{24},N^{25},N^{26}]estaño

$C_{37}H_{42}Cl_2N_4O_2Sn$



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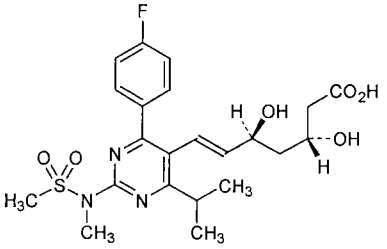
rosuvastatinum

rosuvastatin — (3*R*,5*S*,6*E*)-7-[4-(*p*-fluorophenyl)-6-isopropyl-2-(*N*-methylmethane sulfonamido)-5-pyrimidinyl]-3,5-dihydroxy-6-heptenoic acid

rosuvastatine — acide (3*R*,5*S*,6*E*)-7-[4-(4-fluorophényl)-6-(1-méthyléthyl)-2-[méthyl (méthylsulfonyl)amino]pyrimidin-5-yl]-3,5-dihydroxyhept-6-énoïque

rosuvastatina — ácido (3*R*,5*S*,6*E*)-7-[4-(*p*-fluorofenil)-6-isopropil-2-(*N*-metilmetano sulfonamido)-5-pirimidinil]-3,5-dihidroxi-6-heptenoico

$C_{22}H_{28}FN_3O_6S$



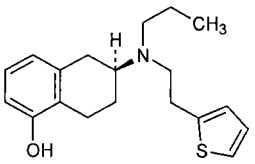
rotigotinum

rotigotine — (-)-(*S*)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol

rotigotine — (-)-(6*S*)-6-[propyl[2-(thiophén-2-yl)éthyl]amino]-5,6,7,8-tétrahydronaphtalén-1-ol

rotigotina — (-)-(*S*)-5,6,7,8-tetrahidro-6-[propil[2-(2-tienil)etil]amino]-1-naftol

$C_{19}H_{25}NOS$



ruplizumabum

ruplizumab — immunoglobulin G 1 (human-mouse monoclonal 5c8 γ1-chain anti-human CD 40 ligand), disulfide with human-mouse monoclonal 5c8 κ-chain, dimer

ruplizumab — immunoglobuline G1 anti-(ligand CD 40 humain) (chaîne γ1 de l'anticorps monoclonal de souris 5c8 humanisé), dimère du disulfure avec la chaîne κ de l'anticorps monoclonal de souris 5c8 humanisé

ruplizumab — inmunoglobulina G 1 anti-(ligando CD 40 humano) (cadena γ1 del anticuerpo monoclonal hombre-ratón 5c8), dímero del disulfuro con la cadena κ del anticuerpo monoclonal hombre-ratón 5c8

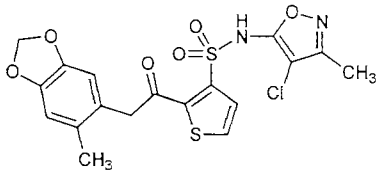
sitaxentanum

sitaxentan — *N*-(4-chloro-3-methyl-5-isoxazolyl)-2-[[4,5-(methylenedioxy)-*o*-tolyl]acetyl]-3-thiophenesulfonamide

sitaxentan — *N*-(4-chloro-3-méthylisoxazol-5-yl)-2-[(6-méthyl-1,3-benzodioxol-5-yl)acétyl]thiophène-3-sulfonamide

sitaxentán — *N*-(4-cloro-3-metil-5-isoxazolil)-2-[[4,5-(metilenodioxi)-*o*-tolil]acetil]-3-tiofenosulfonamida

$C_{18}H_{15}ClN_2O_6S_2$



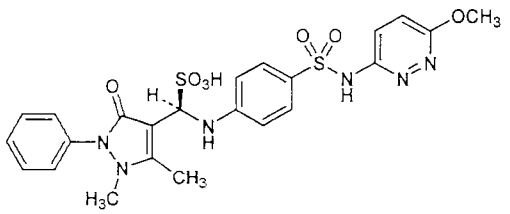
sulfamazonum

sulfamazone — (*RS*)-(1,5-dimethyl-2-phenyl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)[[4-[(6-methoxypyridazin-3-yl)sulfamoyl]phenyl]amino]methanesulfonic acid

sulfamazone — acide (*RS*)-(1,5-diméthyl-2-phényl-3-oxo-2,3-dihydro-1*H*-pyrazol-4-yl)[[4-[(6-méthoxypyridazin-3-yl)sulfamoyl]phényl]amino]méthanesulfonique

sulfamazona — ácido (*RS*)-(1,5-dimetil-2-fenil-3-oxo-2,3-dihidro-1*H*-pirazol-4-il)[[4-[(6-metoxipiridazin-3-il)sulfamoil]fenil]amino]metanosulfónico

$C_{23}H_{24}N_6O_7S_2$



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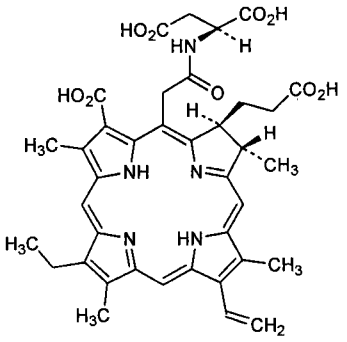
talaporfinum

talaporfin — *N*-[[(2*S*,3*S*)-18-carboxy-2-(2-carboxyethyl)-13-ethyl-2,3-dihydro-3,7,12,17-tetramethyl-8-vinylporphyrin-20-yl]acetyl]-L-aspartic acid

talaporfine — (2*S*)-2-[[[(7*S*,8*S*)-3-carboxy-7-(2-carboxyéthyl)-13-éthényl-18-éthyl-2,8,12,17-tétraméthyl-7,8-dihydroporphyrin-5-yl]acétyl]amino]butanedioïque

talaporfina — *N*-[[(2*S*,3*S*)-18-carboxi-2-(2-carboxietil)-13-etil-2,3-dihidro-3,7,12,17-tetrametil-8-vinilporfirin-20-il]acetil]-ácido-L-aspártico

$C_{38}H_{41}N_5O_9$



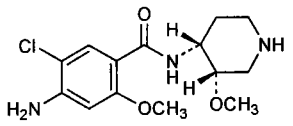
ticalopridum

ticalopride — 4-amino-5-chloro-*N*-[(3*S*,4*R*)-3-methoxy-4-piperidyl]-*o*-anisamide

ticalopride — 4-amino-5-chloro-2-méthoxy-*N*-[(3*S*,4*R*)-3-méthoxypipéridin-4-yl]benzamide

ticaloprida — 4-amino-5-cloro-*N*-[(3*S*,4*R*)-3-metoxi-4-piperidil]-*o*-anisamida

$C_{14}H_{20}ClN_3O_3$



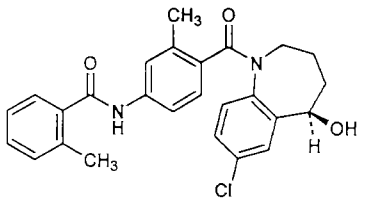
tolvaptanum

tolvaptan — (±)-4'-[(7-chloro-2,3,4,5-tetrahydro-5-hydroxy-1*H*-1-benzazepin-1-yl) carbonyl]-*o*-tolu-*m*-toluidide

tolvaptan — *N*-[4-[[(5*RS*)-7-chloro-5-hydroxy-2,3,4,5-tétrahydro-1*H*-1-benzazépin-1-yl] carbonyl]-3-méthylphényl]-2-méthylbenzamide

tolvaptán — (±)-4'-[(7-cloro-2,3,4,5-tetrahidro-5-hidroxi-1*H*-1-benzazepin-1-il)carbonil]-*o*-tolu-*m*-toluidida

$C_{26}H_{25}ClN_2O_3$



and enantiomer
et énantiomère
y enantiómero

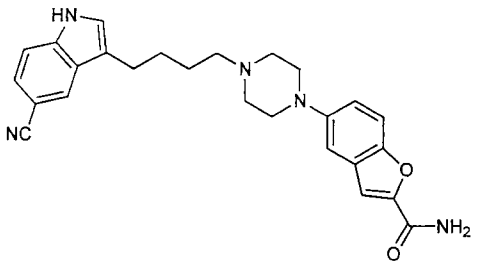
vilazodonum

vilazodone — 5-[4-[4-(5-cyanoindol-3-yl)butyl]-1-piperazinyl]-2-benzofurancarboxamide

vilazodone — 5-[4-[4-(5-cyano-1*H*-indol-3-yl)butyl]pipérazin-1-yl]benzofurane-2-carboxamide

vilazodona — 5-[4-[4-(5-cianoindol-3-il)butil]-1-piperazinil]-2-benzofurancarboxamida

$C_{26}H_{27}N_5O_2$



AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Nonproprietary Names (Rec. INN): List 14
(WHO Chronicle, Vol. 28, No. 10, 1974)

p. 1	*delete*	*insert*
	amfebutamonum	**bupropionum**
	amfebutamone	bupropion

Dénominations communes internationales recommendées (DCI Rec.): Liste 14
(Chronique OMS, Vol. 28, No. 10, 1974)

p. 1	*supprimer*	*insérer*
	amfebutamonum	**bupropionum**
	amfébutamone	bupropione

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 14
(Crónica de la OMS, Vol. 28, No. 10, 1974)

p. 1	*suprimase*	*insértese*
	amfebutamonum	**bupropionum**
	anfebutamona	bupropión

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 30
(Informacion farmacutica de la OMS, Vol. 4, No. 3, 1990)

p. 5	*suprimase*	*insértese*
	enalquireno	enalkireno

Recommended International Nonproprietary Names (Rec. INN): List 42
Dénominations communes internationales recommendées (DCI Rec.): Liste 42
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 42
(WHO Drug Information, Vol. 13, No. 3, 1999)

p. 198	*delete/supprimer/suprimase*	*insert/insérer/insértese*
	olmesartanum	**olmesartanum medoxomilum**
	olmesartan	olmesartan medoxomil
	olmésartan	olmésartan médoxomil
	olmesartán	olmesartán medoxmilo

Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 44
(WHO Drug Information, Vol. 14, No. 3, 2000)

p. 184 **adalimumabum**
adalimumab

sustitúyase la descripción por la siguiente:
inmunoglobulina G1 (anti-factor α de necrosis tumoral humano) (cadena pesada del anticuerpo monoclonal humano D2E7), dímero del disulfuro con la cadena κ del anticuerpo D2E7 monoclonal humano

p. 185 **amiglumidum**
amiglumida

sustitúyase la descripción por la siguiente:
ácido (*R*)-4-(2-naftamido)-*N*,*N*-dipentilglutarámico

p. 193 **evernimicinum**
evernimicina

sustitúyase la descripción por la siguiente:
O-2,3,6-tridesoxi-3-*C*-metil-4-*O*-metil-3-nitro-α-L-*arabino*-hexopiranosil-(1→3)-*O*-2,6-didesoxi-4-*O*-(3,5-dicloro-6-metoxi-4,2-cresotoil)-β-D-*arabino*-hexopiranosil-(1→4)-*O*-(1*R*)-2,6-didesoxi-D-*arabino*-hexopiranosilideno-(1→3-4)-*O*-6-desoxi-3-*C*-metil-β-D-manopiranosil-(1→3)-*O*-6-desoxi-4-*O*-metil-β-D-galactopiranosil-(1→4)-2,6-di-*O*-metil-β-D-manopiranósido de *O*-(1*R*)-2,3-*O*-metileno-4-*O*-(6-metil-β-resorciloil)-D-xilopiranosilideno-(1→3-4)-α-L-lixopiranosilo

p. 196 **irofulvenum**
irofulveno

sustitúyase la descripción por la siguiente:
(*R*)-6'-hidroxi-3'-(hidroximetil)-2',4',6'-trimetilespiro[ciclopropano-1,5'-[5*H*]inden]-7'(6'*H*)-ona

p. 201 **posaconazolum**
posaconazol

sustitúyase la descripción por la siguiente:
4-[*p*-[4-[*p*-[[(3*R*,5*R*)-5-(2,4-difluorofenil)tetrahidro-5-(1*H*-1,2,4-triazol-1-ilmetil)-3-furil]metoxi]fenil]-1-piperazinil]fenil]-1-[(1*S*,2*S*)-1-etil-2-hidroxipropil]-Δ^2-1,2,4-triazolin-5-ona

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the *Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* will be reproduced in uneven numbers of proposed INN lists only.

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internatio-nales applicables aux substances pharmaceutiques* seront publiés seulement dans les numéros impaires des listes des DCIs proposées.

El texto de los *Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas* y de los *Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas* aparece solamente en los números impares de las listas de DCI propuestas.

International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 57

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [*Off. Rec. Wld Health Org.*, 1955, **60**, 3 (Resolution EB15.R7); 1969, **173**, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.
Lists of Proposed (1–91) and Recommended (1–52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 57

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, **60**, 3 (résolution EB15.R7); 1969, **173**, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.
On trouvera d'autres listes de Dénominations communes internationales proposées (1–91) et recommandées (1–52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 57

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, **60**, 3 (Resolución EB15.R7); 1969, **173**, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.
Las listas de Denominaciones Comunes Internacionales Propuestas (1–91) y Recomendadas (1–52) se encuentran reunidas en *Cumulative List No. 11, 2004* (disponible sólo en CD-ROM).

Latin, English, French, Spanish: *Recommended INN*	*Chemical name or description; Molecular formula; Graphic formula*
DCI Recommandée	*Nom chimique ou description; Formule brute; Formule développée*
DCI Recomendada	*Nombre químico o descripción; Fórmula molecular; Fórmula desarrollada*

abagovomabum*

abagovomab — immunoglobulin G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) *Mus musculus* monoclonal antibody OC125] *Mus musculus* monoclonal antibody ACA125, clone 3D5 gamma1 heavy chain disulfide with clone 3D5 kappa light chain; (223-223'':226-226'':228-228'') trisdisulfide dimer

abagovomab — immunoglobuline G1, anti-idiotype anti-[anti-(*Homo sapiens* cancer antigen 125, CA 125, MUC-16) anticorps monoclonal murin OC125] anticorps monoclonal murin ACA125, chaîne lourde gamma1 du clone 3D5 unie par un pont disulfure à la chaîne légère kappa du clone 3D5; dimère (223-223'':226-226'':228-228'')-trisdisulfure

abagovomab — inmunoglobulina G1, anti-idiotipo anti-[anti-(*Homo sapiens* cancer antígeno 125, CA 125, MUC-16) anticuerpo monoclonal murino OC125] anticuerpo monoclonal murino ACA125, cadena pesada gamma1 del clon 3D5 unida por un puente disulfuro a la cadena ligera kappa del clon 3D5; dímero (223-223'':226-226'':228-228'')-trisdisulfuro

Heavy chain/Chaîne lourde/Cadena pesada

```
QVKLQESGAE LARPGASVKL SCKASGYTFT NYWMQWVKQR PGQGLDWIGA  50
IYPGDGNTRY THKFKGKATL TADKSSSTAY MQLSSLASED SGVYYCARGE 100
GNYAWFAYWG QGTTVTVSSA KTTPPSVYPL APGSAAQTNS MVTLGCLVKG 150
YFPEPVTVTW NSGSLSSGVH TFPAVLQSDL YTLSSSVTVP SSTWPSETVT 200
CNVAHPASST KVDKKIVPRD CGCKPCICTV PEVSSVFIFP PKPKDVLTIT 250
LTPKVTCVVV DISKDDPEVQ FSWFVDDVEV HTAQTQPREE QFNSTFRSVS 300
ELPIMHQDWL NGKEFKCRVN SAAFPAPIEK TISKTKGRPK APQVYTIPPP 350
KEQMAKDKVS LTCMITDFFP EDITVEWQWN GQPAENYKNT QPIMDTDGSY 400
FVYSKLNVQK SNWEAGNTFT CSVLHEGLHN HHTEKSLSHS PGK         443
```

Light chain/Chaîne légère/Cadena ligera

```
DIELTQSPAS LSASVGETVT ITCQASENIY SYLAWHQQKQ GKSPQLLVYN  50
AKTLAGGVSS RFSGSGSGTH FSLKIKSLQP EDFGIYYCQH HYGILPTFGG 100
GTKLEIKRAD AAPTVSIFPP SSEQLTSGGA SVVCFLNNFY PKDINVKWKI 150
DGSERQNGVL NSWTDQDSKD STYSMSSTLT LTKDEYERHN SYTCEATHKT 200
STSPIVKSFN RNEC                                        214
```

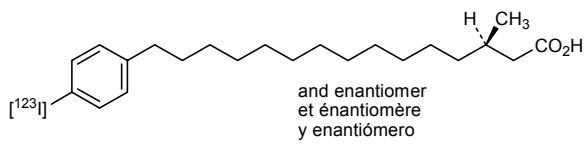
acidum iodofilticum (^{123}I)

iodofiltic acid (^{123}I) — (3*RS*)-15-[4-[^{123}I]iodophenyl]3-methylpentadecanoic acid

acide iodofiltique (^{123}I) — acide (3*RS*)-15-(4-[^{123}I]iodophényl)-3-méthylpentadécanoïque

ácido iodofíltico (^{123}I) — ácido (3*RS*)-15-(4-[^{123}I]iodofenil)-3-metilpentadecanoico

$C_{22}H_{35}{}^{123}IO_2$



and enantiomer
et énantiomère
y enantiómero

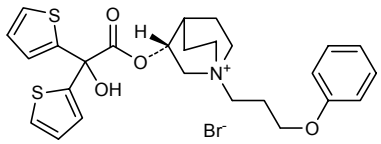
aclidinii bromidum

aclidinium bromide — (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ^5-azabicyclo[2.2.2]octan-1-ylium bromide

bromure d'aclidinium — bromure de (3*R*)-3-[[hydroxybis(thiophén-2-yl)acétyl]oxy]-1-(3-phénoxypropyl)-1-azoniabicyclo[2.2.2]octane

bromuro de aclidinio — bromuro de (3R)-1-(3-fenoxipropil)-3-[(hidroxi)di(tiofen-2-il)acetiloxi]-1λ^5-azabiciclo[2.2.2]octan-1-ilio

$C_{26}H_{30}BrNO_4S_2$



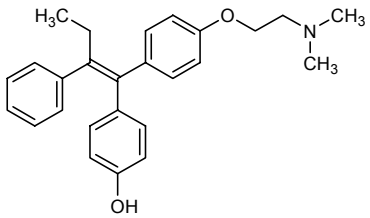
afimoxifenum

afimoxifene — 4-(1-{4-[2-(dimethylamino)ethoxy]phenyl}-2-phenylbut-1-enyl)phenol

afimoxifène — 4-[1-[4-[2-(diméthylamino)éthoxy]phényl]-2-phénylbut-1-énil]phénol

afimoxifeno — 4-[1-[4-[2-(dimetilamino)etoxi]fenil]-2-fenilbut-1-enil]fenol

$C_{26}H_{29}NO_2$



and *Z* isomer
et l'isomère *Z*
y el isómero *Z*

aflibercептum*

aflibercept — des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig-like C2-type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig-like C2-type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 *C*-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

aflibercept — (211-211':214-214')-bisdisulfure du dimère de la dès-432-lysine-[récepteur 1 humain du facteur de croissance endothélial vasculaire-(103-204)-peptide (contenant le domaine Ig-like C2-type 2) protéine de fusion avec le récepteur 2 humain du facteur de croissance endothélial vasculaire-(206-308)-peptide (contenant un fragment du domaine Ig-like C2-type 3) protéine de fusion avec l'immunoglobuline G1 humaine-(227 résidus *C*-terminaux)-peptide (fragment Fc)]

aflibercept

(211-211':214-214')-bisdisulfuro del dímero de la des-432-lisina-[receptor 1 humano del factor de crecimiento endotelial vascular-(103-204)-péptido (que contiene el dominio Ig-like C2-tipo 2) proteína de fusión con el receptor 2 humano del factor de crecimiento endotelial vascular-(206-308)-péptido (que contiene un fragmento del dominio Ig-like C2-tipo 3) proteína de fusión con la inmunoglobulina G1 humana-(227 restos *C*-terminales)-péptido (fragmento Fc)]

$C_{4318}H_{6788}N_{1164}O_{1304}S_{32}$

Monomer / Monomère / Monómero

```
SDTGRPFVEM YSEIPEIIHM TEGRELVIPC RVTSPNITVT LKKFPLDTLI  50
PDGKRIIWDS RKGFIISNAT YKEIGLLTCE ATVNGHLYKT NYLTHRQTNT 100
IIDVVLSPSH GIELSVGEKL VLNCTARTEL NVGIDFNWEY PSSKHQHKKL 150
VNRDLKTQSG SEMKKFLSTL TIDGVTRSDQ GLYTCAASSG LMTKKNSTFV 200
RVHEKDKTHT CPPCPAPELL GGPSVFLFPP KPKDTLMISR TPEVTCVVVD 250
VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN 300
GKEYKCKVSN KALPAPIEKT ISKAKGQPRE PQVYTLPPSR DELTKNQVSL 350
TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS 400
RWQQGNVFSC SVMHEALHNH YTQKSLSLSP G                     431
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

30-79 30'-79' 124-185 124'-185' 211-211' 214-214' 246-306 246'-306' 352-410 352'-410'

aleglitazarum

aleglitazar

(2*S*)-2-methoxy-3-{4-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)ethoxy]-1-benzothiophen-7-yl}propanoic acid

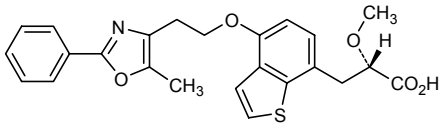
aléglitazar

acide (2*S*)-2-méthoxy-3-[4-[2-(5-méthyl-2-phényl-1,3-oxazol-4-yl)éthoxy]-1-benzothiophén-7-yl]propanoïque

aleglitazar

ácido (2*S*)-3-{4-[2-(2-fenil-1,3-oxazol-5-metil-4-il)etoxi]-1-benzotiofen-7-il}-2-metoxipropanoico

$C_{24}H_{23}NO_5S$



alferminogenum tadenovecum*

alferminogene tadenovec

recombinant human adenovirus 5 (replication-deficient, E1-deleted) containing a human fibroblast growth factor-4 cDNA sequence driven by a cytomegalovirus promoter

alferminogène tadénovec

adénovirus 5 humain recombinant (réplication-déficient, région E1-supprimée) contenant la séquence ADN-copie du facteur 4 de croissance du fibroblaste humain sous contrôle d'un promoteur de cytomégalovirus

alferminogén tadenovec

adenovirus 5 humano recombinante (replicación-deficiente, con delección E1) que contiene la secuencia DNA-copia del factor-4 de crecimiento de fibroblastos humanos controlado por un promotor de citomegalovirus

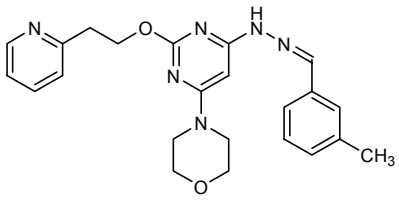
apilimodum

apilimod — 1-[(3-methylphenyl)methylidene]-2-{6-(morpholin-4-yl)-2-[2-(pyridin-2-yl)ethoxy]pyrimidin-4-yl}hydrazine

apilimod — 1-(3-méthylbenzylidène)-2-[6-(morpholin-4-yl)-2-[2-(pyridin-2-yl)=éthoxy]pyrimidin-4-yl]diazane

apilimod — 1-(3-metilbencilideno)-2-[6-(morfolin-4-il)-2-[2-(piridin-2-il)etoxi]=pirimidin-4-il]diazano

$C_{23}H_{26}N_6O_2$



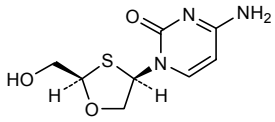
apricitabinum

apricitabine — 4-amino-1-[(2*R*,4*R*)-2-(hydroxymethyl)-1,3-oxathiolan-4-yl]pyrimidin-2(1*H*)-one

apricitabine — (-)-4-amino-1-[(2*R*,4*R*)-2-(hydroxyméthyl)-1,3-oxathiolan-4-yl]=pyrimidin-2(1*H*)-one

apricitabina — (-)-4-amino-1-[(2*R*,4*R*)-2-(hidroximetil)-1,3-oxatiolan-4-il]pirimidin-2(1*H*)-ona

$C_8H_{11}N_3O_3S$



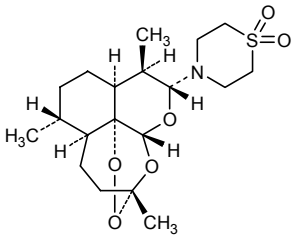
artemisonum

artemisone — 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimethyldecahydro-12*H*-3,12-epoxypyrano[4,3-*j*][1,2]benzodioxepin-10-yl]=thiomorpholine-1,1-dione

artémisone — 1,1-dioxyde de 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-triméthyldécahydro-3,12-époxypyrano[4,3-*j*]-1,2-benzodioxépin-10-yl]thiomorpholine

artemisona — 1,1-dióxido de 4-[(3*R*,5a*S*,6*R*,8a*S*,9*R*,10*R*,12*R*,12a*R*)-3,6,9-trimetildecahidro-3,12-epoxipirano[4,3-*j*]-1,2-benzodioxepin-10-il]=tiomorfolina

$C_{19}H_{31}NO_6S$



ataciceptum*

atacicept

[86-serine,101-glutamic acid,196-serine,197-serine,222-aspartic acid,224-leucine][human tumor necrosis factor receptor superfamily member 13B-(30-110)-peptide (TACI fragment containing TNFR-Cys 1 and TNFR-Cys 2) fusion protein with human immunogobulin G1-(232 *C*-terminal residues)-peptide (γ1-chain Fc fragment), (92-92':95-95')-bisdisulfide dimer

atacicept

(92-92':95-95')-bisdisulfure du dimère de la [86-sérine,101-acide glutamique,196-sérine,197-sérine,222-acide aspartique, 224-leucine]-protéine de fusion du membre 13B humain de la superfamille des récepteurs du facteur de nécrose tumorale-(30-110)-peptide (portion du TACI incluant les deux régions riches en cystéine) avec l'immunoglobuline G1 humaine-(232 résidus *C*-terminaux)-peptide (fragment Fc de la chaîne γ1)

atacicept

92-92':95-95')-bisdisulfuro del dímero de la [86-serina,101-ácido glutámico,196-serina,197-serina,222-ácido aspártico,224-leucina]-proteína de fusión del miembro 13B humano de la superfamilia de receptores del factor de necrosis tumoral-(30-110)-péptido (porción del TACI que incluye las dos regiones ricas en cisteína) con la inmunoglobulina G1 humana-(232 restos *C*-terminales)-péptido (fragmento Fc de la cadena γ1)

$C_{3104}H_{4788}N_{856}O_{950}S_{44}$

Monomer / Monomère / Monómero

```
AMRSCPEEQY  WDPLLGTCMS  CKTICNHQSQ  RTCAAFCRSL  SCRKEQGKFY  50
DHLLRDCISC  ASICGQHPKQ  CAYFCENKLR  SEPKSSDKTH  TCPPCPAPEA  100
EGAPSVFLFP  PKPKDTLMIS  RTPEVTCVVV  DVSHEDPEVK  FNWYVDGVEV  150
HNAKTKPREE  QYNSTYRVVS  VLTVLHQDWL  NGKEYKCKVS  NKALPSSIEK  200
TISKAKGQPR  EPQVYTLPPS  RDELTKNQVS  LTCLVKGFYP  SDIAVEWESN  250
GQPENNYKTT  PPVLDSDGSF  FLYSKLTVDK  SRWQQGNVFS  CSVMHEALHN  300
HYTQKSLSLS  PGK                                            313
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
5-18   5'-18'   21-33   21'-33'   25-37   25'-37'   42-57   42'-57'   60-71
60'-71'   64-75   64'-75'   92-92'   95-95'   127-187   127'-187'   233-291   233'-291'
```

azilsartanum

azilsartan

2-ethoxy-1-{[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)-1,1'-biphenyl-4-yl]methyl}-1*H*-benzimidazole-7-carboxylic acid

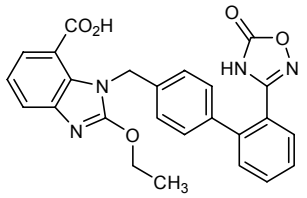
azilsartan

acide 2-éthoxy-1-[[2'-(5-oxo-4,5-dihydro-1,2,4-oxadiazol-3-yl)= biphényl-4-yl]méthyl]-1*H*-benzimidazole-7-carboxylique

azilsartán

ácido 2-etoxi-1-{[2'-(5-oxo-4,5-dihidro-1,2,4-oxadiazol-3-il)bifenil-4-il]metil}-1*H*-bencimidazol-7-carboxílico

$C_{25}H_{20}N_4O_5$



bavituximabum*

bavituximab — immunoglobulin G1, anti-(phosphatidylserine) chimeric monoclonal ch3G4; gamma1 heavy chain (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfide with kappa light chain (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC); (229-229":232-232")-bisdisulfide dimer

bavituximab — immunoglobuline G1, anti-(phosphatidylsérine) anticorps monoclonal chimérique ch3G4; chaîne lourde gamma1 (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfure avec la chaîne légère kappa (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC); dimère (229-229":232-232")-bisdisulfure

bavituximab — inmunoglobulina G1, anti-(fosfatidilserina) anticuerpo monoclonal quimérico ch3G4; cadena pesada gamma1 (*Mus musculus* VH-*Homo sapiens* IGHG1) (223-214')-disulfuro con la cadena ligera kappa (*Mus musculus* V-KAPPA-*Homo sapiens* IGKC), dímero (229-229":232-232")-bisdisulfuro

$C_{6446}H_{9946}N_{1702}O_{2042}S_{42}$

Heavy chain / Chaîne lourde / Cadena pesada

EVQLQQSGPE	LEKPGASVKL	SCKASGYSFT	GYNMNWVKQS	HGKSLEWIGH 50
IDPYYGDTSY	NQKFRGKATL	TVDKSSSTAY	MQLKSLTSED	SAVYYCVKGG 100
YYGHWYFDVW	GAGTTVTVSS	ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK 150
DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT 200
YICNVNHKPS	NTKVDKKVEP	KSCDKTHTCP	PCPAPELLGG	PSVFLFPPKP 250
KDTLMISRTP	EVTCVVVDVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN 300
STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ 350
VYTLPPSRDE	LTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV 400
LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK 450

k Chain / Chaîne k / Cadena k

DIQMTQSPSS	LSASLGERVS	LTCRASQDIG	SSLNWLQQGP	DGTIKRLIYA 50'
TSSLDSGVPK	RFSGSRSGSD	YSLTISSLES	EDFVDYYCLQ	YVSSPPTFGA 100'
GTKLELKRAD	AAPSVFIFPP	SDEQLKSGTA	SVVCLLNNFY	PREAKVQWKV 150'
DNALQSGNSQ	ESVTEQDSKD	STYSLSSTLT	LSKADYEKHK	VYACEVTHQG 200'
LSSPVTKSFN	RGEC			214'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

22-96 22"-96" 23'-88' 23'"-88'" 134'-194' 134'"-194'" 147-203 147"-203"
214'-223 214'"-223" 229-229" 232-232" 264-324 264'-324" 370-428 370"-428"

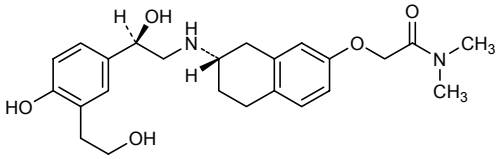
bedoradrinum

bedoradrine — 2-{[(7*S*)-7-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyethyl)phenyl]=ethyl}amino)-5,6,7,8-tetrahydronaphthalen-2-yl]oxy}-*N*,*N*-dimethylacetamide

bédoradrine — (-)-2-[[(7*S*)-7-[[(2*R*)-2-hydroxy-2-[4-hydroxy-3-(2-hydroxyéthyl)=phényl]éthyl]amino]-5,6,7,8-tétrahydronaphtalén-2-yl]oxy]-*N*,*N*-diméthylacétamide

bedoradrina — (-)-2-{[(7*S*)-7-({(2*R*)-2-hidroxi-2-[4-hidroxi-3-(2-hidroxietil)fenil]=etil}amino)-5,6,7,8-tetrahidronaftalen-2-il]oxi}-*N*,*N*-dimetilacetamida

$C_{24}H_{32}N_2O_5$



beperminogenum perplasmidum*

beperminogene perplasmid — plasmid DNA containing human hepatocyte growth factor cDNA sequence driven by a cytomegalovirus promoter

béperminogène perplasmide — ADN plasmidique contenant la séquence ADN-copie du facteur de croissance de l'hépatocyte humain sous contrôle d'un promoteur de cytomégalovirus

beperminogén perplásmido — DNA de plásmido que contiene la secuencia DNA-copia del factor de crecimiento del hepatocito humano controlado por un promotor de citomegalovirus

beroctocogum alfa*

beroctocog alfa — human blood-coagulation factor VIII-(1-740)-peptide complex with human blood-coagulation factor VIII-(1649-2332)-peptide

béroctocog alfa — combinaison du facteur VIII de coagulation humain-(1-740)-peptide (chaîne lourde du facteur VIIIa, isoforme de 92 kDa) avec le facteur VIII de coagulation humain-(1649-2332)-peptide (chaîne légère du facteur VIIIa)

beroctocog alfa — combinación del factor VIII de coagulación humano-(1-740)-péptido (cadena pesada del factor VIIIa, isoforma de 92 kDa) con el factor VIII de coagulación humano-(1649-2332)-péptido (cadena ligèra del factor VIIIa)

$C_{3821}H_{5813}N_{1003}O_{1139}S_{35} + C_{3553}H_{5400}N_{956}O_{1032}S_{35}$

Heavy chain / Chaîne lourde / Cadena pesada

```
ATRRYYLGAV  ELSWDYMQSD  LGELPVDARF  PPRVPKSFPF  NTSVVYKKTL  50
FVEFTDHLFN  IAKPRPPWMG  LLGPTIQAEV  YDTVVITLKN  MASHPVSLHA  100
VGVSYWKASE  GAEYDDQTSQ  REKEDDKVFP  GGSHTYVWQV  LKENGPMASD  150
PLCLTYSYLS  HVDLVKDLNS  GLIGALLVCR  EGSLAKEKTQ  TLHKFILLFA  200
VFDEGKSWHS  ETKNSLMQDR  DAASARAWPK  MHTVNGYVNR  SLPGLIGCHR  250
KSVYWHVIGM  GTTPEVHSIF  LEGHTFLVRN  HRQASLEISP  ITFLTAQTLL  300
MDLGQFLLFC  HISSHQHDGM  EAYVKVDSCP  EEPQLRMKNN  EEAEDYDDDL  350
TDSEMDVVRF  DDDNSPSFIQ  IRSVAKKHPK  TWVHYIAAEE  EDWDYAPLVL  400
APDDRSYKSQ  YLNNGPQRIG  RKYKKVRFMA  YTDETFKTRE  AIQHESGILG  450
PLLYGEVGDT  LLIIFKNQAS  RPYNIYPHGI  TDVRPLYSRR  LPKGVKHLKD  500
FPILPGEIFK  YKWTVTVEDG  PTKSDPRCLT  RYYSSFVNME  RDLASGLIGP  550
LLICYKESVD  QRGNQIMSDK  RNVILFSVFD  ENRSWYLTEN  IQRFLPNPAG  600
VQLEDPEFQA  SNIMHSINGY  VFDSLQLSVC  LHEVAYWYIL  SIGAQTDFLS  650
VFFSGYTFKH  KMVYEDTLTL  FPFSGETVFM  SMENPGLWIL  GCHNSDFRNR  700
GMTALLKVSS  CDKNTGDYYE  DSYEDISAYL  LSKNNAIEPR  S           741
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Light chain / Chaîne légère / Cadena ligera

```
                                                        EI  1650
TRTTLQSDQE  EIDYDDTISV  EMKKEDFDIY  DEDENQSPRS  FQKKTRHYFI  1700
AAVERLWDYG  MSSSPHVLRN  RAQSGSVPQF  KKVVFQEFTD  GSFTQPLYRG  1750
ELNEHLGLLG  PYIRAEVEDN  IMVTFRNQAS  RPYSFYSSLI  SYEEDQRQGA  1800
EPRKNFVKPN  ETKTYFWKVQ  HHMAPTKDEF  DCKAWAYFSD  VDLEKDVHSG  1850
LIGPLLVCHT  NTLNPAHGRQ  VTVQEFALFF  TIFDETKSWY  FTENMERNCR  1900
APCNIQMEDP  TFKENYRFHA  INGYIMDTLP  GLVMAQDQRI  RWYLLSMGSN  1950
ENIHSIHFSG  HVFTVRKKEE  YKMALYNLYP  GVFETVEMLP  SKAGIWRVEC  2000
LIGEHLHAGM  STLFLVYSNK  CQTPLGMASG  HIRDFQITAS  GQYGQWAPKL  2050
ARLHYSGSIN  AWSTKEPFSW  IKVDLLAPMI  IHGIKTQGAR  QKFSSLYISQ  2100
FIIMYSLDGK  KWQTYRGNST  GTLMVFFGNV  DSSGIKHNIF  NPPIIARYIR  2150
LHPTHYSIRS  TLRMELMGCD  LNSCSMPLGM  ESKAISDAQI  TASSYFTNMF  2200
ATWSPSKARL  HLQGRSNAWR  PQVNNPKEWL  QVDFQKTMKV  TGVTTQGVKS  2250
LLTSMYVKEF  LISSSQDGHQ  WTLFFQNGKV  KVFQGNQDSF  TPVVNSLDPP  2300
LLTRYLRIHP  QSWVHQIALR  MEVLGCEAQD  LY                     2332
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
153-179 528-554 1899-1903 2021-2169 2174-2326

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
Asn-41 Asn-239 Asn-582 Asn-1810 Asn-2118

Modifications / Modificaciones
Y = 4-O-sulfotyrosyl

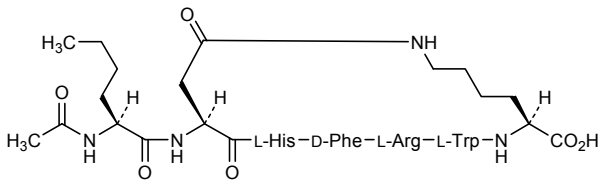
bremelanotidum

bremelanotide — 2,7-anhydro(*N*-acetyl-L-2-aminohexanoyl-L-aspartyl-L-histidyl-D-phenylalanyl-L-arginyl-L-tryptophyl-L-lysine)

brémelanotide — *N*-acétyl-L-2-aminohexanoyl-L-α-aspartyl-L-histidyl-D-phénylalanyl-L-arginyl-L-tryptophyl-L-lysine-(2→7)-lactame

bremelanotida — *N*-acetil-L-2-aminohexanoil-L-α-aspartil-L-histidil-D-fenilalanil-L-arginil-L-triptofil-L-lisina-(2→7)-lactama

$C_{50}H_{68}N_{14}O_{10}$



bucelipasum alfa*

bucelipase alfa — human bile-salt-activated lipase (cholesterol esterase, EC 3.1.1.13), glycoform alfa (recombinant hBSSL)

bucélipase alfa — lipase activée par les sels biliaires humaine (cholestérol estérase, EC 3.1.1.13), glycoforme alpha (recombinante hBSSL)

bucelipasa alfa — lipasa humana activada por las sales biliares (colesterol esterasa, EC 3.1.1.13), glicoforma alfa (recombinante hBSSL)

$C_{3434}H_{5258}N_{894}O_{1041}S_{17}$

```
AKLGAVYTEG  GFVEGVNKKL  GLLGDSVDIF  KGIPFAAPTK  ALENPQPHPG  50
WQGTLKAKNF  KKRCLQATIT  QDSTYGDEDC  LYLNIWVPQG  RKQVSRDLPV  100
MIWIYGGAFL  MGSGHGANFL  NNYLYDGEEI  ATRGNVIVVT  FNYRVGPLGF  150
LSTGDANLPG  NYGLRDQHMA  IAWVKRNIAA  FGGDPNNITL  FGESAGGASV  200
SLQTLSPYNK  GLIRRAISQS  GVALSPWVIQ  KNPLFWAKKV  AEKVGCPVGD  250
AARMAQCLKV  TDPRALTLAY  KVPLAGLEYP  MLHYVGFVPV  IDGDFIPADP  300
INLYANAADI  DYIAGTNNMD  GHIFASIDMP  AINKGNKKVT  EEDFYKLVSE  350
FTITKGLRGA  KTTFDVYTES  WAQDPSQENK  KKTVVDFETD  VLFLVPTEIA  400
LAQHRANAKS  AKTYAYLFSH  PSRMPVYPKW  VGADHADDIQ  YVFGKPFATP  450
TGYRPQDRTV  SKAMIAYWTN  FAKTGDPNMG  DSAVPTHWEP  YTTENSGYLE  500
ITKKMGSSSM  KRSLRTNFLR  YWTLTYLALP  TVTDQEATPV  PPTGDSEATP  550
VPPTGDSETA  PVPPTGDSGA  PPVPPTGDSG  APPVPPTGDS  GAPPVPPTGD  600
SGAPPVPPTG  DSGAPPVPPT  GDSGAPPVPP  TGDSGAPPVP  PTGDAGPPPV  650
PPTGDSGAPP  VPPTGDSGAP  PVTPTGDSET  APVPPTGDSG  APPVPPTGDS  700
EAAPVPPTDD  SKEAQMPAVI  RF                                  722
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
64-80 246-257

Glycosylation sites / Sites de glycosylation / Posiciones de glicosilación
Asn-187 Thr-538 Thr-549 Thr-559 Thr-576 Thr-587
Thr-598 Thr-609 Thr-620 Thr-631 Thr-642

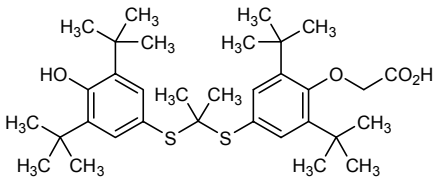
camobucolum

camobucol — 4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphenyl]sulfanyl}propan-2-yl)=sulfanyl]-2,6-di(*tert*-butyl)phenoxy}acetic acid

camobucol — acide 4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphényl]sulfanyl}propan-2-yl)sulfanyl]-2,6-di(*tert*-butyl)phénoxy}acétique

camobucol — ácido 4-{4-[(2-{[3,5-di(*terc*-butil)4-hidroxifenil]sulfanil}propan-2-il)=sulfanil]-2,6-di(*terc*-butil)fenoxi}acético

$C_{33}H_{50}O_4S_2$



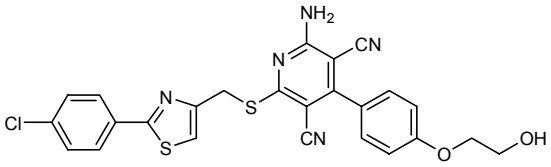
capadenosonum

capadenoson — 2-amino-6-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-4-[4-(2-hydroxyethoxy)phenyl]pyridine-3,5-dicarbonitrile

capadénoson — 2-amino-6-[[[2-(4-chlorophényl)-1,3-thiazol-4-yl]méthyl]sulfanyl]-4-[4-(2-hydroxyéthoxy)phényl]pyridine-3,5-dicarbonitrile

capadenosón — 2-amino-6-({[2-(4-clorofenil)-1,3-tiazol-4-il]metil}sulfanil)-4-[4-(2-hidroxietoxi)fenil]piridina-3,5-dicarbonitrilo

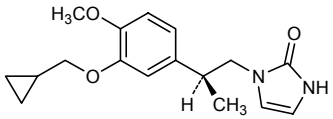
$C_{25}H_{18}ClN_5O_2S_2$



catramilastum

catramilast	1-{(2*S*)-2-[3-(cyclopropylmethoxy)-4-methoxyphenyl]propyl}-1,3-dihydro-2*H*-imidazol-2-one
catramilast	1-[(2*S*)-2-[3-(cyclopropylméthoxy)-4-méthoxyphényl]propyl]-1,3-dihydro-2*H*-imidazol-2-one
catramilast	1-{(2*S*)-2-[3-(ciclopropilmetoxi)-4-metoxifenil]propil}-1,3-dihidro-2*H*-imidazol-2-ona

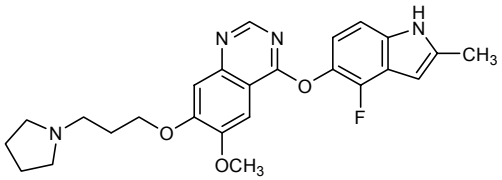
$C_{17}H_{22}N_2O_3$



cediranibum

cediranib	4-[(4-fluoro-2-methyl-1*H*-indol-5-yl)oxy]-6-methoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline
cédiranib	4-[(4-fluoro-2-méthyl-1*H*-indol-5-yl)oxy]-6-méthoxy-7-[3-(pyrrolidin-1-yl)propoxy]quinazoline
cediranib	4-[(4-fluoro-2-metil-1*H*-indol-5-il)oxi]-6-metoxi-7-[3-(pirrolidin-1-il)=propoxi]quinazolina

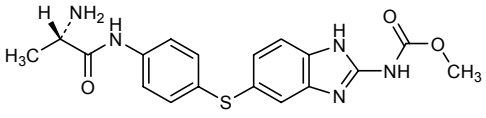
$C_{25}H_{27}FN_4O_3$



denibulinum

denibulin	methyl [5-({4-[(2*S*)-2-aminopropanamido]phenyl}sulfanyl)-1*H*-benzimidazol-2-yl]carbamate
dénibuline	[5-[[4-[[(2*S*)-2-aminopropanamido]phenyl]sulfanyl]-1*H*-benzimidazol-2-yl]carbamate de méthyle
denibulina	[5-({4-[(2*S*)-2-aminopropanamido]fenil}sulfanil)-1*H*-bencimidazol-2-il]carbamato de metilo

$C_{18}H_{19}N_5O_3S$



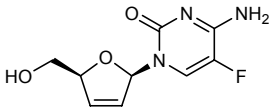
dexelvucitabinum

dexelvucitabine — 4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hydroxymethyl)-2,5-dihydrofuran-2-yl]pyrimidin-2(1*H*)-one

dexelvucitabine — (+)-4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hydroxyméthyl)-2,5-dihydrofuran-2-yl]pyrimidin-2(1*H*)-one

dexelvucitabina — (+)-4-amino-5-fluoro-1-[(2*R*,5*S*)-5-(hidroximetil)-2,5-dihidrofuran-2-il]pirimidin-2(1*H*)-ona

$C_9H_{10}FN_3O_3$



efungumabum*

efungumab — immunoglobulin scFv fragment, anti-(heat shock protein 90 homolog from *Candida albicans* (yeast)), methionylalanyl-[human monoclonal HSP90mab VH domain (120 residues)]-tris[(tetraglycyl)seryl]-[human monoclonal HSP90mab V-KAPPA domain (107 residues)]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine

éfungumab — immunoglobuline fragment scFv, anti-(homologue de la protéine de choc thermique 90 de *Candida albicans* (levure)), methionylalanyl-[domaine VH (120 residus) de l'anticorps monoclonal humain HSP90mab]-tris[(tetraglycyl)seryl]-[domaine V-KAPPA (107 residus) de l'anticorps monoclonal humain HSP90mab]-[arginyl-trialanyl-leucyl-glutamyl]-hexahistidine

efungumab — inmunoglobulina fragmento scFv, anti-(homólogo de la proteína de choc térmico 90 de *Candida albicans*), metionilalanil-[dominio VH (120 restos) del anticuerpo monoclonal humano HSP90mab]-tris[(tetraglicil)seril]-[dominio V-KAPPA (107 restos) del anticuerpo monoclonal humano HSP90mab]-[arginil-trialanil-leucil-glutamil]-hexahistidina

```
 MAEVQLVES GAEVKKPGES LRISCKGSGC IISSYWISWV RQMPGKGLEW
MGKIDPGDSY INYSPSFQGH VTISADKSIN TAYLQWNSLK ASDTAMYYCA
RGGRDFGDSF DYWGQGTLVT VSSGGGGSGG GGSGGGGSDV VMTQSPSFLS
AFVGDRITIT CRASSGISRY LAWYQQAPGK APKLLIYAAS TLQTGVPSRF
SGSGSGTEFT LTINSLQPED FATYYCQHLN SYPLTFGGGT KVDIKRAAA
LEhhhhhh
```

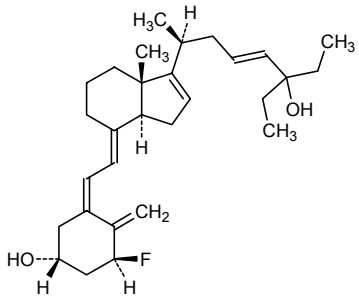
elocalcitolum

elocalcitol — (1*S*,3*R*,5*Z*,7*E*,23*E*)-1-fluoro-26,27-dihomo-9,10-secocholesta-5,7,10(19),16,23-pentaene-3,25-diol

élocalcitol — (1*R*,5*S*)-3-[(1*Z*)-2-[(3a*S*,4*E*,7a*S*)-1-[(1*S*,3*E*)-5-éthyl-5-hydroxy-1-méthylhept-3-ényl]-7a-méthyl-3,3a,5,6,7,7a-hexahydro-4*H*-indén-4-ylidène]éthylidène]-5-fluoro-4-méthylidènecyclohexanol

elocalcitol — (1*S*,3*R*,5*Z*,7*E*,23*E*)-1-fluoro-26,27-dihomo-9,10-secocolesta-5,7,10(19),16,23-pentaeno-3,25-diol

$C_{29}H_{43}FO_2$



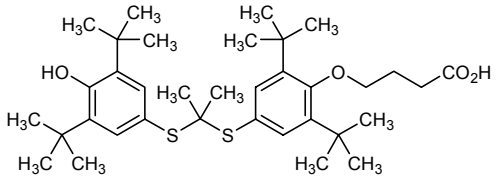
elsibucolum

elsibucol — 4-{4-[(2-{[3,5-di-*tert*-butyl-4-hydroxyphenyl]sulfanyl}propan-2-yl)=sulfanyl]-2,6-di-*tert*-butylphenoxy}butanoic acid

elsibucol — acide 4-[4-[[1-[[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phénoxy]butanoïque

elsibucol — ácido 4-{4-[(2-{[3,5-di-*terc*-butil-4-hidroxifenil]sulfanil}propan-2-il)=sulfanil]-2,6-di-*terc*-butilfenoxi}butanoico

$C_{35}H_{54}O_4S_2$



epoetinum theta

epoetin theta — human erythropoietin-(1-165)-peptide, glycoform θ

époétine thêta — érythropoïétine humaine-(1-165)-peptide, glycoforme θ

epoetina zeta — eritropoyetina humana-péptido-(1-165), glicoforma θ

$C_{809}H_{1301}N_{229}O_{240}S_5$

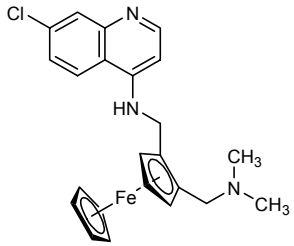
ferroquinum

ferroquine — *N'*-(7-chloroquinolin-4-yl)-*N*,*N*-dimethyl-*C*,*C'*-(ferrocene-1,2-diyl)= dimethanamine

ferroquine — *N'*-(7-chloroquinoléin-4-yl)-*N*,*N*-diméthyl-*C*,*C'*-(férrocène-1,2-diyl)= diméthanamine

ferroquina — *N'*-(7-cloroquinolin-4-il)-*N*,*N*-dimetil-*C*,*C'*-(ferroceno-1,2-diil)= dimetanamina

$C_{23}H_{24}ClFeN_3$



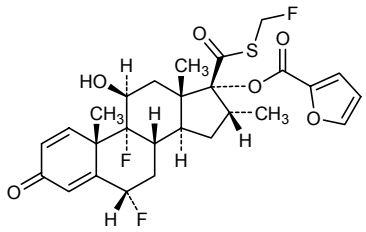
fluticasonum furoas

fluticasone furoate — 6α,9-difluoro-17{[(fluoromethyl)sulfanyl]carbonyl}-11β-hydroxy-16α-methyl-3-oxoandrosta-1,4-dien-17α-yl furan-2-carboxylate

furoate de fluticasone — furane-2-carboxylate de 6α,9-difluoro-17-[[(fluorométhyl)sulfanyl]= carbonyl]-11β-hydroxy-16α-méthyl-3-oxoandrosta-1,4-dién-17α-yle

furoato de fluticasona — furano-2-carboxilato de 6α,9-difluoro-17-[[(fluorometil)sulfanil]= carbonil]-11β-hidroxi-16α-metil-3-oxoandrosta-1,4-dien-17α-ilo

$C_{27}H_{29}F_3O_6S$



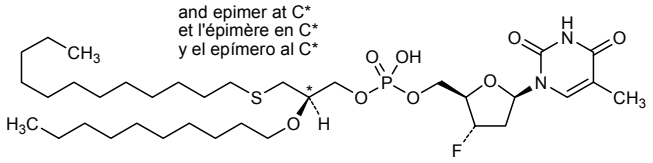
fosalvudinum tidoxilum

fosalvudine tidoxil — (2*RS*)-2-(decyloxy)-3-[(dodecyl)sulfanyl]propyl [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-methyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tetrahydrofuran-2-yl]methyl hydrogen phosphate

fosalvudine tidoxil — hydrogénophosphate de (2*RS*)-2-(décyloxy)-3-(dodécylsulfanyl)= propyle et de [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-méthyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)tétrahydrofuran-2-yl]méthyle

fosalvudina tidoxilo — hidrógenofosfato de (2*RS*)-2-(deciloxi)-3-[(dodecil)sulfanil]propilo y [(2*R*,3*S*,5*R*)-3-fluoro-5-(5-metil-2,4-dioxo-3,4-dihidropirimidin-1(2*H*)-il)tetrahidrofuran-2-il]metilo

$C_{35}H_{64}FN_2O_8PS$



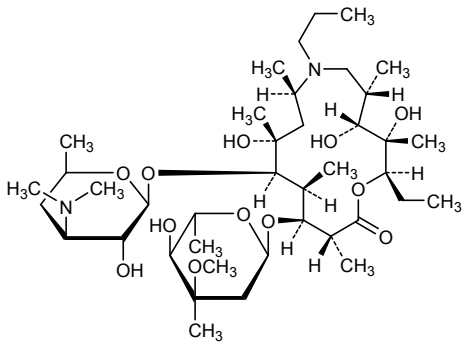
gamithromycinum

gamithromycin — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexamethyl-7-propyl-11-{[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy}-1-oxa-7-azacylopentadecan-15-one

gamithromycin — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-didésoxy-3-*C*-méthyl-3-*O*-méthyl-α-L-*ribo*-hexopyranosyl)oxy]-2-éthyl-3,4,10-trihydroxy-3,5,8,10,12,14-hexaméthyl-7-propyl-11-[[3,4,6-tridésoxy-3-(diméthylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-7-azacyclopentadécan-15-one

gamitromicina — (2*R*,3*S*,4*R*,5*S*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-didesoxi-3-*C*-metil-3-*O*-metil-α-L-*ribo*-hexopiranosil)oxi]-2-etil-3,4,10-trihidroxi-3,5,8,10,12,14-hexametil-7-propil-11-{[3,4,6-tridesoxi-3-(dimetilamino)-β-D-*xylo*-hexopiranosil]oxi}-1-oxa-7-azaciclopentadecan-15-ona

$C_{40}H_{76}N_2O_{12}$



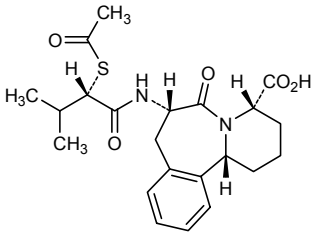
ilepatrilum

ilepatril — (4*S*,7*S*,12b*R*)-7-[(2*S*)-2-(acetylsulfanyl)-3-methylbutanamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-*a*][2]benzazepine-4-carboxylic acid

ilépatril — acide (4*S*,7*S*,12b*R*)-7-[[(2*S*)-2-(acétylsulfanyl)-3-méthylbutanoyl]=amino]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]=benzazépine-4-carboxylique

ilepatrilo — ácido (4*S*,7*S*,12b*R*)-7-{[(2*S*)-2-(acetilsulfanil)-3-metilbutanoil]amino}-6-oxo-1,2,3,4,6,7,8,12b-octahidropirido[2,1-*a*][2]benzazepina-4-carboxílico

$C_{22}H_{28}N_2O_5S$



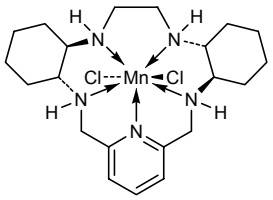
imisopasemum manganum

imisopasem manganese — (*PBPY*-7-11-2344'3')-dichloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahydro-7,11-(azeno)dibenzo[*b,h*][1,4,7,10]=tetraazacycloheptadecine-κ^4*N*^{5},*N*^{13},*N*^{18},*N*^{21},*N*^{22}]manganese

imisopasem manganèse — (*PBPY*-7-11-2344'3')-dichloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahydro-11,7-nitrilo-7*H*-dibenzo[*b,h*][1,4,7,10]=tétraazacycloheptadécine-κ*N*^{5},κ*N*^{13},κ*N*^{18},κ*N*^{21},κ*N*^{22}]manganèse

imisopasem manganeso — (*PBPY*-7-11-2344'3')-dicloro[(4a*R*,13a*R*,17a*R*,21a*R*)-1,2,3,4,4a,5,6,12,13,13a,14,15,16,17,17a,18,19,20,21,21a-icosahidro-7,11-(azeno)dibenzo[*b,h*][1,4,7,10]=tetraazaciclohheptadecino-κ^4*N*^{5},*N*^{13},*N*^{18},*N*^{21},*N*^{22}]manganeso

$C_{21}H_{35}Cl_2MnN_5$



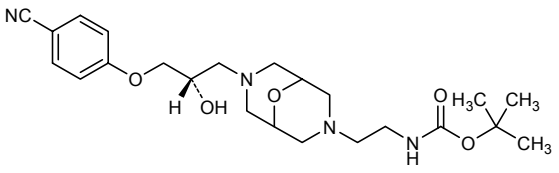
inakalantum

inakalant — *tert*-butyl (2-{7-[(2*S*)-3-(4-cyanophenoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]nonan-3-yl}ethyl)carbamate

inakalant — [2-[7-[(2S)-3-(4-cyanophénoxy)-2-hydroxypropyl]-9-oxa-3,7-diazabicyclo[3.3.1]non-3-yl]éthyl]carbamate de 1,1-diméthyléthyle

inakalant — (2-{7-[(2*S*)-3-(4-cianofenoxi)-2-hidroxipropil]-9-oxa-3,7-diazabiciclo=[3.3.1]nonan-3-il}etil)carbamato de *terc*-butilo

$C_{23}H_{34}N_4O_5$



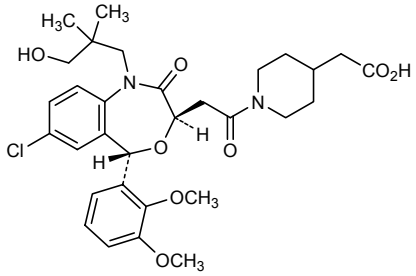
lapaquistatum

lapaquistat — (1-{[(3*R*,5*S*)-1-(3-hydroxy-2,2-dimethylpropyl)-7-chloro-5-(2,3-dimethoxyphenyl)-2-oxo-1,2,3,5-tetrahydro-4,1-benzoxazepin-3-yl]acetyl}piperidin-4-yl)acetic acid

lapaquistat — acide (1-{[(3*R*,5*S*)-1-(3-hydroxy-2,2-diméthylpropyl)-7-chloro-5-(2,3-diméthoxyphényl)-2-oxo-1,2,3,5-tétrahydro-4,1-benzoxazépin-3-yl]acétyl}pipéridin-4-yl)acétique

lapaquistat — ácido (1-{(3*R*,5*S*)-1-[3-hidroxi-2,2-dimetilpropil)]-7-cloro-5-(2,3-dimetoxifenil)-2-oxo-1,2,3,5-tetrahidro-4,1-benzoxazepin-3-il]acetil}piperidin-4-il)acético

$C_{31}H_{39}ClN_2O_8$



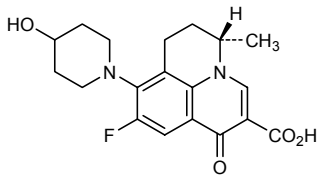
levonadifloxacinum

levonadifloxacin — (5*S*)-9-fluoro-8-(4-hydroxypiperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylic acid

lévonadifloxacine — (-)-acide (5*S*)-9-fluoro-8-(4-hydroxypipéridin-1-yl)-5-méthyl-1-oxo-6,7-dihydro-1*H*,5*H*-benzo[*ij*]quinolizine-2-carboxylique

levonadifloxacino — ácido (5*S*)-9-fluoro-8-(4-hidroxipiperidin-1-il)-5-metil-1-oxo-6,7-dihidro-1*H*,5*H*-benzo[*ij*]quinolizina-2-carboxílico

$C_{19}H_{21}FN_2O_4$



lexatumumabum*

lexatumumab — immunoglobulin G1, anti-[human tumor necrosis factor receptor superfamily member 10B (TNFRSF10B, death receptor 5, TNF-related apoptosis-inducing ligand receptor 2, TRAIL-R2, CD262)] human monoclonal HGS-ETR2; gamma1 heavy chain (*Homo sapiens* VH-IGHG1) (224-213')-disulfide with lambda light chain (*Homo sapiens* V-LAMBDA- IGLC2); (230-230":233-233")-bisdisulfide dimer

lexatumumab

immunoglobuline G1, anti-[membre 10B de la superfamille des récepteurs du facteur de nécrose tumorale humain (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticorps monoclonal humain HGS-ETR2; chaîne lourde gamma1 (*Homo sapiens* VH-IGHG1) (224-213')-disulfure avec la chaîne légère lambda (*Homo sapiens* V-LAMBDA- IGLC2); dimère (230-230'':233-233'')-bisdisulfure

lexatumumab

inmunoglobulina G1, anti-[miembro 10B de la superfamilia de receptores del factor de necrosis tumoral humano (TNFRSF10B, death receptor 5, TRAIL-R2, CD262)] anticuerpo monoclonal humano HGS-ETR2; cadena pesada gamma1 (*Homo sapiens* VH-IGHG1) (224-213')-disulfuro con la cadena ligera lambda (*Homo sapiens* V-LAMBDA- IGLC2); dímero (230-230'':233-233'')-bisdisulfuro

$C_{6346}H_{9832}N_{1720}O_{2002}S_{42}$

Heavy chain / chaîne lourde / cadena pesada

```
EVQLVQSGGG  VERPGGSLRL  SCAASGFTFD  DYGMSWVRQA  PGKGLEWVSG  50
INWNGGSTGY  ADSVKGRVTI  SRDNAKNSLY  LQMNSLRAED  TAVYYCAKIL  100
GAGRGWYFDL  WGKGTTVTVS  SASTKGPSVF  PLAPSSKSTS  GGTAALGCLV  150
KDYFPEPVTV  SWNSGALTSG  VHTFPAVLQS  SGLYSLSSVV  TVPSSSLGTQ  200
TYICNVNHKP  SNTKVDKRVE  PKSCDKTHTC  PPCPAPELLG  GPSVFLFPPK  250
PKDTLMISRT  PEVTCVVVDV  SHEDPEVKFN  WYVDGVEVHN  AKTKPREEQY  300
NSTYRVVSVL  TVLHQDWLNG  KEYKCKVSNK  ALPAPIEKTI  SKAKGQPREP  350
QVYTLPPSRE  EMTKNQVSLT  CLVKGFYPSD  IAVEWESNGQ  PENNYKTTPP  400
VLDSDGSFFL  YSKLTVDKSR  WQQGNVFSCS  VMHEALHNHY  TQKSLSLSPG  450
K
```

Lambda chain / chaîne lambda / cadena lambda

```
SSELTQDPAV  SVALGQTVRI  TCQGDSLRSY  YASWYQQKPG  QAPVLVIYGK  50
NNRPSGIPDR  FSGSSSGNTA  SLTITGAQAE  DEADYYCNSR  DSSGNHVVFG  100
GGTKLTVLGQ  PKAAPSVTLF  PPSSEELQAN  KATLVCLISD  FYPGAVTVAW  150
KADSSPVKAG  VETTTPSKQS  NNKYAASSYL  SLTPEQWKSH  RSYSCQVTHE  200
GSTVEKTVAP  TECS
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
22-96    22'-87'    22''-96''    22'''-87'''  136'-195'  136'''-195'''  148-204  148''-204''
213'-224 213'''-224'' 230-230''  233-233''    265-325    265''-325''    371-429  371''-429''
```

lificiguatum

lificiguat

[5-(1-benzyl-1*H*-indazol-3-yl)furan-2-yl]methanol

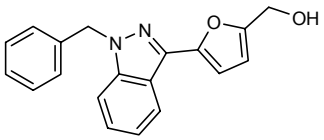
lificiguat

[5-(1-benzyl-1*H*-indazol-3-yl)furan-2-yl]méthanol

lificiguat

[5-(1-bencil-1*H*-indazol-3-il)furan-2-il]metanol

$C_{19}H_{16}N_2O_2$



lobeglitazonum

lobeglitazone

(5*RS*)-5{[4-(2-{[6-(4-methoxyphenoxy)pyrimidin-4-yl]methylamino}=ethoxy)phenyl]methyl}-1,3-thiazolidine-2,4-dione

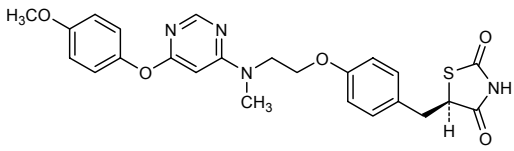
lobéglitazone

(5*RS*)-5-[4-[2-[[6-(4-méthoxyphénoxy)pyrimidin-4-yl]méthylamino]=éthoxy]benzyl]thiazolidine-2,4-dione

lobeglitazona

(5*RS*)-5-[4-(2-{[6-(4-metoxifenoxi)pirimidin-4-il]metilamino}etoxi)=bencil]-1,3-tiazolidina-2,4-diona

$C_{24}H_{24}N_4O_5S$



and enantiomer
et énantiomère
y enantiómero

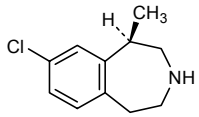
lorcaserinum

lorcaserin (1*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine

lorcasérine (1*R*)-8-chloro-1-méthyl-2,3,4,5-tétrahydro-1*H*-3-benzazépine

lorcaserina (1*R*)-8-cloro-1-metil-2,3,4,5-tetrahidro-1*H*-3-benzazepina

$C_{11}H_{14}ClN$



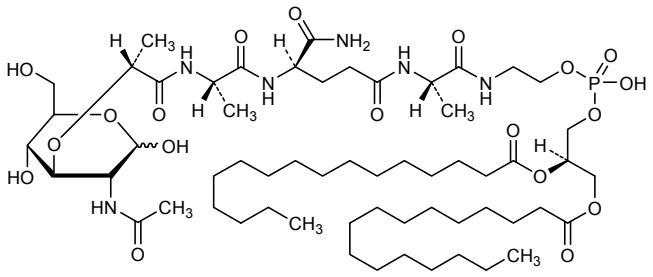
mifamurtidum

mifamurtide 2-[(*N*-{(2*R*)-[(2-acetamido-2,3-dideoxy-D-glucopyranos-3-yl)oxy]= propanoyl}-L-alanyl-D-isoglutaminyl-L-alanyl)amino]ethyl (2*R*)-2,3-bis(hexadecanoyloxy)propyl hydrogen phosphate

mifamurtide hydrogénophosphate de 2-[[*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(acétylamino)-2,5-dihydroxy-6-(hydroxyméthyl)tétrahydro-2*H*-pyran-4-yloxy]propanoyl]-L-alanyl-D-isoglutaminyl-L-alanyl]amino]éthyle et de (2*R*)-2,3-bis(hexanoyloxy)propyle

mifamurtida hidrógenofosfato de 2-[[*N*-[(2*R*)-2-[(3*R*,4*R*,5*S*,6*R*)-3-(acetilamino)-2,5-dihidroxi-6-(hidroximetil)tetrahidro-2*H*-piran-4-iloxi]propanoil]-L-alanil-D-isoglutaminil-L-alanil]amino]etilo y de (2*R*)-2,3-bis(hexanoiloxi)propilo

$C_{59}H_{109}N_6O_{19}P$



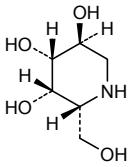
migalastatum

migalastat (2*R*,3*S*,4*R*,5*S*)-2-(hydroxymethyl)piperidine-3,4,5-triol

migalastat (+)-(2*R*,3*S*,4*R*,5*S*)-2-(hydroxyméthyl)pipéridine-3,4,5-triol

migalastat (2*R*,3*S*,4*R*,5*S*)-2-(hidroximetil)piperidina-3,4,5-triol

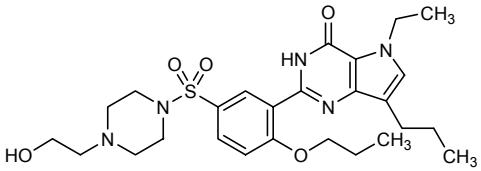
$C_6H_{13}NO_4$



mirodenafilum

mirodenafil	5-ethyl-2-(5-{[4-(2-hydroxyethyl)piperazin-1-yl]sulfonyl}-2-propoxyphenyl)-7-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
mirodénafil	5-éthyl-2-[5-[[4-(2-hydroxyéthyl)pipérazin-1-yl]sulfonyl]-2-propoxyphenyl]-7-propyl-3,5-dihydro-4*H*-pyrrolo[3,2-*d*]pyrimidin-4-one
mirodenafilo	5-etil-2-(5-{[4-(2-hidroxietil)piperazin-1-il]sulfonil}-2-propoxifenil)-7-propil-3,5-dihidro-4*H*-pirrolo[3,2-*d*]pirimidin-4-ona

$C_{26}H_{37}N_5O_5S$



motavizumabum*

motavizumab	immunoglobulin G1, anti-(human respiratory syncytial virus glycoprotein F) humanized monoclonal MEDI-524; gamma1 heavy chain [humanized VH (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGHG1] (223-213')-disulfide with kappa light chain [humanized V-KAPPA (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; (229-229'':232-232'')-bisdisulfide dimer
motavizumab	immunoglobuline G1, anti-(glycoprotéine de fusion du virus syncytial respiratoire humain) anticorps monoclonal humanisé MEDI-524; chaîne lourde gamma1 [VH humanisé (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGHG1] (223-213')-disulfure avec la chaîne légère kappa [V-KAPPA humanisé (*Homo sapiens* FR/*Mus musculus* CDR)-*Homo sapiens* IGKC]; dimère (229-229'':232-232'')-bisdisulfure
motavizumab	inmunoglobulina G1, anti-(glicoproteína de fusión del virus sincitial respiratorio humano) anticuerpo monoclonal humanizado MEDI-524; cadena pesada gamma1 [VH humanizada (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGHG1] (223-213')-disulfuro con la cadena ligera kappa [V-KAPPA humanizada (*Homo sapiens* FR/*Mus musculus* CDR)- *Homo sapiens* IGKC]; (229-229'':232-232'')-bisdisulfide dimer

$C_{6476}H_{10014}N_{1706}O_{2008}S_{48}$

γ-1-Chain / Chaîne γ-1 / Cadena γ-1

QVTLRESGPA	LVKPTQTLTL	TCTFSGFSLS	TAGMSVGWIR	QPPGKALEWL	50
ADIWWDDKKH	YNPSLKDRLT	ISKDTSKNQV	VLKVTNMDPA	DTATYYCARD	100
MIFNFYFDVW	GQGTTVTVSS	ASTKGPSVFP	LAPSSKSTSG	GTAALGCLVK	150
DYFPEPVTVS	WNSGALTSGV	HTFPAVLQSS	GLYSLSSVVT	VPSSSLGTQT	200
YICNVNHKPS	NTKVDKRVEP	KSCDKTHTCP	PCPAPELLGG	PSVFLFPPKP	250
KDTLMISRTP	EVTCVVVDVS	HEDPEVKFNW	YVDGVEVHNA	KTKPREEQYN	300
STYRVVSVLT	VLHQDWLNGK	EYKCKVSNKA	LPAPIEKTIS	KAKGQPREPQ	350
VYTLPPSREE	MTKNQVSLTC	LVKGFYPSDI	AVEWESNGQP	ENNYKTTPPV	400
LDSDGSFFLY	SKLTVDKSRW	QQGNVFSCSV	MHEALHNHYT	QKSLSLSPGK	450

κ Chain / Chaîne κ/ Cadena κ

DIQMTQSPST	LSASVGDRVT	ITCSASSRVG	YMHWYQQKPG	KAPKLLIYDT	50'
SKLASGVPSR	FSGSGSGTEF	TLTISSLQPD	DFATYYCFQG	SGYPFTFGGG	100'
TKVEIKRTVA	APSVFIFPPS	DEQLKSGTAS	VVCLLNNFYP	REAKVQWKVD	150'
NALQSGNSQE	SVTEQDSKDS	TYSLSSTLTL	SKADYEKHKV	YACEVTHQGL	200'
SSPVTKSFNR	GEC				213'

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

22-97 22''-97'' 23'-87' 23'''-87''' 133'-193' 133'''-193''' 147-203 147''-203''
213'-223 213'''-223'' 229-229'' 232-232'' 264-324 264''-324'' 370-428 370''-428''

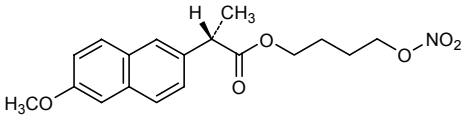
naproxcinodum

naproxcinod — 4-(nitrooxy)butyl (2*S*)-2-(6-methoxynaphthalen-2-yl)propanoate

naproxcinod — (2*S*)-2-(6-méthoxynaphtalén-2-yl)propanoate de 4-(nitrooxy)butyle

naproxcinod — (2*S*)-2-(6-metoxinaftalen-2-il)propanoato de 4-(nitrooxi)butilo

$C_{18}H_{21}NO_6$



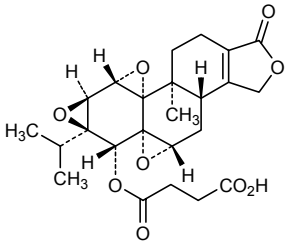
omtriptolidum

omtriptolide — 4-{[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-methyl-6a-(propan-2-yl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahydrotrisoxireno=[4b,5:6,7:8a,9]phenanthro[1,2-*c*]furan-6-yl]oxy}-4-oxobutanoic acid

omtriptolide — acide 4-[[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-méthyl-6a-(1-méthyléthyl)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodécahydrotrisoxiréno[4b,5:6,7:8a,9]phénanthro[1,2-*c*]furan-6-yl]=oxy]-4-oxobutanoïque

omtriptolida — ácido 4-{[(3b*S*,4a*S*,5a*R*,6*R*,6a*S*,7a*S*,7b*S*,8a*S*,8b*S*)-8b-metil-6a-(propan-2-il)-1-oxo-1,3,3b,4,4a,6,6a,7a,7b,8b,9,10-dodecahidrotrisoxireno[4b,5:6,7:8a,9]fenantro[1,2-*c*]furan-6-il]oxi}-4-oxobutanoico

$C_{24}H_{28}O_9$



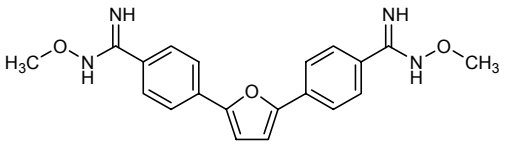
pafuramidinum

pafuramidine — 4,4'-(furan-2,5-diyl)bis(*N*-methoxybenzenecarboximidamide)

pafuramidine — 4,4'-(furane-2,5-diyl)bis(*N*-méthoxybenzènecarboximidamide)

pafuramidina — 4,4'-(furano-2,5-diil)bis(*N*-metoxibencenocarboximidamida)

$C_{20}H_{20}N_4O_3$



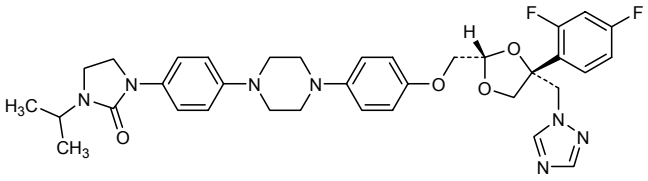
pramiconazolum

pramiconazole — 1-(4-{4-[4-({(2*S*,4*R*)-4-(2,4-difluorophenyl)-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolan-2-yl}methoxy)phenyl]piperazin-1-yl}phenyl)-3-(propan-2-yl)imidazolidin-2-one

pramiconazole — (+)-1-[4-[4-[4-[[(2*S*,4*R*)-4-(2,4-difluorophényl)-4-[(1*H*-1,2,4-triazol-1-yl)méthyl]-1,3-dioxolan-2-yl]méthoxy]phényl]pipérazin-1-yl]phényl]-3-(1-méthyléthyl)imidazolidin-2-one

pramiconazol — 1-(4-{4-[4-({(2*S*,4*R*)-4-(2,4-difluorofenil)-4-[(1*H*-1,2,4-triazol-1-il)metil]-1,3-dioxolan-2-il}metoxi)fenil]piperazin-1-il}fenil)-3-(propan-2-il)imidazolidin-2-ona

$C_{35}H_{39}F_2N_7O_4$



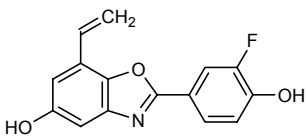
prinaberelum

prinaberel — 7-ethenyl-2-(3-fluoro-4-hydroxyphenyl)-1,3-benzoxazol-5-ol

prinabérel — 7-éthényl-2-(3-fluoro-4-hydroxyphényl)-1,3-benzoxazol-5-ol

prinaberel — 7-etenil-2-(3-fluoro-4-hidroxifenil)-1,3-benzoxazol-5-ol

$C_{15}H_{10}FNO_3$



rilonaceptum*

rilonacept — [653-glycine][human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type 1 interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with human immunoglobulin G1-(229 *C*-terminal residues)-peptide (Fc fragment)], (659-659':662-662')-bisdisulfide dimer

rilonacept — (659-659':662-662')-bisdisulfure du dimère de la [653-glycine][protéine accessoire du récepteur de l'interleukine-1 humaine-(1-339)-peptide (fragment du domaine extracellulaire) protéine de fusion avec le récepteur de type I humain de l'interleukine-1-(5-316)-peptide (fragment du domaine extracellulaire) protéine de fusion avec l'immunoglobuline G1 humaine-(229 résidus *C*-terminaux)-peptide (fragment Fc)]

rilonacept — (659-659':662-662')-bisdisulfuro del dímero de la [653-glicina][proteína accesoria del receptor de la interleukina-1 humana-(1-339)-péptido (fragmento del dominio extracelular) proteína de fusión con el receptor de tipo I humano de la interleukina-1-(5-316)-péptido (fragmento del dominio extracelular) proteína de fusión con la inmunoglobulina G1 humana-(229 restos *C*-terminales)-péptido (fragmento Fc)]

$C_{9030}H_{13932}N_{2400}O_{2670}S_{74}$

Monomer / Monomère / Monómero

```
SERCDDWGLD  TMRQIQVFED  EPARIKCPLF  EHFLKFNYST  AHSAGLTLIW  50
YWTRQDRDLE  EPINFRLPEN  RISKEKDVLW  FRPTLLNDTG  NYTCMLRNTT  100
YCSKVAFPLE  VVQKDSCFNS  PMKLPVHKLY  IEYGIQRITC  PNVDGYFPSS  150
VKPTITWYMG  CYKIQNFNNV  IPEGMNLSFL  IALISNNGNY  TCVVTYPENG  200
RTFHLTRTLT  VKVVGSPKNA  VPPVIHSPND  HVVYEKEPGE  ELLIPCTVYF  250
SFLMDSRNEV  WWTIDGKKPD  DITIDVTINE  SISHSRTEDE  TRTQILSIKK  300
VTSEDLKRSY  VCHARSAKGE  VAKAAKVKQK  VPAPRYTVEK  CKEREEKIIL  350
VSSANEIDVR  PCPLNPNEHK  GTITWYKDDS  KTPVSTEQAS  RIHQHKEKLW  400
FVPAKVEDSG  HYYCVVRNSS  YCLRIKISAK  FVENEPNLCY  NAQAIFKQKL  450
PVAGDGGLVC  PYMEFFKNEN  NELPKLQWYK  DCKPLLLDNI  HFSGVKDRLI  500
VMNVAEKHRG  NYTCHASYTY  LGKQYPITRV  IEFITLEENK  PTRPVIVSPA  550
NETMEVDLGS  QIQLICNVTG  QLSDIAYWKW  NGSVIDEDDP  VLGEDYYSVE  600
NPANKRRSTL  ITVLNISEIE  SRFYKHPFTC  FAKNTHGIDA  AYIQLIYPVT  650
NSGDKTHTCP  PCPAPELLGG  PSVFLFPPKP  KDTLMISRTP  EVTCVVVDVS  700
HEDPEVKFNW  YVDGVEVHNA  KTKPREEQYN  STYRVVSVLT  VLHQDWLNGK  750
EYKCKVSNKA  LPAPIEKTIS  KAKGQPREPQ  VYTLPPSRDE  LTKNQVSLTC  800
LVKGFYPSDI  AVEWESNGQP  ENNYKTTPPV  LDSDGSFFLY  SKLTVDKSRW  850
QQGNVFSCSV  MHEALHNHYT  QKSLSLSPGK                          880
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
4-102    4'-102'   27-94    27'-94'   117-161  117'-161'  140-192  140'-192'  246-312
246'-312' 341-422  341'-422' 362-414  362'-414' 339-482  339'-482' 460-514  460'-514'
566-630  566'-630' 659-659' 662-662' 694-754  694'-754'  800-858   800'-858'
```

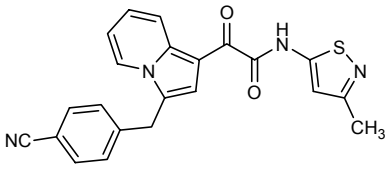
rosabulinum

rosabulin — 2-{3-[(4-cyanophenyl)methyl]indolizin-1-yl}-*N*-(3-methyl-1,2-thiazol-5-yl)-2-oxoacetamide

rosabuline — 2-[3-(4-cyanobenzyl)indolizin-1-yl]-*N*-(3-méthylisothiazol-5-yl)-2-oxoacétamide

rosabulina — 2-{3-[(4-cianofenil)metil]indolizin-1-il}-*N*-(3-metilisotiazol-5-il)-2-oxoacetamida

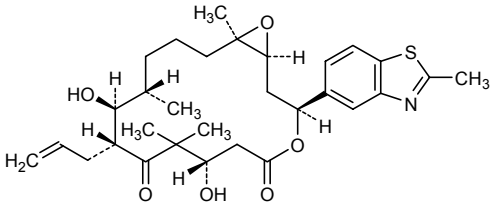
$C_{22}H_{16}N_4O_2S$



sagopilonum

sagopilone	(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,12,16-tetramethyl-3-(2-methyl-1,3-benzothiazol-5-yl)-10-(prop-2-enyl)-4,17-dioxabicyclo[14.1.0]heptadecane-5,9-dione
sagopilone	(-)-(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihydroxy-8,8,12,16-tétraméthyl-3-(2-méthyl-1,3-benzothiazol-5-yl]-10-(prop-2-ényl)-4,17-dioxabicyclo[14.1.0]heptadécane-5,9-dione
sagopilona	(1*S*,3*S*,7*S*,10*R*,11*S*,12*S*,16*R*)-7,11-dihidroxi-8,8,12,16-tetrametil-3-(2-metil-1,3-benzotiazol-5-il)-10-(prop-2-enil)-4,17-dioxabiciclo[14.1.0]heptadecano-5,9-diona

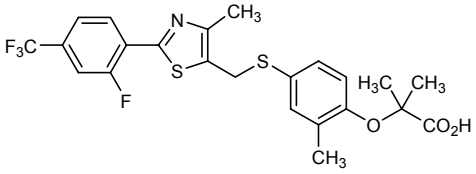
$C_{30}H_{41}NO_6S$



sodelglitazarum

sodelglitazar	2-{4-[({2-[2-fluoro-4-(trifluromethyl)phenyl]-4-methyl-1,3-thiazol-5-yl}methyl)sulfanyl]-2-methylphenoxy}-2-methylpropanoic acid
sodelglitazar	acide 2-[4-[[[2-[2-fluoro-4-(trifluorométhyl)phényl]-4-méthyl-1,3-thiazol-5-yl]méthyl]sulfanyl]-2-méthylphénoxy]-2-méthylpropanoïque
sodelglitazar	ácido 2-{4-[({2-[2-fluoro-4-(trifluorometil)fenil]-4-metil-1,3-tiazol-5-il}metil)sulfanil]-2-metilfenoxi}-2-metilpropanoico

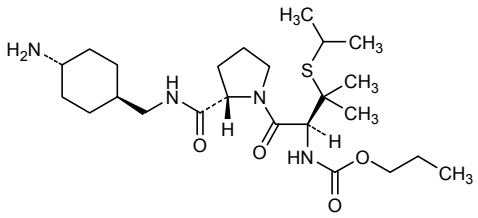
$C_{23}H_{21}F_4NO_3S_2$



sofigatranum

sofigatran	propyl {(1*S*)-1-{(2*S*)-2-[(*trans*-4-aminocyclohexylmethyl)carbamoyl]= pyrrolidine-1-carbonyl}-2-methyl-2-[(propan-2-yl)sulfanyl]propyl}= carbamate
sofigatran	[(1*S*)-1-[[(2*S*)-2-[[(*trans*-4-aminocyclohexyl)méthyl]carbamoyl]= pyrrolidin-1-yl]carbonyl]-2-méthyl-2-[(1-méthyléthyl)sulfanyl]propyl]= carbamate de propyle
sofigatrán	[(1*S*)-1-[[(2*S*)-2-[[(*trans*-4-aminociclohexil)metil]carbamoil]pyrrolidin-1-il]carbonil]-2-metil-2-[(propan-2-il)sulfanil]propil]carbamato de propilo

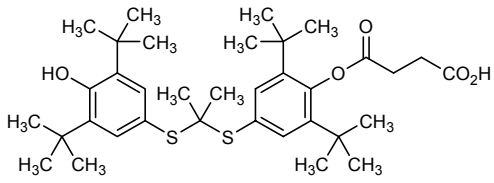
$C_{24}H_{44}N_4O_4S$



succinobucolum

succinobucol	4-{4-[(2-{[3,5-di(*tert*-butyl)-4-hydroxyphenyl]sulfanyl}propan-2-yl)= sulfanyl]-2,6-di(*tert*-butyl)phenoxy}-4-oxobutanoic acid
succinobucol	acide 4-[4-[[1-[[3,5-bis(1,1-diméthyléthyl)-4-hydroxyphényl]sulfanyl]-1-méthyléthyl]sulfanyl]-2,6-bis(1,1-diméthyléthyl)phénoxy]-4-oxobutanoïque
succinobucol	ácido 4-{4-[(2-{[3,5-di(*terc*-butil)4-hidroxifenil]sulfanil}propan-2-il)= sulfanil]-2,6-di(*terc*-butil)fenoxi}-4-oxobutanoico

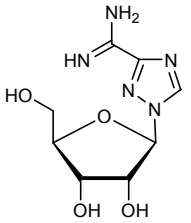
$C_{35}H_{52}O_5S_2$



taribavirinum

taribavirin	1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboximidamide
taribavirine	1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboximidamide
taribavirina	1-β-D-ribofuranosil-1*H*-1,2,4-triazol-3-carboximidamida

$C_8H_{13}N_5O_4$



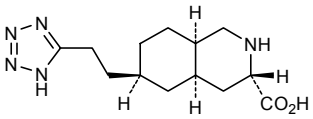
tezampanelum

tezampanel (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid

tézampanel (-)-acide (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tétrazol-5-yl)éthyl]= décahydroisoquinoléine-3-carboxylique

tezampanel (-)-ácido (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1*H*-tetrazol-5-il)etil]= decahidroisoquinolina-3-carboxílico

$C_{13}H_{21}N_5O_2$



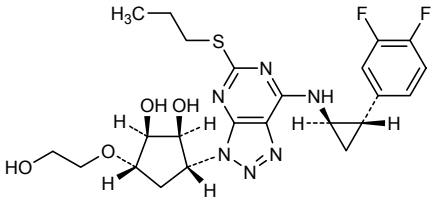
ticagrelorum

ticagrelor (1*S*,2*S*,3*R*,5*S*)-3-(7-{[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]= amino}-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl)-5-(2-hydroxyethoxy)cyclopentane-1,2-diol

ticagrélor (1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophényl)cyclopropyl]= amino]-5-(propylsulfanyl)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyéthoxy)cyclopentane-1,2-diol

ticagrelor (1*S*,2*S*,3*R*,5*S*)-3-(7-{[(1*R*,2*S*)-2-(3,4-difluorofenil)ciclopropil]amino}-5-(propilsulfanil)-3*H*-[1,2,3]triazolo[4,5-*d*]pirimidin-3-il)-5-(2-hidroxietoxi)ciclopentano-1,2-diol

$C_{23}H_{28}F_2N_6O_4S$



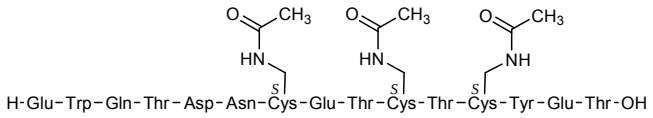
tigapotidum

tigapotide — L-glutamyl-L-tryptophyl-L-glutaminyl-L-threonyl-L-aspartyl-L-asparaginyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-glutamyl-L-threonyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-threonyl-*S*-[(acetamido)methyl]-L-cysteinyl-L-tyrosyl-L-glutamyl-L-threonine

tigapotide — S^{37}-S^{40},S^{42}-tris[(acétylamino)méthyl]bêta-microséminoprotéine humaine (protéine PSP94 sécrétée par la prostate)-(31-45)-peptide

tigapotida — S^{37}-S^{40},S^{42}-tris[(aceltilamino)metil]beta-microseminoproteína humana (proteína PSP94 secretada por la próstata)-(31-45)-péptido

$C_{82}H_{119}N_{21}O_{34}S_3$



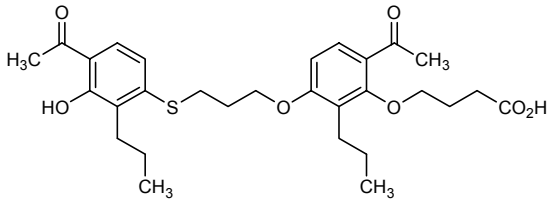
tipelukastum

tipelukast — 4-(6-acetyl-3-{3-[(4-acetyl-3-hydroxy-2-propylphenyl)sulfanyl]=propoxy}-2-propylphenoxy)butanoic acid

tipélukast — acide 4-[6-acétyl-3-[3-[(4-acétyl-3-hydroxy-2-propylphényl)sulfanyl]=propoxy]-2-propylphénoxy]butanoïque

tipelukast — ácido 4-[6-acetil-3-[3-[(4-acetil-3-hidroxi-2-propilfenil)sulfanil]=propoxi]-2-propilfenoxi]butanoico

$C_{29}H_{38}O_7S$



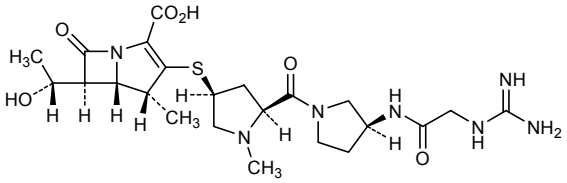
tomopenemum

tomopenem — (4*R*,5*S*,6*S*)-3-({(3*S*,5*S*)-5-[(3*S*)-3-(carbamimidamidoacetamido)=pyrrolidine-1-carbonyl]-1-methylpyrrolidin-3-yl}sulfanyl)-6-[(1*R*)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid

tomopénem — (-)-acide (4*R*,5*S*,6*S*)-3-[[(3*S*,5*S*)-5-[[(3*S*)-3-[[(carbamimidoylamino)=acétyl]amino]pyrrolidin-1-yl]carbonyl]-1-méthylpyrrolidin-3-yl]=sulfanyl]-6-[(1*R*)-1-hydroxyéthyl]-4-méthyl-7-oxo-1-azabicyclo[3.2.0]=hept-2-ène-2-carboxylique

tomopenem — ácido (4*R*,5*S*,6*S*)-3-{[(3*S*,5*S*)-5-({(3*S*)-3-(carbamimidamidoacetamido)pirrolidin-1-il}carbonil)-1-metilpirrolidin-3-il]sulfanil}-6-[(1*R*)-1-hidroxietil]-4-metil-7-oxo-1-azabiciclo[3.2.0]=hept-2-eno-2-carboxílico

$C_{23}H_{35}N_7O_6S$



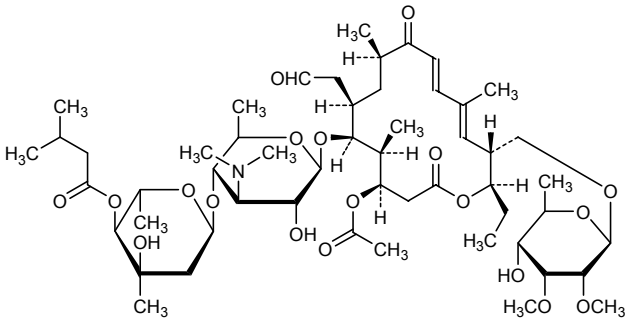
tylvalosinum

tylvalosin — (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-{[(6-deoxy-2,3-di-*O*-methyl-β-D-allopyranosyl)oxy]methyl}-6-({3,6-dideoxy-4-*O*-[2,6-dideoxy-3-*C*-methyl-4-*O*-(3-methylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(dimethylamino)-β-D-glucopyranosyl}oxy)-16-ethyl-5,9,13-trimethyl-2,10-dioxo-7-(2-oxoethyl)oxacyclohexadeca-11,13-dien-4-yl acetate

tylvalosine — (-)-acétate de (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-[[(6-désoxy-2,3-di-*O*-méthyl-β-D-allopyranosyl)oxy]méthyl]-6-[[3,6-didésoxy-4-*O*-[2,6-didésoxy-3-*C*-méthyl-4-*O*-(3-méthylbutanoyl)-α-L-*ribo*-hexopyranosyl]-3-(diméthylamino)-β-D-glucopyranosyl]oxy]-16-éthyl-5,9,13-triméthyl-2,10-dioxo-7-(2-oxoéthyl)oxacyclohexadéca-11,13-dién-4-yle

tilvalosina — (-)-acetato de (4*R*,5*S*,6*S*,7*R*,9*R*,11*E*,13*E*,15*R*,16*R*)-15-[[(6-desoxi-2,3-di-*O*-metil-β-D-alopiranosil)oxi]metil]-6-[[3,6-didesoxi-4-*O*-[2,6-didesoxi-3-*C*-metil-4-*O*-(3-metilbutanoil)-α-L-*ribo*-hexopiranosil]-3-(dimetilamino)-β-D-glucopiranosil]oxi]-16-etil-5,9,13-trimetil-2,10-dioxo-7-(2-oxoetil)oxaciclohexadeca-11,13-dien-4-ilo

$C_{53}H_{87}NO_{19}$



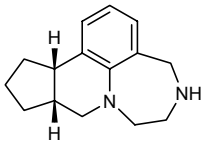
vabicaserinum

vabicaserin — (9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-decahydrocyclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinoline

vabicasérine — (-)-(9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-décahydrocyclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinoléine

vabicaserina — (-)-(9a*R**,12a*S**)-4,5,6,7,9,9a,10,11,12,12a-decahidrociclopenta[*c*][1,4]diazepino[6,7,1-*ij*]quinolina

$C_{15}H_{20}N_2$



or enantiomer, (-)-isomer
ou énantiomère, (-)-isomère
o enantiómero, (-)-isómero

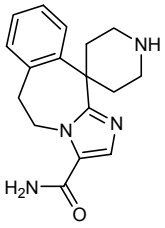
vapitadinum

vapitadine — 5,6-dihydrospiro(imidazo[2,1-*b*][3]benzazepine-11,4'-piperidine)-3-carboxamide

vapitadine — 5,6-dihydrospiro[11*H*-imidazo[2,1-*b*][3]benzazépine-11,4'-pipéridine]-3-carboxamide

vapitadina — 5,6-dihidrospiro(11*H*-imidazo[2,1-*b*][3]benzazepina-11,4'-piperidina)-3-carboxamida

$C_{17}H_{20}N_4O$



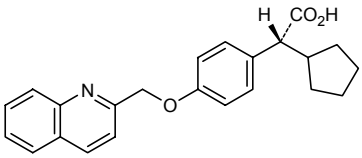
veliflaponum

veliflapon — (2*R*)-cyclopentyl{4-[(quinolin-2-yl)methoxy]phenyl}acetic acid

véliflapon — (+)-acide (2*R*)-cyclopentyl[4-(quinoléin-2-ylméthoxy)phényl]acétique

veliflapón — (+)-ácido (2*R*)-ciclopentil[4-(quinolin-2-ilmetoxi)fenil]acético

$C_{23}H_{23}NO_3$



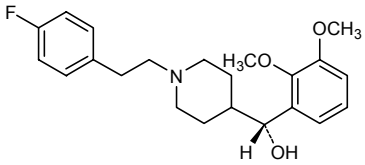
volinanserinum

volinanserin — (*R*)-(2,3-dimethoxyphenyl){1-[2-(4-fluorophenyl)ethyl]piperidin-4-yl}=methanol

volinansérine — (+)-(*R*)-(2,3-diméthoxyphényl)[1-[2-(4-fluorophényl)éthyl]pipéridin-4-yl]méthanol

volinanserina — (+)-(*R*)-(2,3-dimetoxifenil)[1-[2-(4-fluorofenil)etil]piperidin-4-il]metanol

$C_{22}H_{28}FNO_3$



AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Recommended International Non Proprietary Names (Rec. INN): List 53
Dénominations communes internationales recommandées (DCI Rec.): Liste 53
Denominaciones Comunes Internacionales recomendadas (DCI Rec.): Lista 53
(WHO Drug Information, Vol. 19, No. 1, 2005)

p. 80	*delete/supprimer/suprímase*	*insert/insérer/insertése*
	gantacurium chloridum	gantacurii chloridum

p. 88 **panitumumabun**

panitumumab	*replace the molecular formula by the following*
panitumumab	*remplacer la formule brute par la suivante*
panitumumab	*sustitúyase la fórmula molecular por la siguiente*

$C_{6398}H_{9878}N_{1694}O_{2016}S_{48}$

p. 88 **pelitinibum**

pelitinib — *sustitúyase el nombre químico por el siguiente:*

(2*E*)-*N*-[3-ciano-4-[(3-cloro-4-fluorofenil)amino]-7-etoxiquinolin-6-il]-4-(dimetilamino)-2-butenamina

Recommended International Non Proprietary Names (Rec. INN): List 55
Dénominations communes internationales recommandées (DCI Rec.): Liste 55
Denominaciones Comunes Internacionales recomendadas (DCI Rec.): Lista 55
(WHO Drug Information, Vol. 20, No. 1, 2006)

p. 45	*suprimáse*	*insértese*
	nebicapone	nebicapona

* Electronic structure available on Mednet: http://mednet.who.int/
* Structure électronique disponible sur Mednet: http://mednet.who.int/
* Estructura electrónica disponible en Mednet: http://mednet.who.int/

Procedure and Guiding Principles / Procédure et Directives / Procedimientos y principios generales

The text of the *Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* and *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* will be reproduced in proposed INN lists only.

Les textes de la *Procédure à suivre en vue du choix de dénominations communes internationales recommandées pour les substances pharmaceutiques* et des *Directives générales pour la formation de dénominations communes internationales applicables aux substances pharmaceutiques* seront publiés seulement dans les listes des DCI proposées.

El texto de los *Procedimientos de selección de denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas* y de los *Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas* aparece solamente en las listas de DCI propuestas.

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United States Adopted Name (USAN) Drug Finder

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- [ ] **APP Pharmaceuticals LLC-A company of the Fresenius Kabi Group (1)**

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YEAR APPROVED:

- [ ] **USAN (1)**
- [ ] **United States Adopted Names (1)**
- [ ] **Treatment of hematologic malignancies (1)**
- [ ] **Treatment (1)**
- [ ] **MGD006 S80880 RES234 (1)**
- [ ] **Generic (1)**
- [ ] **Flotetuzumab (1)**
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- [ ] **2017 (44)**
- [ ] **2016 (152)**

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2138 Results

Most Relevant

IBROLIPIM
USAN File Number: (NN-01)
CAS Registry Number: 133208-93-2
UNII: N/A
WHO Number: N/A

NAPABUCASIN
USAN File Number: (BC-107)
CAS Registry Number: 83280-65-3
UNII: Z1HHM49K7O
WHO Number: 9848

IBIPINABANT
USAN File Number: (TT-91)
CAS Registry Number: 464213-10-3

UNII: N/A
WHO Number: N/A

AFEGOSTAT
USAN File Number: (TT-109)
CAS Registry Number: 169105-89-9
UNII: N/A
WHO Number: N/A

ATEZOLIZUMAB
USAN File Number: (CD-146)
CAS Registry Number: 1380723-44-3
UNII: 52CMI0WC3Y
WHO Number: 9814

NAVOXIMOD
USAN File Number: (EF-77)
CAS Registry Number: 1402837-78-8
UNII: 926SHL95NC
WHO Number: 10392

ROLAPITANT
USAN File Number: (cd-170)
CAS Registry Number: 552292-08-7
UNII: NLE429IZUC
WHO Number: 8882

EMAPALUMAB
USAN File Number: (DE-170)
CAS Registry Number: 1709815-23-5
UNII: 3S252O2Z4X
WHO Number: 10319

LIAFENSINE
USAN File Number: ZZ-01
CAS Registry Number: 1198790-53-2
UNII: N/A
WHO Number: 9750

PATIROMER SORBITEX CALCIUM
USAN File Number: (bc-83)
CAS Registry Number: 1415477-49-4
UNII: 7T97I3787N
WHO Number: N/A

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C12N 15/13, C07K 16/24, A61K 39/395, C12L 5/08

A3

(11) International Publication Number: **WO 95/14780**

(43) International Publication Date: 1 June 1995 (01.06.95)

(21) International Application Number: PCT/US94/13188

(22) International Filing Date: 21 November 1994 (21.11.94)

(30) Priority Data:
93402846.5 23 November 1993 (23.11.93) EP
(34) Countries for which the regional or international application was filed: AT et al.

(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: GARRONE, Pierre [FR/FR]; 15, rue des Alouettes, F-69008 Lyon (FR). DJOSSOU, Odile [FR/FR]; Chemin du Gareizin, F-69340 Francheville (FR). FOSSIEZ, François [FR/FR]; 51, résidence de la Voie-Romaine, F-69290 Craponne (FR). BANCHEREAU, Jacques [FR/FR]; 25, avenue Paul-Santy, F-69130 Ecully (FR).

(74) Agent: BLASDALE, John, H., C.; Schering-Plough Corporation, Patent Dept. K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States: AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MN, NO, NZ, PL, RO, RU, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
22 June 1995 (22.06.95)

(54) Title: HUMAN MONOCLONAL ANTIBODIES AGAINST HUMAN CYTOKINES AND METHODS OF MAKING AND USING SUCH ANTIBODIES

(57) Abstract

Human monoclonal antibodies against a human cytokine (such as a human interleukin, e.g., human IL-1α) and fragments of such antibodies are disclosed, together with pharmaceutical compositions and methods employing the human monoclonal antibodies and fragments, methods for screening for human monoclonal antibodies against a human protein, methods for producing a cDNA library enriched in DNA encoding V_H and/or V_L chains of a human monoclonal antibody, cell lines for making the human monoclonal antibodies, and isolated DNA for making the human monoclonal antibodies and fragments of the invention.

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INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 94/13188

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/13 C07K16/24 A61K39/395 C12N5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y A	EP,A,0 267 611 (OTSUKA PHARMACEUTICAL CO.) 18 May 1988 see example 2 --- EP,A,0 314 402 (SCHERING BIOTECH CORP.) 3 May 1989 see page 3, line 5 - line 43 see page 4, line 18 - line 31 --- WO,A,90 06371 (COMMISSARIAT A L'ENERGIE ATOMIQUE) 14 June 1990 see page 8, line 15 - line 30 --- -/--	1-4,6, 21-23 29-32 5 1-3,15, 18,20-28 29-32 7-17 1-4 14

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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2

Date of the actual completion of the international search	Date of mailing of the international search report
9 May 1995	19. 05. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Gurdjian, D

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP,A,0 434 879 (LABORATOIRES UNICET) 3 July 1991 see claims 1-9 & WO,A,91 09115 cited in the application	29-32
X	EP,A,0 364 778 (OTSUKA PHARMACEUTICAL CO.LTD.) 25 April 1990 see claims 1-9	1-3

INTERNATIONAL SEARCH REPORT

...ormation on patent family members

Interna... ...l Application No
PCT/US 94/13188

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0267611	18-05-88	DE-A-	3785994	01-07-93
		DE-T-	3785994	11-11-93
		ES-T-	2054644	16-08-94
		JP-A-	6339394	13-12-94
		JP-B-	7020438	08-03-95
		JP-A-	63258595	26-10-88
EP-A-0314402	03-05-89	US-A-	5041381	20-08-91
		AU-B-	611750	20-06-91
		AU-A-	2782789	23-05-89
		DE-D-	3886760	10-02-94
		DE-T-	3886760	08-09-94
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		EP-A-	0375743	04-07-90
		ES-T-	2061736	16-12-94
		JP-B-	6098020	07-12-94
		JP-T-	3503118	18-07-91
		WO-A-	8903846	05-05-89
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INN Working Doc. 17.408
January 2017
Distr.: PUBLIC
ENGLISH ONLY

63rd Consultation on International Nonproprietary Names for Pharmaceutical Substances
Geneva, 18-21 October 2016

Executive Summary

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

63rd Consultation on International Nonproprietary Names for Pharmaceutical Substances

Geneva, 18-21 October 2016

EXECUTIVE SUMMARY

INTRODUCTIONS

The new Director of Essential Medicines and Health Products (EMP), Dr Sue Hill, introduced herself and welcomed all participants to the 63rd INN Consultation. She expressed her gratitude to the work done by the INN Experts and the WHO INN team, especially with the increasing number of applications for new INN being received and the new policies being developed for advanced therapies, vaccines and monoclonal antibodies.

Increased access to biotherapeutic products was recently identified as a global public health priority, articulated in resolution WHA67.21 of the World Health Assembly, which called on WHO to provide more support to member states on biotherapeutics. Dr Hill has therefore initiated a cross-departmental project on access to biotherapeutics. The aim is to bring all of the assets of the department – its policy development and health technology assessment work in addition to its normative and regulatory support work – to provide a comprehensive framework of support and advice to member states on biotherapeutics. The ongoing work on the BQ initiative will be an important consideration in the context of this holistic approach. To guide this work, a meeting of an *ad hoc* committee is being planned for Q1 of 2017.

WHO senior management has welcomed the drive and innovation of the INN Programme, which not only directs the science of nomenclature, but also fulfils the mandate of promoting, disseminating and advocating INN. The strength of INN, Dr Hill noted, was indeed their use and acceptance worldwide.

Dr David Wood, Coordinator, Technologies Standards and Norms (TSN) Team thanked Dr Hill for her remarks and welcomed her to the 63rd INN Consultation. With the ongoing and increasing workload of INN which is reliant of the diligence of the Experts, he also expressed his gratitude to them.

The Chair, Dr Patience Holland, highlighted the innovative nature of the INN Programme, with its drive to move forward and being the first WHO committee to go paperless.

Dr Raffaella Balocco-Mattavelli, Group Lead, INN Programme, joined with the others in welcoming all participants to the Consultation.

NOTES OF CONSULTATION

The Notes of Consultation of the 62nd INN Consultation was tabled and approved.

NOMENCLATURE of INN

During the 63rd Consultation, a total of 211 INN requests were discussed, including:

- 137 new INN requests, including 75 for biological substances
- 66 outstanding requests
- 8 previously selected proposed INN, against which a formal objection had been raised.

As a result of these discussions, 185 names were selected, which are planned to be published in List 117 of Proposed INNs (p.INN), while 15 requests were deferred for future discussion. Eight requests were rejected by the INN Expert Group, as the substances did not conform to the criteria for INN selection. One application already had a published INN and 2 were withdrawn just before the Consultation. Five amendments are planned to be published in a forthcoming List of p.INN and 3 objections could not be retained. Two new stems/substems were selected and 2 suffixes were promoted to the pre-stem list.

Outstanding applications and objections

The Secretariat highlighted that formal objection to proposed INN (p.INN) by an applicant can result in many rounds of discussion, often with the application on hold. These take up considerable time and the Secretariat suggested that where the delay is voluntary on the part of the applicant, it should charge a fee after a set number of rounds of discussion. With some regulatory agencies, having an established non-proprietary name, e.g. a USAN, was a prerequisite for marketing, and if the applicant did not provide all necessary information, the application could be withdrawn.

INN rules provide for several options regarding formal objection. Where the INN Experts re-confirm a p.INN, the Secretariat would request the objector to withdraw the objection. If the objection is withdrawn the p.INN becomes a recommended INN (r.INN). Where the objection is not withdrawn, the p.INN remains a p.INN. Formal objections themselves have to be valid, for example, if an objection conflicts well-established INN rules, it would be invalid.

Review of use of *–anib* and *–tinib* stems

The *-anib* stem is for angiogenesis inhibitors, a pharmacological property that can be achieved via different modes of action. The *-tinib* stem is for tyrosine kinase inhibitors which constitute a true mode of action although there are many types of tyrosine kinases including one which is linked to angiogenesis inhibition.

The *-tinib* stem has limited value and indicates only that the drug is probably an antineoplastic. Substems of *-tinib* are also unlikely to be of use, except for EGFR inhibitors which present a common profile of side effects. In contrast the *-anib* stem is important, as inhibitors of angiogenesis have a common profile of side effects, especially cardiovascular effects. Consequently, where possible, preference should be given to use of the *-anib* stem.

Discussion focussed on how to deal with the vastly overcrowded *-tinib* stem. Changing from one stem (or suffix) to another should not be undertaken lightly, and especially not when a stem/suffix is in use for a marketed product, or when several INN have already been assigned with a particular stem/suffix. For example, for *-brutinib*, three INN have been assigned and this is probably too many now to assign an alternative stem when it is appropriate to use it. It remains however that *-tinib* is too large a category with several different substems, and if only one or two INN have been assigned with a particular *-tinib* substem, there should not be undue concern in creating a new stem.

The cancer pharmaceutical industry is now developing drugs no longer by histological subtype but by targeting mutations in e.g. EGFR, BRAF, and this would lead to a different clustering of anti-cancer drugs. Potentially, INN should follow this and group new drugs to kinases and not kinase inhibitors. Ultimately, when devising new names, there should be more serious consideration from the start as to whether a substance fits in the *-tinib* stem or is indeed first-in-class and should be assigned a standalone name that could be a future new stem, and the potential usefulness of that stem.

SCHOOL of INN (SoINN)

The Expert Group was informed of progress in the development of a 'School of INN' (SoINN), beginning with a preview of a cartoon video showing the use and value of INN. It was pointed out however that the choice of INN used in the video – *salbutamol* – was perhaps unfortunate as the USAN has a different name *–albuterol* – for this substance. Either the USAN can be used for the USA or a totally different INN used in the video. Whatever is decided, the intent is to make the info-graphics video available on the WHO website following final amendments.

An expert on educational technology had also advised the SoINN working group on making best use of WHO technical platforms, commercial platforms and the web in general. The group was advised that it would be overly ambitious to target everyone from the start and instead should target a subset, for example teachers, and then follow-up with industry buy-in and also practitioners.

Teaching materials should begin with publications in various media, covering awareness of the use of INN. The first could be the report of the recent survey conducted on INN awareness amongst practitioners and students in specific French and English speaking countries. Further publications

could involve pharmacological classes, groups of INN and INN construction, and on naming biological medicines, in educational journals or pharmacological textbooks.

The International Pharmaceutical Federation (FIP) is willing to assist and an INN educational presentation could be made at one of its conferences in 2017 and again in 2018. There would be a revised plan for the January 2017 INN training course. It was also suggested that the established model of WHO collaborating centres could be used to promote INN in different regions of the world although this would require volunteers e.g. in universities to establish this.

The full data set of 1074 responses of the survey into INN awareness had now been analysed and was being prepared for publication. The survey of lecturers and students revealed that the majority knew what an INN is but were weak on how they are constructed.

DUTIES, OBLIGATIONS and CONFLICTS of INTEREST

The meeting was addressed by two internal WHO experts, one on the duties and obligations of meeting participants to WHO, the other on conflicts of interest.

The INN Expert Group is a technical expert group governed by WHO regulations, and WHO relies on the contributions of such external experts to fulfil its work in public health. The Regulations state that expert members provide advice on a personal basis and not as part of an organisation; thus they should not seek or accept any instructions from any government or other authority, including their employer. External experts must respect the impartiality and independence of WHO, and perform their duties with the highest integrity with nothing that would call their work into question. Confidentiality is critically important and deliberations within a meeting must not be disclosed to any person outside the Group, including an employer. Experts agree to adhering to WHO rules and respecting confidentiality by signing a Memorandum of Agreement. Finally, it was pointed out that all rights in any work performed within an expert group belong to WHO.

Submission of a Declaration of Interest (DoI) form is also an important process for WHO. DoI forms are required when WHO requires expert advice at technical meetings, when WHO needs to reach a conclusion, provide advice, or support research. They ensure trust and the credibility of the work performed by experts. Completion of a DoI is to determine if any conflict of interest exists and external experts cannot contribute to expert groups until such a form is submitted, assessed and approved by management. Assessing DoI forms relies on full and complete disclosure. The types of interest to be declared include personal financial gain, family members with similar interests, and intellectual bias; any interest that may affect or be perceived to affect and create an advantage to the expert must be declared. Declaration of a potential conflict does not necessarily disqualify an expert member from contributing; occasionally there may be conditional participation, with a conflict publically disclosed and reported in the meeting report. Such an approach is no different from that of many similar organisations.

Two years ago, the WHO strengthened its rules on public disclosure, with any relevant interest being disclosed at the beginning of a meeting and reported, to ensure trust, integrity and transparency of the work done. Prior to the start of any meeting, a brief biography of each expert is now published on the WHO website for public consumption. The full DoI is not disclosed; these are available only to the meeting secretariat and the compliance and ethics office.

One Expert commented that advice had been sought from their own agency prior to a meeting in order to provide information to the INN Committee. This was deemed to be in order as long as the agency in question did not dictate to the expert how to assess or deal with certain matters. In addition, deliberations within WHO meetings are confidential and should not be disclosed to an employer. Even when deliberations are made public, the background to such deliberations must remain confidential.

With regard to funds obtained by educational (and other) establishments which are for the benefit of the university with no personal gain, Experts were informed that such funding should be disclosed so that WHO is aware of them. This might seem excessive but WHO is under close scrutiny from both

the press and the public, and as a rule of thumb, if an expert is unsure about a particular interest, it should be declared to let WHO manage the situation; disclosure does not mean exclusion.

AD HOC MEETING on BIOLOGICALS, SEPT 2016

Overview

In September, 2016, a group of INN biological experts met to review the current INN approach to naming specific classes of biologicals, to discuss whether existing policies and established nomenclature were applicable to emerging medicines, and to make recommendations for consideration at the 63rd INN Consultation. The biological experts reported back on the specific issues discussed including nomenclature for mAbs, cell therapies and vaccine-like substances.

With regard to the general background of the INN Programme, it was highlighted that nomenclature was driven by the science of the substances being assigned INN, this being especially true for biologicals. Also, whilst the INN Group has to adopt a global approach, each member state has its own legislative requirements and may choose to adopt a particular stance, or not. It was also acknowledged that much of the Committee's work goes to waste, as only 15-20% of the substances named ever get onto the market.

It was noted that names for biologicals are more complex, reflecting the structure of the substances, with greater use of sub-stems and of two-word names. What is also clear is the significant rise in the proportion of applications for INN for biologicals, rising from less than 20% in 2002, to 50% by 2016, and the WHO working document 'INN for biological and biotechnological substances (a review)' (the 'BioReview') has been updated regularly following such specific INN meetings on biologicals.

mAbs

INN applications for mAbs have increased especially and an algorithm was presented showing the number of unique names that could be created depending on the number of sub-stems and the overall number of syllables used. From this it could be extrapolated that the INN Programme will run out of usable names for mAbs within a couple of years. The current mAb naming scheme comprises a *–mab* stem, two infixes, one to designate the target and one to designate the species, and a random prefix. An assessment of assigned mAb INN reveals that the vast majority make use of only two of the target infixes and only two of the origin infixes. Dropping one of the infixes would provide more options but would still result in eventually running out of names. Dropping both infixes altogether and use of the *-mab* stem alone with a random prefix would achieve maximum flexibility. A reasonable and logical proposal by the Antibody Society that involved the creation of an alternative species infix was considered not to enable the Expert Group to devise the volume of unique names required in the foreseeable future. There was no general consensus on the way forward although removal of the source infix was favoured.

In a follow-up teleconference with the US CBER, it was expressed that CBER desired to drop the species infix, and furthermore CBER disagreed with the current species infix calculation, maintaining that the J-region should be included. CBER also had a view that the target infix should be more specific, although in reality this would be difficult as sponsors typically modified and expanded the indication.

During the Consultation, given that the species infix was becoming clinically less relevant with no direct correlation between species and safety profile, including immunogenicity, many Experts were in favour of dropping it. Indeed, there was some evidence that sponsors were using the species infix to enable marketing. However, there being no firm recommendation from the *Ad hoc* meeting and no agreement during the Consultation on the way forward, it was proposed that a small working group be set up to finalise a new mAb scheme, and to review information to be included in the Definition in a standardised, possibly computer-readable, manner.

Fusion proteins

Fusions proteins are new entities derived from one nucleotide sequence and are unique single substances. At the *Ad hoc* meeting, there was no consensus regarding assigning one or two word names to fusion proteins although opinion favoured one word. If the name comprises one word only, further deliberation was needed on how to devise short names. The possibility of a new stem specific for fusion proteins was mooted. For conjugated proteins, the current policy of a two word name should remain. In contrast to a conjugated mAb, when a fusion protein contains a mAb, there should be no requirement for a separate INN for the stand-alone mAb.

Glycoproteins

Nomenclature for glycoproteins should continue with the current policy, i.e. the use of Greek letters with the first name being assigned *alfa*. For mAbs, Greek letters are assigned only to the second and subsequent mAb with an identical amino acid sequence, beginning with *beta*.

Cell therapies

The *Ad hoc* group agreed that there should be alignment of nomenclature for advanced therapies. There was also agreement that names had too much scientific content and were too long as a result. Furthermore, a modified application form for cell therapy applications is needed that requests information to be used in the Definition and omits requests for CAS numbers and structure.

Genetically modified autologous cell therapy had previously been considered by INN to be *ex vivo* gene therapy (in parallel with the EU definition) whilst USAN had named such substances as cell therapy. Consequently distinct INN and USAN had been assigned and applicants were unsure of the situation. The recommended solution was to retain the one-word scheme for cell therapies (non-genetically modified), retain the two-word scheme for gene therapies, and introduce a two-word scheme for genetically modified cell therapies, where the first word identifies the gene (as in Gene Therapy (GT) nomenclature) and the second word identifies the cell. It was recommended however, to keep the second word short by omitting the vector infix and having a random prefix followed by the cell type only. 'This two-word rule would be applied to both autologous and allogeneic genetically modified cell therapies

There was also a strong recommendation to improve the information received from applicants defining the cell types, to standardise cell descriptions and develop key words for Definitions as different names were being assigned to substances with similar definitions.

Vaccine-like substances

At present, vaccines were not included within the INN system with the WHO Expert Committee for Biological Standardisation (ECBS) having a system in place for naming prophylactic vaccines for infectious diseases. Consequently, the *Ad hoc* group considered that this *status quo* should be maintained. However, although the INN Programme had not received any requests for INN for defined recombinant proteins used as active substances in vaccines, it could continue to assign these INN upon request. Defined recombinant nucleic acids (used as active substances in vaccines) similarly could be assigned INN. Vaccine-like substances for anti-cancer immunotherapy, such as oncoviruses, can be handled within existing INN policies and the *Ad hoc* group recommended that INN could be assigned to engineered live viruses and bacteria.

The Future Environment

In concluding the feedback from the *Ad Hoc* meeting, a variety of viewpoints from industry were presented that would require future consideration. These included: how would the 'target' infix be assigned to engineered mAbs that recognise two different targets? If a mAb was present in a fusion protein to target a cytokine or an enzyme to a specific tissue, and a two word name was applied, use of the stem *–mab* in one of the words may cause confusion. Where proteins were conjugated with more than one kind of small molecule or payload, might the names of these substances comprise multiple words? How would micro-organisms that secrete therapeutic antibodies and being used

directly as a therapeutic get named? What naming scheme would apply to platforms such as bacteria, viruses or particles that carried one or many antigens/neoantigens to induce an immune response?

In concluding the feedback session, the Chair thanked the biological experts for their contributions and noted that there was plenty to discuss in future deliberations.

BIOREVIEW

An update of the working document 'INN for biological and biotechnological substances (a review)' (the 'BioReview') was presented. The 2016 version contained a new 'General policies for pegylated substances' (Section 2.5), a new 'Summary of INN assigned to immunomodulators, both stimulant/suppressive and stimulant' (Section 3.18), a new annex with a 'List of INN for pegylated substances' (Annex 3), whilst the BioReview had been updated with INN from proposed List 114.

Other changes included revision of 'Introduction' and 'Current Challenges', removal of the section on 'Pharmacological classification of biological and biotechnological substances', and revision of the sections on 'General policies for vaccines', 'Monoclonal antibodies' (organized by target), 'Peptide vaccines/recombined vaccines' (renamed to 'Vaccine-like substances'). The previous Annex 1: 'List of INN for composite proteins published' had been divided into two annexes: Annex 1: 'List of INN for fusion proteins' and Annex 2: 'List of INN for conjugated proteins', whilst bi-specific monoclonal antibodies had been removed from these lists.

Planned changes for the next version would include recommendations from the recent *Ad hoc* meeting on Biologicals, a new section on advanced therapies incorporating cell, gene, and genetically modified cell therapies and vaccine-like substances, plus a review of general policies for fusion proteins, a new section on conjugated substances, and a review of the general policies for mAbs.

ISBT 128 and CELL THERAPY NOMENCLATURE

The ICCBBA (International Council for Commonality in Blood Banking Automation) is responsible for the management and development of the ISBT 128 Standard, the global information standard for Medical Products of Human Origin (MPHO). It is a not-for-profit nongovernmental organization in official relations with the WHO. WHO began the MPHO initiative in 2013 with the WHA requesting WHO to work with Member States on a global consensus on issues such as ethical principles and traceability. MPHO's include blood, cell, tissue, milk and organ products, and the objective of ISBT 128 is to provide global standards to support their traceability. It recognizes that one donor may be the source of many types of MPHO and that effective traceability must ensure all products derived from one donor could be traced internationally. It is a well-established standard, currently used in licensed facilities in 80 countries, and the product database included 45 cell therapy classes and 1,700 products. It involved a barcode system that includes the product code along with the donation number, which is highly important for traceability.

The label on cell therapy products assigned an INN will have two names, the brand name and the INN. Those also assigned an ISBT code will also show an ISBT name. Having three names on the label is not good practice so the ISBT proposal is to incorporate the INN into the ISBT 128 code, with the INN being treated as a new class within the non-proprietary category of the code. It will also be important to harmonise naming to avoid ISBT and INN creating distinct names, with the same holding true for INN and USAN.

In discussion, it was highlighted that some products may have a USAN but no INN, but where both existed harmonisation was being sought. It was also felt that the ISBT code and the INN served different purposes, with traceability for virus safety reasons being important for ISBT and not covered by INN, and so the benefit of having the INN within the code was not clear.

POSSIBILITY of a COMMON NEW STEM for FUSION PROTEINS

A proposal was tabled that a unique stem for fusion proteins gets created, such as *-fusp*, *-ftin* or *-fep*, which could be broadened for example to *-zafusp* where '*-z-*' would indicate an enzyme, and '*-a-*' would indicate an antibody. An alternative could be a combination of the pre-existing stems *-mab* and

-ase, to give *-mabase* (where the fusion comprises a mAb and an enzyme, which is likely to be the majority of cases), although it was stressed that the use of two strong stems in one word could cause confusion in prescription.

The INN Group firstly further discussed a one versus a two-word name. For a (mAb-enzyme) fusion protein, it was deemed difficult to define which moiety comprised the principal activity; for many it would be the enzyme that was the primary active component, although without the mAb moiety, it would not be targeted and thus exert its activity in a more defined manner. Two-word names would provide more flexibility; this could be especially important as fusion proteins became more complex. Feedback from industry would be needed.

To minimise prescription errors, a one word name would be better. For example, errors could arise where the same mAb was used in more than one different fusion proteins with distinct enzyme activities. Further, with a one word name, it would be easier to add a Greek letter for glycosylated proteins or an additional word for conjugated fusion proteins. A simple name would be more user-friendly; fusions are single protein entities and full information regarding the protein could be incorporated in the Definition. There had been near misses from patients not remembering long complex names for their medicines.

The name needs to flag that an enzyme (or other) activity was being presented in a different manner; the clinician was unlikely to note that it was a fusion protein. The stem *-ase* remained important and should not be masked by the use of a single letter '*-z-*'. Possibly, *-fusp* could be used for mAb fusion proteins only and alternative distinct stems could be created for other fusions.

Ultimately, many Experts leant towards a one word name, although there was by no means agreement on the use of a *-fusp* stem. To move ahead, the Chair proposed that the *-fusp* stem is trialled for two outstanding requests while new requests for fusions got deferred, and that the discussion continued at the planned Consultation in April 2017.

BIOLOGICAL QUALIFIER UPDATE

The new Director of EMP appreciated that biologicals were an important issue, but that various aspects were spread across WHO departments and not restricted to the INN Programme. In taking into consideration WHA resolutions on biologicals including greater access for Member States, she had set up a small group from various sections to discuss biologicals at a holistic level. The group had already met a few times but a major meeting was planned for February 2017 with additional participants. The focus would be on access although the BQ discussion would be an important item on the agenda as this could have a significant impact on access.

This did not prevent the INN Secretariat from proceeding with regulators in developing a BQ pilot scheme although the Secretariat was not at liberty at the 63rd Consultation to say with which regulators it was in discussion. Memoranda of understanding (MoU) were being set up with specific regulators and others had expressed an interest. The Director was in agreement with this dialogue and had already signed the first MoU. The software necessary for the project had been developed and ready to be used.

COLLABORATORS' UPDATES

British Pharmacopoeia (BP)

BP 2017 was published in August 2016 with 29 new monographs and 127 revised. The BP was also following ICH Q3D for elemental impurities. BAN 2017 was published and contained 29 new entries involving those INNs on the UK market.

European Directorate for the Quality of Medicines & HealthCare (EDQM)

The 9th edition of the European Pharmacopeoia had been published in early 2016. Changes included deletion of tests for heavy metals following implementation of ICH Q3D, Guideline for Elemental Impurities. The draft general chapter 5.20. Chemical imaging, was also published in Pharmeuropa in

2016. This publication contained recommendations to assess the performance of chemical imaging systems, e.g. mid-infrared, near-infrared and Raman spectroscopy.

Pharmeuropa 28.4, the list of draft monographs out for comment, included a draft monograph for *infliximab*; with comments due by the end of 2016. This was the first monograph for a monoclonal antibody, and the commenting period would form part of the pilot phase for such monographs. It had also come to light that certain regions were using monographs to try to demonstrate bio-similarity instead of a proper biosimilar exercise, which was clearly not the intention of a pharmacopoeial monograph.

Finally, work had started on the preparation of a paediatric formulary, the aim of which was to provide a compilation of appropriate extemporaneous formulations for paediatric use, where no licensed product was available. Formulations from existing national or regional formularies would be selected and evaluated, making them freely available in order to help fill the gap until approved medicines were available.

European Medicines Agency (EMA)

The Name Review Group of the European Medicines Agency had met six times in the past year and considered around 350 names.

A review of EudraVigilance data for biologicals was currently underway to measure identification of biologicals in ADR reports received from European clinical practice between 2011 and 2016. The focus of the study was biologicals for which two or more products shared the same INN (biosimilars or related biologicals). More than 50,000 reports were included in the study and the results were reassuring. The exact product could be identified in approximately 93% of the reports, but as the reports were still being reviewed this was considered to be a conservative figure. The final figure was expected to be similar to previous studies for earlier time periods (around 96%).

Ministry of Food and Drug Safety (MFDS), Republic of Korea

Currently, the use of INN for pharmaceutical substances was not required by national legislation in Korea, but in accordance with the Regulation on Product Approval and Review of Medicines and Biopharmaceuticals, a Korean product name may be assigned according to the Guideline for Drug Nomenclature administered by the MFDS. An English name may be given according to the INN or the Guideline for Drug Nomenclature. The Guideline for Drug Nomenclature was established by the Department of Pharmaceutical Review in June 2010 and subsequently revised in December 2015. This guideline covered part of the naming rules for biopharmaceuticals (mainly biotherapeutics). The INN information book for therapeutics published in April 2009 was a useful reference.

In Korea, approval was granted to a brand name, not to pharmaceutical substances, so naming pharmaceutical substances based on drug nomenclature was not mandatory. However, MFDS is committed to promoting international harmonization through, for example, the Guideline for Drug Nomenclature which was developed based on the WHO INN system.

MFDS has no plan to introduce the BQ scheme yet, because it is implementing a traceability system through pharmacovigilance. However, it will monitor the developments of the BQ system and consider its necessity.

Pharmaceuticals and Medical Devices Agency (PMDA), Japan

The Division of Pharmacopoeia and Standards for Drugs within the PMDA was responsible for preparing the Japanese Accepted Name (JAN) and the Japanese Pharmacopeia (JP). The JAN committee met four times from April to September 2016, from which 35 names were published. The 17th edition of the JP was published in March 2016, the English version which could be downloaded from the website was made available for free in August 2016.

The International Meeting of World Pharmacopoeias was held in Tokyo in September 2016, hosted by WHO, the Japanese Ministry of Health and PMDA. Immediately following this, the JP held its 130th anniversary symposium, also in Tokyo.

United States Adopted Names (USAN)

The 2016 Summer USAN Council meeting took place on July 21-22 at the American Pharmacists Association Headquarters in Washington D.C., where names for 42 drug substances were reviewed and discussed. Nine new stems or infixes with existing stems were approved and added to USAN's stem list. Policy discussions included biosimilar drug nomenclature, cellular therapy nomenclature revisions for genetically manipulated cells, monoclonal antibody proposed naming revisions and ISMP medication errors reports.

Thirty-five INN applications for proposed USAN were prepared and forwarded to the INN Programme to be discussed at the 63rd INN Consultation. Through September, 2016 USAN staff would have processed, researched and made recommendations for 127 new USAN applications and forwarded this information to the USAN Council for their review and selection. Also through September 2016, 92 USAN, 18 modified USAN and 5 revised USAN would have been adopted for 2016. Revenue was realized for an additional 12 negotiations.

The 2017 winter meeting of the USAN council was scheduled to occur on January 12-13 in Miami.

United States Food and Drug Administration (FDA)

The US FDA recently approved two more biosimilars, Amjevita (*adalimumab-atto*), a biosimilar to Hospira (*adalimumab*), and Inflectra (*infliximab-dyyb*), a biosimilar to Remicade (*infliximab*). Recently, the FDA representative, during a Webex meeting with the INN Secretariat and some INN Experts, indicated support for a modified mAb naming scheme in which 1 or 2 infixes get deleted. The FDA looks forward to having further Webex meetings with WHO to discuss harmonisation of BQ suffixes and also to reach more formal conclusions on modifications to schemes for gene therapy, cell therapy and monoclonal antibodies.

United States Pharmacopoeia (USP)

As a global organization, the USP also continued to expand its activities; for example, within the food safety area, it had developed a growing food fraud database to track incidents of economically motivated adulteration in the global food supply.

In another active arena, the USP continued to revise and develop standards for pharmaceutical compounding. Recognizing the need for individualized therapies for patient groups such as pediatric patients, the Compounding Committee was developing monographs for compounded formulations.

Finally, the Nomenclature and Labeling committee recently approved the name for new dosage form that had grown in popularity within the dietary supplement category – chewable gels. Although some had referred to this delivery format as "gummies," the confectionery-related nature of that category and concerns about children's safety counsel the use of different terminology to describe health care products.

These efforts, among many others, reflect the USP's continued commitment to the development of public standards.

CLOSE OF MEETING

The Chair closed the meeting, thanking all participants for their time and efforts contributed both before and during the Consultation, and acknowledged also the support provided by the INN Secretariat.

Next Meeting

The 64th INN Consultation will take place in Geneva on 4-7 April, 2017.

Open Session for INN Stakeholders

63rd INN Consultation on International Nonproprietary Names (INN) for Pharmaceutical Substances

Geneva, 18 October 2016

Dr David Wood, Technologies Standards and Norms Team Coordinator, welcomed stakeholders to the Open Session of the 63rd INN Consultation. At these sessions, INN users are invited to provide feedback, either in the form of general comments on policy matters, or regarding individual applications for an INN. INN Experts were also welcomed and thanked for their contributions to the INN Programme. The increasing number of new applications suggested that the innovation pipeline is strong, and this was good news for public health. For the United Nations, access to pharmaceutical products is a key part of its sustainable goal of access to a wide range of health care by 2030. Having non-proprietary names in place is an important part of that goal.

Dr Wood also informed stakeholders and Experts that a new director of Essential Medicines and Health Products, Dr Sue Hill, had recently been appointed, bringing new energy and enthusiasm.

Dr Raffaella Balocco-Mattavelli, INN Lead, also gave a welcome to stakeholders and INN Experts. She also acknowledged her INN team, without whom the meeting could not take place.

Dr Patience Holland, INN Chair, welcomed stakeholders on behalf of the INN Experts. The Open Session provides an opportunity for the Experts to learn what is new, what topical issues are, and how to find solutions. She also highlighted to stakeholders that all information presented and discussed at the meeting was strictly confidential until the meeting report was adopted and made public.

PRESENTATIONS on the PROPOSED BIOLOGICAL QUALIFIER

Alliance for Safe Biologics Medicines (ASBM)

Since it was four years ago that the issue of naming biosimilars globally was first raised by INN, the ASBM stressed the need to act, especially since there had been a great increase in biosimilar approvals, from 24 to 52, in that four year period, and that more than 40 biosimilars were in development worldwide for seven key biologics. The ASBM was very appreciative of the INN committee for its care, openness and fairness, but urged the Committee to finalise a policy as the danger in delaying creates a policy vacuum. There is no other entity with the gravitas and the experience to solve this global challenge and WHO leadership is awaited by regulators worldwide supportive of the WHO's efforts. BQ implementation will particularly aid countries with no strong pharmacovigilance system for biologics. In urging action, the ASBM understood the challenges, e.g. mergers and acquisitions; however, to date no biosimilars had been sold to another party after approval. In mergers, biosimilars had not lost their corporate identity and so can retain their original BQ; concerns were unwarranted and slight changes can be accommodated. Since the previous (62nd) INN Consultation, the US FDA has approved two more biosimilars, assigning potentially BQ-compatible 4-letter random suffixes and it was repeated that the INN needs to act soon.

ASBM surveys have cumulatively obtained opinions of about 2,500 clinicians. In its most recent survey, of Australian prescribers, more than three-quarters were of the opinion that the TGA should insist upon distinct non-proprietary names for all biosimilar and biologics

medicines it approves. These results were consistent with other surveys of physicians worldwide and highlight the need for global consistency led by the WHO. Also, the ASBM remained supportive of meaningful rather than random suffixes as surveys showed that clinicians worldwide support a manufacturer suffix.

Pharmacists have a history of avoiding look-alike/sound-alike names, and a great majority feel that distinguishable names for biologics should be used, which is in contrast to that of US Pharmacist Associations. Furthermore, in surveys of pharmacists, there was a consistent and clear majority with a preference for a meaningful name with little support for a random suffix. Current opinion supported that now is the time for WHO to implement a scheme for distinguishable non-proprietary names for all biologics.

Global Alliance for Patient Access (GAfPA)

Within the USA, the Alliance for Patient Access (AfPA) comprises a national network of physicians whose mission is to ensure patient access to approved therapies and appropriate clinical care. It achieves this through educating physicians on policy priorities and training them to be effective advocates for their patients. It works closely with the Global Alliance for Patient Access (GAfPA) and with other physician/patient initiatives and medical societies. The Alliance engages with policy makers globally across many different disease states, and much of the work is focussed on biologic therapies including biosimilars. With patient organisations anxious to understand these new medicines, it provides training, educational materials and advocacy.

The GAfPA's biologics viewpoint reflected the WHO's BQ in that it supported naming policies that reflect inherent differences between biologics and biosimilars. Distinguishable names would benefit patients through robust pharmacovigilance. Upon switching from a biologic to a biosimilar, patients need to be assured of their efficacy and safety, and as more and more patients have access to biosimilars, data that assures robust pharmacovigilance was needed and the Alliance believes that the BQ will achieve this.

The Alliance's educational work includes briefing patients through conferences, white papers and web-based info-graphics which are easily accessed and user friendly. Information is provided in several languages and the Alliance will soon release a video in Spanish, outlining the BQ proposal and urging regulators to adopt it. The Alliance wants to increase confidence amongst physicians and patients that when switching to biosimilars, a robust pharmacovigilance system is in place by promoting a truly global naming system that distinguishes biologics from biosimilars.

GAfPA's view is that the WHO BQ would provide distinct INN that reflect subtle but potentially meaningful differences among biologics and biosimilars, that it will facilitate pharmacovigilance and that it will give physicians confidence in their ability to precisely prescribe, administer and monitor these treatments.

Generics Pharmaceutical Association (GPhA)

GPhA's presentation focussed on convergence of the proposed WHO BQ and the US FDA's draft guidance on biosimilar naming. The WHO 'biological qualifier' proposes a consonants only 4-letter non-meaningful code with an optional 2-digit checksum. It would follow the INN but not be part of it. It would be assigned by WHO, be voluntary, and be applied to all biosimilars/biologics. It remains unclear if it would be applied retrospectively including to reference products. The FDA draft scheme also comprises a 4-letter non-meaningful code, but with vowels and consonants, and no-checksum. It would be attached to the USAN/INN via a hyphen. It would be assigned by the FDA with input from the applicant and it is not

voluntary. The FDA has approved four biosimilars along with 4-letter suffix codes. In the FDA system, the 'proper' name for a product would be the 'core' name (USAN/INN) plus the 4-letter suffix.

With these differences between the BQ and FDA draft schemes, convergence would limit confusion. The FDA will assess the impact of its scheme on pharmacovigilance over the next four years. GPhA recommended that the BQ scheme is not implemented until consensus has been reached between FDA and WHO, and that due to the increased risk of confusion regarding prescribing, dispensing and substitution with attached suffixes, the identified systems should be independently tested to ensure they improve identification and reduce safety risks.

The GPhA presented a substantial list of questions on the proposed BQ pilot scheme to the INN Committee, including on the inclusion of the FDA suffix in the pilot scheme, on the assignment of identical FDA and BQ codes, and on the application of the BQ to innovator products.

The Chair was appreciative of the GPhA's comments and questions, and noted that the WHO was addressing such questions with all WHO member states and not just the US FDA.

In discussion, the FDA representative noted that the attached suffix would only be part of the product name, as it only labels products, and there was no intention to modify the name of the drug substance. The BQ, whilst not part of the INN, could however be on the product label. The FDA also needed to work with the USP on harmonising monographs, as the USP title becomes the official name of an FDA approved product. For example, for a specific biologic/biosimilar with two different names because of two different suffix codes, it is not yet clear how this would work with the USP monographs. However, many monographs are not published until the product has been on the market for several years.

Medicines for Europe/Biosimilars Medicines Group

Medicines for Europe highlighted recent developments relevant to the debate on the proposed WHO BQ. First, the new EMA Good Pharmacovigilance Practice chapter for Biologicals, which came into effect in August 2016, highlights that the information to be provided when reporting suspected adverse reactions includes the product name and batch number. Second, the EU Falsified Medicines Directive is in implementation phase and includes the use of a 2D data matrix code in which the batch number is a key element. Any additional element such as a BQ should be avoided to avoid confusion. Third, implementation of ISO IDMP standards is ongoing within the EU (covering also the unique identification of substances). This is a complex but important development, going beyond the EU,. Abbreviated regional testing was performed by the ICH Parties to guarantee interoperability across regulatory and healthcare communities Medicines for Europe also presented a series of important questions with regard to the BQ pilot scheme including the extent to which a limited number of prospective approvals can provide sufficient data to evaluate the scheme, when the retrospective application of the scheme be addressed, how local pharmacovigilance systems will be taken into account, the interoperability of the BQ with other systems, and how the US FDA suffix (at product level) would fit into a pilot scheme. Other areas under question were the criteria for evaluating the impact on access to medicines, the organisation of the pilot scheme and how the added value would be assessed.

Medicines for Europe recommended that ISO IDMP standards be implemented first by those countries involved in their development and that the implementation of the BQ scheme and the impact study is decoupled. The organisation again called for a moratorium of the provisional implementation of the BQ scheme and for further international exchange and

dialogue; implementation without a prior regulatory impact assessment could contribute to a proliferation of different identifiers . Finally, a prior impact study in every "BQ volunteering country" in line with the WHO draft GRP guidelines is essential to ensure that, the BQ does not lead to any confusion or medical errors in the global healthcare arena.

In discussion, it was highlighted that ISO standards have to be adopted globally to be useful. For example, the ISO standard on how to present dates on documents has never been adopted globally, and in reference to the 2D matrix code on packaging, the BQ could be included with very little problem as it takes very little space within the code.

It was acknowledged that the Australian regulatory authority would publish an impact statement on implementation, but it remained unclear how other countries might implement the BQ. Meeting participants were informed by the Secretariat that discussions on BQ implementation with individual regulatory authorities were ongoing but remained confidential.

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Medicines for Europe recommended that implementation of the BQ is firstly by those countries implementing ISO IDMP. The organisation again called for a moratorium on implementation of the BQ scheme and for further international exchange and dialogue; implementation without a prior impact assessment on regulators could contribute to a proliferation of different qualifiers. Finally, a prior impact study is essential to ensure that prior to any provisional implementation scheme, the BQ does not lead to any confusion or medical errors in the global healthcare arena.

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PRESENTATIONS on INN ASSIGNMENTS

AMGEN Biosimilars

Amgen expressed its concern regarding the lack of implementation of the Greek letter policy for mAbs (no Greek letter for the first application, the use of *beta* and further Greek letters for additional applications for a mAb with the same amino acid sequence where there are glycosylation differences). Amgen had approached the INN at its Open Session two years ago to request clarification at which time it had illustrated the need for application of the policy by reference to the distinct critical quality attributes (afucosylation profiles) of an originator and two biosimilar mAbs.

In this session, Amgen presented Australian data on the high level of ambiguity (41%) on attributing AERs to a specific product where the same INN was assigned (*filgrastim*), versus the low level of ambiguity (5%) when distinguishable non-proprietary names were available (*epoetin* '*alfa*', '*beta*', '*lambda*'). Amgen further noted that in 2015, WHO reaffirmed its Greek letter policy, although Amgen currently remains unable to secure recommended INN for several follow-on mAbs. Furthermore, Amgen is aware that two second versions of originator mAbs had proposed INNs including Greek letter second words.. Furthermore, despite glycan differences, several licensed biosimilars do not have a distinguishable INN, whilst others do. It is not clear under what circumstance distinguishable INN are assigned.

As a sponsor of both biosimilar and originator biologics, Amgen reiterated its 2014 request for access to differentiate non-proprietary names. Several drug agencies are interested in approving these biologics using distinguishable non-proprietary names but are awaiting WHO's decision on a recommended INN. The INN Programme needs to follow its reaffirmed policy for the Greek letter option, or fully implement the BQ programme of which Amgen is fully in favour.

The INN Secretariat responded that some proposed INN for mAbs had not yet been promoted to recommended INN because official objections had been received, but that these objections could not be upheld, and so the names are likely to become recommended INN; these will be considered during the 63rd Consultation.

The Chair added that with respect to differences in glycan structure, the INN Committee often do not receive sufficient data from applicants for the Experts to decide whether a new Greek letter is warranted.

Biogen

Biogen's representation was similar to Amgen's in requesting the assignment of '*beta*' to its new version of the mAb *daclizumab*. The new version (Daclizumab HYP) is being manufactured from a new production cell line and under a new manufacturing process. This had resulted in a distinct and consistent glycosylation profile, markedly different from the version of *daclizumab* previously marketed by Roche (Zenapax). *Daclizumab beta* had indeed been originally assigned by the INN Experts to Biogen's mAb in May 2015, but the Company was informed in February 2016 that there had been an official objection to the use of '*beta*' as the Greek letter should not be used to indicate glycosylation differences for mAbs. Biogen emphasised that this appeared to be inconsistent with published WHO policy and respectfully requested that *daclizumab beta* was re-assigned.

The INN Secretariat assured Biogen that this would be discussed during the plenary Consultation.

CLOSE OF SESSION

The Chair thanked the Stakeholders for their contributions to the Open Session and closed the meeting.

INN Working Doc. 17.416
May 2017
Distr.: GENERAL
ENGLISH ONLY

Revised monoclonal antibody (mAb) nomenclature scheme
Geneva, 26 May 2017

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

Revised monoclonal antibody (mAb) nomenclature scheme

International Nonproprietary Names (INN) facilitate the identification of pharmaceutical substances or active pharmaceutical ingredients. Each INN is a unique name that is globally recognized and is public property.

Except for the first INN for a monoclonal antibody (mAb) (*muromonab-CD3 (59)(29)*), mAbs have been allocated an INN using a consistent although evolving nomenclature scheme. To date, each INN for a mAb is composed by a random/fantasy prefix, which contributes to an euphonious and distinctive name, by a substem A, which indicates the target (molecule, cell and organ) class of the mAb, by a substem B, which indicates the species on which the immunoglobulin sequence of the mAb is based, and by the stem *-mab*. This stem is used for all molecules which contain an immunoglobulin variable domain, which binds to a defined target. This includes intact immunoglobulins of all classes, fragments such as Fab and smaller molecules such as single-chain variable fragments (scFv). This nomenclature scheme has been used since the early 1990s to allocate INN to over five hundred mAbs.

However, more recently concerns have been raised with the INN nomenclature scheme for mAbs. Firstly, the number of applications for INN for mAbs has been increasing significantly, with the outcome that identifying new, distinct, pronounceable-by-all and not too long INN is becoming very difficult. Secondly, the substem B that indicates the species has been used as a marketing tool; some particular infixes compared to others have been considered 'better' and with an advantageous immunogenicity profile than some other infixes, even though scientific data does not support it.

In view of these concerns, the INN Expert Group has decided to revise the nomenclature scheme that assigns INN for mAbs. A broad consultative process has taken place, both during the INN Consultations (see the Executive Summaries – http://www.who.int/medicines/services/inn/meetings/en/) and '*ad-hoc*' meetings with third parties and national nomenclature bodies. As a result of this process, during the 64th INN Consultation, the INN Expert Group recommended to discontinue the substem B (source infix), except the pre-substem *-vet-* for *veterinary use*, which will be included in substem A list. This will ease the difficulty in finding new INN free of conflicts and not liable to be confused with names already in use. This could allow a longer 'fantasy prefix', which should lead to greater diversity in possible INN for mAbs. In some cases, it may be necessary to alter the target infix to avoid confusion between the old and new INN nomenclature scheme, for

example *-t(u)-* (for *tumour*) will no longer be used and it will be replaced by *-ta-* (for more examples, kindly see Table 2).

It is reasoned that the description at the level of publication will provide more extensive information about the precise origin of the mAbs. Indeed, the information, regarding the species on which the immunoglobulin sequence of the mAb is based, will continue to be included in the definition of INN for mAbs.

Table 1: Previous mAb nomenclature scheme.

Prefix:	**Substem A:** target class	**Substem B:** the species	**Stem:**
random	*-b(a)-* bacterial *-am(i)-* serum amyloid protein (SAP)/amyloidosis *(pre-substem)* *-c(i)-* cardiovascular *-f(u)-* fungal *-gr(o)-* skeletal muscle mass related growth factors and receptors *(pre-substem)* *-k(i)-* interleukin *-l(i)-* immunomodulating *-n(e)-* neural *-s(o)-* bone *-tox(a)-* toxin *-t(u)-* tumour *-v(i)-* viral	*-a-* rat *-axo-* rat-mouse *(pre-substem)* *-e-* hamster *-i-* primate *-o-* mouse *-u-* human *-vet-* veterinary use *(pre-substem)* *-xi-* chimeric *-xizu-* chimeric-humanized *-zu-* humanized	*-mab*

Table 2: New mAb nomenclature scheme.

Prefix:	**Substem A*:** target class	**Stem:**
random	*-ba-* bacterial *-ami-* serum amyloid protein (SAP)/amyloidosis *(pre-substem)* *-ci-* cardiovascular *-fung-* fungal *-gros-* skeletal muscle mass related growth factors and receptors *(pre-substem)* *-ki-* interleukin *-li-* immunomodulating *-ne-* neural *-os-* bone *-toxa-* toxin *-ta-* tumour *-vet-* veterinary use *(pre-stem)* *-vi-* viral	*-mab*

* The substem A is currently under revision.

28 April 2016
EMA/458317/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zinbryta

International non-proprietary name: daclizumab

Procedure No. EMEA/H/C/003862/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

AI	Autoinjector
ADA	Anti-Drug Antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AED	Antiepileptic Drug Use
BPF	Brain Parenchymal Fraction
CBC	Complete Blood Counts
CDA	Clinical Disease Activity
CD	cluster of differentiation
CDC	complement dependent cytotoxicity
CDP	Confirmed Disability Progression
CSR	Clinical Study Report
DAC	Daclizumab
DAC HYP	Daclizumab High Yield Process
DDI	Drug-Drug Interaction
DIS	Dissemination In Space
DIT	Dissemination In Time
DMT	Disease modifying Therapy
ECL	electrochemiluminescence
ELISA	enzyme linked immunosorbent assay
FAS	Full Analysis Set
FS	Functional Score
Gd	Gadolinium
GD-CEL	Gadolinium Contrast Enhancing Lesion
GLP	Good Laboratory practice
HLT	High Level Term
HV	Healthy Volunteer
IAR	infusion-associated reactions
IL	Interleukin
INEC	Independent Neurology Evaluation Committee

ISS	Integrated summary of safety
mAb	monoclonal Antibody
MeDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance imaging
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
MSIS-29	Multiple Sclerosis Impact Scale-29
N/A	Not Applicable
NAb	Neutralising antibody
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PPMS	Primary Progressive Multiple Sclerosis
QoL	Quality of Life
PFP	PreFilled Pen
PFS	PreFilled Syringe
PIP	Pediatric Investigation Plan
RAP	Relapse Adjudication Panel
RMP	Risk Management Plan
RMS	Relapsing Remitting Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAD	Sustained Accumulation of Disability
SC	Subcutaneous
SCS	Summary of Clinical Safety
SF-12	SF-12^{R} Health survey
SRD	Sustained Reduction in Disability (reverse of SAD)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Biogen Idec Ltd submitted on 6 March 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zinbryta, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Zinbryta is indicated in adult patients for the treatment of relapsing forms of multiple sclerosis (RMS).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The applicant indicated that daclizumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicant's own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0147/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance daclizumab contained in the above medicinal product to be considered as a new active substance in comparison to the known daclizumab previously authorised in the European Union as Zenapax and claimed that daclizumab (Zinbryta) is a biological substance previously authorised as a medicinal product in the European Union, but differing from the known daclizumab previously authorised in the EU as Zenapax in molecular structure, nature of the source material or manufacturing process.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes

- The application was received by the EMA on 6 March 2015.
- The procedure started on 25 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2015.
- PRAC assessment overview, adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 July 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 October 2015.
- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:

  A GCP inspection was conducted in Serbia and Russia at 2 investigator sites between August and September 2015. The integrated inspection report of the inspection carried out was issued on 2nd November 2015. At the inspection of Clinical Center of Vojvodina (Inspection Site 1 - Serbia) there were no critical, 5 major and 12 minor findings. The major findings were related to the Research Ethics Committee, clinical conduct of the trial, data management and source data. At the inspection of Clinic Medinef (Inspection Site 2 - Russia) there were no critical, 2 major and 14 minor findings. The major findings were related to clinical conduct of the trial and source data. The conclusion of the report states that “it appears that the data in the CSR are sufficiently reliable for assessment for the marketing authorisation with no issues noted from these two sites that would cast serious doubt on their reliability.”
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 26 November 2015.
- PRAC assessment overview, adopted by PRAC on 3 December 2015.
- During the CHMP meeting on 17 December 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of

Outstanding Issues to all CHMP members on 5 February 2016.

- PRAC assessment overview, adopted by PRAC on 11 February 2016.
- During the CHMP meeting on 30 March 2016, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 28 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zinbryta.

2. Scientific discussion

2.1. Executive summary

Multiple sclerosis is a chronic autoimmune and neurodegenerative disorder of the central nervous system (CNS) that is characterized by inflammation, demyelination, and neuronal loss.
The pathological changes underlying MS are believed to be mediated by activated, autoreactive lymphocytes which cross the blood-brain barrier (BBB) and initiate an immune-mediated cascade of events that injures both the grey and white matter of the brain [Frohman 2006]. MS affects approximately 2.5 million people worldwide and is the most common cause of neurological disability among young adults. It is usually diagnosed between the ages of 20 to 40 years, with twice as many women affected as men.

Relapsing MS (RMS) is the most common clinical presentation of the disease. The diagnosis of RMS is usually made on the basis of both clinical and radiographic criteria and it requires that a patient experience at least 2 neurologic events, consistent with demyelination separated both in time and in location in the CNS. Patients with RMS experience discrete episodes of neurological dysfunction (referred to as relapses, exacerbations, or attacks), each lasting several days to several weeks, that occur intermittently over many years. Typical symptoms of relapse include weakness, sensory loss, visual loss, and imbalance.

Early in the course of the disease (the relapsing-remitting MS [RRMS] phase), the physical symptoms of relapse tend to subside completely after each attack. However, the CNS inflammatory process that accompanies the clinical relapses during the RRMS phase results in lasting brain injury as detected by early grey-matter atrophy and increased lesion load on magnetic resonance imaging (MRI) that predispose individuals to long-term disability [Dalton 2004; Fisniku 2008]. Over time, the clinical recovery from relapses tends to be incomplete, leading to the accumulation of functional disability and the frequent onset of secondary progressive MS.

The prevention of clinical relapses and disability progression as well as the subclinical brain injuries that occur during the relapsing phase of MS are recognized as important therapeutic benefits for MS patients. Clinical relapses impair essential activities of daily life and frequently result in hospitalization. An estimated 42% to 57% of relapses are associated with residual neurological deficits [Hirst 2008; Lublin 2003]. The goal of relapse prevention applies to patients with both relapsing-remitting MS and other forms of relapsing MS (such as secondary relapsing MS), and recent consensus panels on the treatment and classification of MS have underscored the importance of inflammatory activity (as defined by the presence of clinical relapses and new MRI lesions) in both relapsing and progressive forms of MS as an indication for disease-modifying treatment [Costello 2014; Lublin 2014]. Without effective treatment, approximately half of all RMS patients are unable to walk without assistance within 15 years of their diagnosis, and more than half may eventually die from disease-related complications.

MS pathology in the cerebral white matter is characterized by focal areas of demyelination and axonal injury and, in acute lesions, by activated T-lymphocytes in the adjacent perivascular spaces and migration of inflammatory cells through a compromised BBB. Autoreactive T-cells directed against myelin antigens in the CNS play a role in the initiation and propagation of MS lesions, contributing to the destruction of myelin, axons, and oligodendrocytes through both direct and indirect effects of inflammation.

MS pathology in the cerebral grey matter is now recognized to be an important contributor to disability progression in MS. MS grey matter or cortical pathology has distinct characteristics from white matter pathology because it is generally devoid of parenchymal lymphocytes and is closely associated with the presence of ectopic lymphoid tissue in the meningeal and subpial regions. Cortical injury can occur independently of white matter pathology where it may contribute to disability progression independently of clinical relapses or focal lesions on brain MRI.

Daclizumab works through a novel, reversible modulation of IL-2 signalling, inhibiting CD25- dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact [Martin 2010]. This signalling modulation results in several well-characterized immunologic changes that were hypothesized to result in selective targeting of both white and grey matter MS pathology while also preserving key protective functions of the immune system, as follows:

- Since activated but not resting T-cells express CD25 and depend on the high-affinity receptor to respond efficiently to IL-2, daclizumab selectively inhibits activated T-cells without causing a nonspecific immunodepletion of lymphocytes.
- Daclizumab (Zinbryta) treatment results in an expansion of immunoregulatory NK cells, the CD56bright natural killer (NK) cell. CD56bright NK cells have been shown to selectively target activated but not resting T-cells in MS, and the magnitude of their expansion post-treatment has correlated with the therapeutic response to daclizumab.
- Regula tory T-cells (Tregs) express CD25 and play an important role in immune system homeostasis and regulation. While there is a reversible decrease in the number of circulating Tregs during Zinbryta treatment, Tregs express high levels of the intermediate affinity IL-2 receptor, thereby enabling continued response to IL-2 signals. The cellular proliferation status, cytokine production profile, and epigenetic markers of the FOXP3 promoter indicate that a stable and functionally competent population of Tregs is maintained in the presence of long-term daclizumab treatment despite CD25 antagonism. Compared to previously authorised daclizumab (Zenapax), daclizumab (Zinbryta) has a decreased amount of antibody-dependent cellular cytotoxicity in vitro, and this was considered to be advantageous for maintaining Treg cell populations during long-term use.

In summary, the novel IL-2 signalling modulation of daclizumab (Zinbryta) represents a targeted and reversible therapeutic approach to MS treatment that can selectively impact both grey and white matter MS pathology without causing nonspecific immunodepletion. Daclizumab's mechanism of action is distinct and differentiated from other therapies available to treat RMS. The impact of daclizumab (Zinbryta) on Tregs has been an area of potential concern but the demonstration of functional adaptation by Tregs during Zinbryta use as well as the expansion of other immunoregulatory cell populations provided a basis for managing any potential impact on Tregs. Therefore, daclizumab (Zinbryta) was systematically evaluated in clinical studies to define its risks and benefits in relapsing MS.

Current Treatments for Multiple Sclerosis and Unmet Need

Therapies for MS include symptomatic treatments (e.g., steroids) and disease-modifying therapies (DMTs). The available therapies entail difficult trade-offs between efficacy, safety, tolerability, and convenience that make RMS a challenging condition to treat successfully, and that result in substantial need to provide new options that can improve these balances for some patients.

Commonly used RMS and RRMS therapies include the interferon-beta (IFN β) therapies and glatiramer acetate (GA) that, depending upon the agent, require either intramuscular (IM) or subcutaneous (SC) injections, from as few as every 2 weeks to as many as 7 times a week. While these treatments have

well-established safety and efficacy profiles, many subjects continue to experience significant MS disease activity while on treatment. Furthermore, these therapies are associated with known side effects, such as flu-like symptoms for the IFN-β therapies, and lipoatrophy and other injection site pathologies for GA, which can be a significant burden for some patients. Available data suggest that approximately 40% of MS patients may not adhere to prescribed injectable therapies for MS out of fear of, or the inconvenience associated with, such frequent injections.

Dimethyl fumarate, fingolimod, and teriflunomide are oral DMTs that are approved for the treatment of RRMS. While these therapies offer an improved route of administration for some patients, they nonetheless require daily administration and furthermore some patients may not tolerate them or continue to experience disease activity while on treatment. Oral therapies have also been associated with clinically important side effects, such as lymphopenia for dimethyl fumarate; bradycardia, atrioventricular block, and macular oedema for fingolimod; and hepatotoxicity and lymphopenia for teriflunomide. These risks may necessitate exclusion of vulnerable patients and require specialized monitoring both during and prior to initiation of therapy.

Other available DMTs include natalizumab, which, although highly effective, is associated with the risk of progressive multifocal leukoencephalopathy (PML). Therefore, in some regions, natalizumab is authorized as a second-line therapy in patients with highly active disease and as a first-line therapy in patients with rapidly evolving severe disease.

Alemtuzumab is a monoclonal antibody that has shown superior efficacy to IFN β-1a but that entails risks of life-threatening autoimmune disorders, including fatal thrombocytopenia and nephropathies; additionally, autoimmune thyroid disease is common during treatment. For these reasons, in some regions its use is restricted to those patients who have failed other therapies or is not approved for patients with inactive disease.

Mitoxantrone is another therapy that is also associated with significant risks, including cardiotoxicity, which increases with cumulative dose; therefore, mitoxantrone is mainly used as a third-line therapy in patients with severe MS who have already failed other therapies. In summary, while several DMTs are currently available, MS patients face difficult trade-offs between benefits and risks when selecting a therapy. These risks include inadequate disease control, life-threatening adverse events (AEs), need for frequent injections or daily oral therapy, and/or tolerability problems that reduce treatment adherence and quality of life. Given the heterogeneity of MS and of patients' response to therapy, disease control is frequently incomplete after initiation of treatment, and patients must often switch from one treatment to another as their disease progresses, or their response to a given treatment proves to be unsatisfactory based on safety, efficacy, or tolerability.

Therefore, there remains an unmet medical need for new, alternative high-efficacy treatment options that have demonstrated superior efficacy to current standards of MS care, that offer advantages in terms of frequency of administration, and that have manageable risks. Daclizumab, the active substance in Zinbryta,was developed to address this unmet need.

2.2. Quality aspects

2.2.1. Introduction

Daclizumab is a humanized monoclonal antibody (mAb) that binds to CD25, the alpha subunit of the human high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling.

The final product, Zinbryta, is presented in a pre-filled syringe or pre-filled pen with a nominal amount of 150 mg per dose for subcutaneous administration.

2.2.2. Active Substance

General information

The active substance is a recombinant humanized IgG1 monoclonal antibody expressed in a NS0 cell line, purified to a high degree of purity. Daclizumab binds to the alpha subunit (CD25) of the human high-affinity interleukin-2 (IL-2) receptor, which is expressed on the surface of activated lymphocytes. The isotype of daclizumab is IgG1κ.

Daclizumab is glycosylated at amino acid 296 of both heavy chain subunits with the major oligosaccharide form existing as a core fucosylated biantennary structure. The N-terminus of the daclizumab heavy chain exists as three major forms of charge variants. The C-terminus of the heavy chain exists with and without the C-terminal lysine residue. The major form lacks the C-terminal lysine residue, resulting in a C-terminal glycine.

Manufacture, characterisation and process controls

Daclizumab is expressed in NS0 cells (a mouse myeloma cell line) using recombinant DNA technology. The cell culture process is conventional, expanding the culture via shake flasks and progressively larger bioreactors to inoculate a production bioreactor. The purification steps include harvest, several chromatography and viral inactivation/filtration steps, and ultra/diafiltration, before dispensing into containers for storage at 2-8°C.

Manufacturing flow charts identifying the various controlled parameters and in-process controls/tests for each step were presented.

A comprehensive batch numbering system identifies the stage of manufacture, the year and the consecutive numbering of batches of that active substance for the year.

Cell banking system, characterisation, and testing

Daclizumab is produced by expression in NS0 cells that have been stably transfected with a single expression vector, expressing both the daclizumab humanized light and heavy chain genes encoding the region that binds to the alpha subunit (CD25) of the IL-2 receptor.

A two-tiered cell banking system using master cell banks (MCB) and working cell banks (WCB) is in place. The source, history and production of the NS0 cells, MCB and WCB have been described and documented in detail, including methods and reagents used during culture, *in-vitro* cell age studies, and storage conditions according to ICHQ5B. Both MCB and WCB have been qualified and characterised by extensive testing for mycoplasma, sterility and adventitious viruses to establish purity.

Cell culture

Detailed descriptions of the fermentation and harvest process have been provided and include the identification of controlled parameters as well as acceptance criteria.

Sequential time lapses are identified and minimal hold times, from expansion to production bioreactor harvest, are of no concern.

Throughout each stage of the inoculum expansion step, from the flask to the bioreactor expansion phases as well as for the production bioreactor phase, the target cell density is defined and the culture medium volume adjusted. Cell density and culture time are defined for all the culture steps. Clarification was provided on the calculation of the cumulative cell growth present in the cell culture mass used in the production bioreactor phase. Limits on cumulative cell age are defined and remain below the *in vitro* cell age as qualified during process development.

Purification and formulation

Each manufacturing step of the purification process has been described along with detailed descriptions of the processing conditions and in process controls.

The purification process consists of multiple chromatography steps. Column integrity is checked prior to application of the next batch. Resin reuse is defined for each chromatography column based on both prospective scaled-down development studies and manufacturing scale data.

In addition, viral inactivation/filtration steps are performed.

The active substance is then concentrated by ultrafiltration/diafiltration prior to filtration and dispensing into containers for storage.

Purification is sufficiently described. For all column resins reuse conditions are defined. The hold times were defined at each step based on scaled-down hold time studies on various process intermediates to assess both microbial and biochemical stability. Maximum hold times were set supported by these studies.

The manufacturing process is sufficiently described and controlled parameters along with in-process tests and in-process controls are described for each of the steps in process description.

The final bulk preparation obtained after a final filtration includes a possible re-processing step consisting of a final re-filtration. It was adequately demonstrated that there was no impact on the quality of the active substance.

The active substance is stored in single use flexible containers for which compliance has been demonstrated.

Control of Materials

Selection of the clone, sub-cloning strategy and generation of the seed bank is sufficiently described. The seed bank was found to be negative for mycoplasma, bacterial, and fungal contamination and was genetically characterized before being used to prepare the MCB and WCB. Sequencing data matched the known reference sequences.

The qualification program of the cell banks is generally in agreement with ICH requirements. Identity of the cell banks was confirmed to be of murine origin. Safety studies included the tests for sterility, mycoplasma and adventitious viruses, as expected for a cell line of murine origin. Genetic stability was confirmed in MCB and extended end-of-production cell bank (EEPCB) cells used to determine the limit of *in vitro* cell age.

Safety testing to demonstrate absence of adventitious agents in the cell banks was performed on the MCB, WCB lots and on the EEPCB derived from those WCB. Bovine and porcine viruses were tested on MCB and EEPCB. This is acceptable as no animal-derived materials are introduced in the manufacturing process. Viral safety testing is also performed for the unprocessed bulk harvest.

An adequate control of adventitious agents is performed on cells banks. During early development of the cell line, foetal bovine serum (FBS) was used in the cell culture medium. However, no material of animal or human origin is used in the entire commercial manufacturing process. The Certificate of Analysis and the EDQM Certificate of Suitability for the FBS used during preparation of the seed bank were provided.

Certificates of Analyses (CoAs) for all raw materials were provided.

The information provided on raw materials listed as non-compendial and compendial is sufficient. Adequate microbial control of these materials is ensured prior to use in the manufacturing process.

Control of critical steps and intermediates

All the process input and output parameters tested were presented. The rationale is based on previous process knowledge and development and validation studies.

Microbial controls are implemented at various process steps with set limits.

Neither product-related impurities nor process-related impurities are tested as in process controls. The omission of testing for the process-related impurities was accepted based on the outcome of the impurity clearance validation performed (see process validation). Validation of the manufacturing process ensures that host cell proteins, host cell DNA and other process-related impurities are cleared to safe levels. Viral safety is assured by in process testing and viral clearance studies.

Process validation and/or evaluation

Process consistency validation was performed and the results of both the input and the output parameters of each process step for the batches assessed were provided. These batches are considered to have satisfactorily qualified the production bioreactors. The results provide assurance that the cell culture, harvest, purification, formulation, and filtration steps of the active substance manufacturing process are under control and perform consistently within the pre-defined action limits and specifications.

Process-related impurities clearance validation was performed. Impurity clearance validation with multiple batches provided the basis for omitting the testing as in process controls or to be included in active substance specifications. As those methods are not part of the specifications information on method qualification was presented. Data to support suitability of those analytical methods for their intended use has been provided.

Sufficient detailed strategy for on resin and membrane lifetime validation has been presented. Viral removal studies were performed with new and aged resins.

The shipping verification demonstrates that the shippers can maintain temperature for well beyond the duration required for daclizumab active substance transport, even with worst case variation of external temperature profiles.

Manufacturing process development

Daclizumab active substance has been manufactured at three production bioreactor scales in three different facilities. In addition, daclizumab has been developed at two product concentrations: 100 mg/mL (clinical material) and 150 mg/mL (clinical and commercial material). Both concentrations were provided in a formulation of succinate, sodium chloride, polysorbate 80 and water for injections, pH 6.0.

Daclizumab for clinical studies and commercial use was manufactured using the same NS0 cell line and the same high yield process.

The information provided in support of the actual commercial manufacturing process and control strategy based on initial process development studies, clinical manufacturing experience, process characterization (robustness and range finding) studies, and process and product risk assessments is considered sufficient.

The description of all scaled-down systems used for process development has been provided.

The control strategy is based on product and process risk assessment evaluations conducted to determine the criticality of individual process or product parameters. A Risk Priority Number (RPN) was calculated for Product and Process separately by multiplying the assigned values of Severity, Occurrence, and Detection (RPN = Severity × Occurrence × Detection). High RPN scores are assigned to product or process parameters that have a clear and direct impact on product safety and efficacy, such as adventitious agents and functional potency, or parameters for which there is limited knowledge. The risk assessments followed the Failure Mode and Effects Analysis (FMEA) approach. Correspondence between risk priority number, process parameter classification and risk mitigation was presented.

Changes were introduced during development to support the scale-up of the process. This included changes to the number of seed bioreactors and consequently the purification scale. The changes are considered acceptable.

Likewise, modifications to the daclizumab cell culture parameters were introduced in the commercial manufacturing process. Additional changes were made to the purification steps for the commercial process with experience gained.

No changes were made in the formulation and the overall formulation and filtration process was the same. The minor changes introduced between manufacturing campaigns using the commercial process did not imply a new manufacturing process as the modifications did not change the purification scheme, column cycling strategy, and operating set point conditions. Analytical data was provided from batches manufactured during the clinical and process validation campaigns as well as a post-process validation/conformance campaign run. Results in comparability support this improvement in process control.

Characterisation

The primary amino acid sequence of daclizumab active substance was confirmed, as well as the disulphide linkages. The sixteen cysteine residues are coupled as eight disulphides at locations consistent with those of a typical IgG1 molecule.

Sequence information as well as disulphide linkage analysis obtained from peptide mapping studies allowed consistent identification of close to 100% of predicted sequence.

Charge heterogeneity resulting from heavy chain (HC) N-terminal variants, as well as variable trimming of C-terminal lysine was analysed.

The charge variants distribution gave consistent results for all the validation batches.

Analysis of the N- glycans was performed. The data demonstrated a consistent glycosylation profile across batches, and the presence of glycans that are typically observed on monoclonal antibodies. The predominant glycan species are asialylated core-fucosylated bi-antennary structures. Low abundance of high mannose forms and other non-fucosylated forms is sufficiently controlled.

The secondary and tertiary structural characterization showed consistency between reference standard and the active substance batches for which overlaid spectra were superimposable.

The purity and impurities were also assessed as part of characterization testing, including assessment of aggregate and clipped species.

In addition, biological properties related to the antibody's Fc function were characterized by the binding to the FcγRIIIa and FcγRI receptors and also by the ability of the antibody to induce antibody-dependent cellular cytotoxicity (ADCC). The ability of daclizumab to mediate complement dependent cytotoxicity (CDC) was also tested and the antibody was found to lack CDC activity.

Specification

The control of daclizumab active substance includes a potency assay to measure the binding of daclizumab to its cognate target antigen - CD25 (the alpha subunit of the high affinity IL-2 receptor), and a cell-based functional assay measuring the inhibition of IL-2-induced proliferation of a T-cell line that expresses the IL-2 receptor.

The potency and the functional assay were also used to determine the activity of the isolated charged variants of daclizumab active substance. All of the variants isolated and purified presented equivalent biological activity to daclizumab by both methods.

Process-related impurities that are present or potentially present in the active substance were tested for all the consistency validation and conformance batches as part of process validation. The levels of process-related impurities from the manufacture of the active substance were consistent among the process consistency validation and conformance batches. Also the clearance of these impurities using the commercial manufacturing process was validated. As such, based on the low level results obtained and the calculated removal capacity, none of these impurities are part of the release testing. As the active substance and finished product are the same in terms of formulation and protein concentration, safety assessments apply equally to daclizumab active substance and to finished product.

Microbial testing is performed as in-process controls and as release specifications.

Sufficient information is provided for all tests included in the specifications. Validation of all the methods developed as well as those compendia that require demonstration of suitability was adequately provided.

Justification of specifications

A limited number of batches serve as basis for the definition of the commercial manufacturing specification combining batches produced with two manufacturing processes for which comparability was demonstrated. The justification provided is considered adequate.

Quantitative specifications were defined based on a statistical approach. Certain specifications were defined slightly larger to accommodate expected process variability that might occur when more batches are tested ensuring that future batches will fall within the limits defined.

Stability specifications were set based on the trending of the stability data.

Reference standards

The product quality data from release and extended characterization tests demonstrate that the primary reference standard is representative of the clinical daclizumab batches and thus suitable as a primary reference standard for future working reference standard qualifications.

The selected tests used for working reference standard qualification include relevant key product attributes e.g. primary structure, molecular mass, carbohydrate structure, secondary and tertiary structure, biological activity, purity, and levels of impurities (product-related). The acceptance criteria are

generally the same as for release except for functional biological activity which was set tighter for eligibility purposes.

Stability

The proposed shelf-life at 2-8ºC in the active substance storage containers is acceptable based on the adequate and exhaustive analytical and stability comparability data provided in-between historical and commercial batches produced with different manufacturing process, and in-between commercial batches produced at different stages of the pharmaceutical/clinical development.

For all batches tested at long-term/real conditions compliance with the proposed active substance shelf-life was demonstrated. Validation of the methods selected to be stability indicating was provided.

The post-approval protocol, annual stability protocol and stability commitments have been provided and found to be acceptable.

Container closure system

The container closure system comprises a bioprocess single use container assembled with a filter. Eachables were identified and toxicity studies were performed with scaled-down models. The calculations provided indicate a sufficient safety margin for the intended use.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is a colorless to slightly yellow, clear to slightly opalescent liquid, which is essentially free of visible particles and is supplied in a 1 mL sterile, Type 1 glass pre-filled syringe (PFS).

Two presentations, with a nominal amount of 150 mg per dose, are available for subcutaneous administration; a PFS that consists of the syringe assembled with a finger flange and plunger rod, and a pre-filled pen (PFP) which encloses the PFS container closure inside the final assembled PFP.

The daclizumab pre-filled pen (PFP) is a single-use, disposable, injection device that is designed to assist with the delivery of a single dose of daclizumab finished product from the daclizumab pre-filled syringe (PFS).

Satisfactory details of the description and composition of the PFP components have been provided. The safety (biocompatibility) and robustness of the PFP have been satisfactorily established.

The following excipients are contained in the finished product: Sodium succinate, Succinic acid, Sodium chloride, Polysorbate 80, Water for injections.

The functions, concentrations, and characteristics of the components of the formulation including the active substance and each excipient chosen have been adequately described. Daclizumab has been shown to be compatible with the chosen excipients based upon long-term stability data obtained for active substance and finished product.

Pharmaceutical Development

During non-clinical and clinical development, two different concentrations of daclizumab active substance and finished product (100 mg/mL and 150 mg/mL; the latter intended for commercialization) and three different immediate packaging materials for the finished product were described in detail and fully compared. A pre-filled syringe (PFS) was selected as the commercial primary packaging.

As both PFS and PFP presentations proposed for commercialization are identical in respect to the formulated product and the immediate packaging materials, the development of the formulation

performed for the PFS applies also to the PFP presentation. The pre-formulation studies were described in detail taking in account the intended administration route for the finished product, i.e. subcutaneous use. Various variables were considered including buffer pH, buffer concentration, and choice of excipients and their respective concentrations.

Moreover stress tests were also performed to establish the finished product storage conditions which included temperature cycling, freeze-thaw, shaking stress, and light exposure studies.

The results of the light exposure studies on the finished product led to the recommendation of the avoidance of direct exposure of the finished product to light for extended durations.

During development the robustness of the formulation was also assessed by analyzing the impact of small changes in the formulation on stability, namely variations in pH, protein concentration, sodium succinate buffer, sodium chloride and polysorbate 80 concentrations in the presence of stressed conditions (freeze-thaw, shaking, exposure to room temperature and/or light or thermal stress). These stress conditions were chosen on the expected worse-case scenario to mimic potential situations likely to occur during manufacturing and/or shipping.

The only processing occurring during the manufacture of the finished product is the sterile filtration and aseptic filling into syringes of the active substance formulation. Aseptic manufacturing and sterile filtration was selected because the active substance is heat sensitive and thus thermal sterilization could not be used.

Development studies were performed to support the storage, transportation, sterile filtration and PFS filling and included freeze-thaw, temperature cycling, shaking stress, suitability of the fill pump and fill needle, hold times and material compatibility.

Manufacture of the product and process controls

Daclizumab PFS and PFP finished product is manufactured by Biogen (Denmark) Manufacturing ApS.

Each daclizumab PFS lot is manufactured from a single active substance bag. The manufacturing process of finished product consists only of the sterile filtering and aseptic filling of the daclizumab active substance formulation into syringes. Detailed flow charts and descriptions of each operation of the manufacturing process have been provided for the PFS and PFP. No reprocessing steps are planned for the manufacturing of the PFS and assembly of PFP.

Packaging information for the PFS and PFP has been provided, including qualified shipping conditions.

The PFS finished product manufacturing process steps are controlled by controlled parameters, in-process tests and in-process controls. Sterile filtration and aseptic syringe filling were identified as the critical steps of the PFS finished product manufacturing process.

Process validation

The process validation performed for the manufacture of the PFS and PFP finished product, included the following aspects: Process consistency validation, Hold time validation, and aseptic processing validation. Process performance consistency, process characterization, and syringe functionally were also presented.

Process consistency was validated using multiple batches of PFS finished product covering the minimum and maximum PFS lot sizes.

The performed process validation studies overall demonstrate that the PFS manufacturing process is robust and consistently yields finished product that meets the predetermined quality attributes. The analytical procedures used for the validation of the various critical steps of the manufacturing process of

the PFS and PFP finished products were described and adequately validated or the absence of validation justified.

Control of excipients

Adequate information has been provided on the control of the excipients. Sodium succinate, anhydrous is the only non-compendial substance and it is sufficiently described and testing methods provided. The methods have been validated according to ICH Q2(R1).

For all excipients, compendial and non-compendial, Certificates of Analysis issued by the respective vendors/manufacturers and by the active substance/ finished product manufacturer were provided.

Product specification

The finished product specifications share many of the tests used for the control of daclizumab active substance. Specific parameters related to PFS finished product include particulates, microbial and physical safety, as well as PFS functionality.

The release and shelf-life specifications for PFS finished product apply also to PFP. Additionally PFP is tested for device functionality.

Batch analysis was provided for clinical and commercial lots of PFS. The results presented show compliance of all batches of finished product used in clinical studies and manufactured for commercialization with the release specifications in place at the time. Several analytical methods were validated as stability indicating. The tests for purity, microbial safety, and particulates further assure the finished product safety.

Stability of the product

A shelf-life of 36 months at 2°C–8°C is proposed for PFS finished product with an allowance of up to 30 days at a temperature up to 30ºC.

Comparability of commercial with historical batches stability data allowed the conclusion that the stability trends at long-term, accelerated and stressed storage conditions of commercial lots were consistent with data from historical batches and thus the finished product administered to patients in clinical trials is comparable to the one proposed for commercialization.

A photostability study performed with PFS finished product demonstrated that the active substance is sensitive to light when packaged in PFS and that the selected secondary commercial packaging gives adequate protection.

Supply chain temperature cycling and ambient storage simulation studies were performed allowing the establishment of a maximum Time out of Refrigeration.

Based on the stability data presented the proposed storage 2ºC-8ºC for 36 month is considered acceptable. The post-approval stability commitment as well as the annual stability protocol were found to be adequate.

Container closure system

The description of the container closure system is given in sufficient detail and adequate information regarding the materials is presented. Drawings for the packaging components have been provided. Specifications for the syringe barrel and the plunger stopper for the primary packaging have been provided. The syringe barrel and rubber stopper comply with requirements of Ph. Eur. The primary container closure system has been shown to be compatible with the finished product.

The silicone used in the syringe barrel complies with the Ph. Eur. Requirements.

The sterilisation process of the staked needle syringes with rigid needle shield was described and adequately validated. Rubber plungers are also sterilised. Sterilisation of each of the PFS components is performed according to relevant pharmacopoeia and ISO standards.

Two types of device performance test for PFP acceptance are defined.

Medical Device

The pre-filled pen (PFP) is a single-use, disposable, injection device that is designed to assist with the delivery of a single dose of finished product from the pre-filled syringe (PFS).

According to the provisions of Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, this product is to be placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and is not reusable. Accordingly, this product is governed by Directive 2001/83/EC. The device element of the product is therefore not CE marked.

Satisfactory details of the description and composition of the PFP components have been provided as has a comparison of the device used in clinical studies compared with that intended for commercialisation. It is accepted that finished product quality attributes will be evaluated on PFP process validation lots to confirm no effect on the finished product quality after assembly into and delivery from the commercial PFP and its comparability with the PFS.

The safety (biocompatibility) and robustness of the PFP have been satisfactorily established. Appropriate details of the assembly process have been provided.

Adventitious agents

In the commercial manufacturing process no material from animal or human origin is used. The risk of TSE contamination from the raw materials used in early development when establishing the cell banks is negligible.

The NS0 cell line used for the production is well characterised. MCB, WCB and EEPCB have been characterised for the absence of contaminating viruses according to ICHQ5A. Extensive tests for rodent viruses, bovine and porcine viruses as well as sterility and mycoplasma have been conducted for the cell banks.

A virus validation study was performed according to CPMP/BWP/268/95 with different model viruses. The capability of several orthogonal process steps (chromatography steps and viral inactivation/filtration steps) to reduce the amount of adventitious viruses has been adequately demonstrated using spiking studies in scaled-down models. Viruses for the clearance studies can be considered to represent a wide range of physico-chemical properties that demonstrates the ability of the system to eliminate the viruses in general.

The control of mycoplasma, bacteria and fungi is performed using compendial methods and at appropriate steps of manufacture. The provided information is considered adequate.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance and finished product was of acceptable quality. The manufacturing processes are well described and properly controlled both for active substance and finished product. Specification limits and analytical methods are suitable to control the quality of the active substance and the finished product. The finished product was well characterised. The stability

program is considered satisfactory. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The active substance and the finished product have been appropriately characterised and satisfactory documentation has been provided. The results indicate that the active substance as well as the finished product can be reproducibly manufactured. No major objections have been identified in the initial assessment. The deficiencies and points for clarification were appropriately addressed by the Applicant during the review process.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended an additional point for further investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Daclizumab targets the alpha subunit (CD25) of the high-affinity receptor for IL-2. By inhibiting IL-2 signalling, it is proposed to reduce T cell proliferation and activation which leads to a reduction in pro-inflammatory autoimmune directed T cell activity in patients with multiple sclerosis. The dataset presented addressed only in vitro pharmacology of daclizumab (Zinbryta).

The product is presented at 150 mg/ml as a solution for injection in a pre-filled syringe or pen for subcutaneous injection in packs containing 1 or 3 syringes or pens. The proposed dose is one subcutaneous injection of 150 mg per month.

2.3.2. Pharmacology

The nonclinical program evaluated test article representative of the drug product (DP) used in clinical development, and DP intended for commercial supply as required.

The pharmacodynamics of daclizumab is well characterized. Daclizuman is a humanized IgG1 monoclonal antibody that binds specifically to CD25, the alpha subunit of the high-affinity interleukin 2(IL-2) receptor. Daclizumab modulates IL-2 signalling, blocking CD25-dependent, high-affinity IL-2 receptor signalling but leaving intermediate-affinity IL-2 receptor signalling intact. Modulation of IL-2 signalling via antagonism of the high-affinity IL-2 receptor results in distinct immunologic changes that target both activated T cells and ectopic lymphoid aggregates. These effects are hypothesized to reduce both the grey and white matter pathology that underlie the key clinical manifestations of multiple sclerosis (MS) and represent a therapeutic approach for the treatment of MS.

Considering the specific binding of daclizumab to CD25, no secondary pharmacodynamic studies were performed by the Applicant, which was considered acceptable.

Additionally, as there would be limited value in the qualitative and quantitative projection of clinical interactions between therapeutic proteins and drug metabolizing enzymes from in vitro or in vivo nonclinical drug interaction studies, nonclinical drug interaction studies were not conducted, which was also considered acceptable.

Safety pharmacology of daclizumab was performed in cynomolgus monkeys (Macaca fascicularis), by subcutaneous administration. Overall studies showed a good safety profile.

2.3.3. Pharmacokinetics

Pharmacokinetic (PK)/toxicokinetic (TK) profiles of daclizumab were comprehensively evaluated in single dose intravenous IV and single and repeat-dose SC studies (acute, sub-chronic, chronic, reproductive, embryo-foetal, and pre- and post-natal toxicology studies) in cynomolgus monkeys. Daclizuman demonstrated very consistent and linear PK profiles in the 5 to 200 mg dose ranges tested in cynomolgus monkeys over multiple studies, showing predictable PK/TK characteristics of monoclonal antibodies. The overall low incidence of immunogenicity allowed for exclusion of anti-drug antibodies (ADA) positive animals, where the observed decrease of serum daclizumab concentration due to ADA was substantial (>20% of group average), and did not compromise the TK or the toxicological evaluations in any of the studies.

The PK profile of daclizumab, observed after single IV administration, is consistent with that known of mAbs, with a long half-life (t1/2) of (approximately average ~10 days), low systemic clearance (0.167 mL/hr/kg), and a small volume of distribution (54 mL/kg). SC administration of daclizumab, following single and multiple doses, demonstrated slow absorption (time to attain Cmax ~2-3 days), with an approximate dose proportional increase in exposures. Overall, it demonstrated dose proportional linear PK/TK, with no gender difference in any of the PK/TK parameters, and moderate accumulation (~2-fold), predictable based on its terminal half-life (8-16 days range), after repeat SC dosing every 2 weeks. No difference in daclizumab TK parameters were observed in pregnant versus non-pregnant cynomolgus female monkeys and, while the serum ratio of daclizumab in infant: corresponding mother was observed to be 1.0, suggesting good transplacental transfer of daclizumab, the ratio of daclizumab in milk: serum (≤ 0.122%) in lactating cynomolgus monkeys suggested very low excretion of daclizumab via milk in lactating mothers.

A clinical TPDI study in lieu of nonclinical studies was conducted to evaluate the effect of daclizumab on CYP activities. Results indicate that daclizumab has no effect on the activities of the major CYP enzymes.

2.3.4. Toxicology

To evaluate potential systemic effects of daclizumab administration, a single dose GLP intravenous toxicology study was conducted in cynomolgus monkeys (PDL.DAC-06.003/ TR07133), which included a 16-day observation period post-dose. The no- observable-adverse-effect level (NOAEL) for this study was considered to be the highest dose tested, 30 mg/kg.

Repeat-dose toxicology studies were conducted with daclizumab administered SC (clinical and commercial route of administration) q2W.

Two 9-month chronic toxicology studies were conducted. In the first study (PDL.Dac-04.006/TR07185_3), a NOAEL was not determined due to skin findings, and a significant number of control animals (93%) had detectable levels of anti-drug antibodies (ADA). The second study (P019-11-01) was conducted to define a NOAEL. The first study (PDL.Dac-04.006/ TR07185_3) evaluated daclizumab doses of 10, 50, 200 mg/kg and the second study evaluated daclizumab doses of 10, 35, 200 mg/kg. The 35 mg/kg dose was tested in the second study to try to find the highest no observed effect level (NOEL) for a daclizumab-related CNS finding (discussed in more detail below).

The toxicology studies identified the skin and CNS as target organs. The NOAELs for the repeat dose studies were driven by findings in these tissues, depending upon the study. Table 1 describes the findings from the repeat dose toxicology.

Table 1 summary of repeat dose toxicology findings

Study TR Number Study Report Number	Duration of Dosing	Doses (mg/kg)	NOAEL mg/kg	Key Findings (Basis for NOAEL)
TR04236 PDL.Dac-04.002	4-Weeks	5, 50, 125, 200	200[1]	None
TR05395_1 PDL.Dac-04.005	13-Weeks	0, 5, 50, 125, 200	5	Microglial Aggregates
TR07185_3 PDL.Dac-04.006	39-Weeks	0, 10, 50, 200	Not Established	Skin findings
P019-11-01	39-Weeks	0, 10, 35, 200	10	Microglial Aggregates

TR = Technical Report Number
[1]Maximum tolerated dose

In addition to a single IV dose local tolerance study conducted in rabbits, local tissue tolerance was monitored in the repeat dose toxicity studies by clinical observations and histopathology of the injection sites. The repeated SC administration was well tolerated without any adverse injection site reactions.

Daclizumab-related skin changes were observed in both of the 39-week toxicology studies, but not in studies of shorter duration. These findings were characterized grossly as red, dry, scaly areas on body extremities (ears, legs and tail) and orifices (mouth and perianal areas), and on the inguinal, ventral and dorsal areas of the trunk with a microscopic correlate of acanthosis/hyperkeratosis and/or inflammation. These findings were noted in all DAC HYP groups; however, there was no dose-relationship for lesion severity. Although similar findings were present in control animals, they were more prevalent in the DAC HYP groups (i.e., increased incidence, earlier occurrence, multifocal distribution, and longer duration), and as such are considered to be related to the administration of daclizumab. The occurrence of skin findings had a median onset time of 6 months.

Table 2 Incidence of clinical skin findings in the first 39-week study (PDL.Dac-04.006/TR 07185_3)

Dose (mg/kg)	Dry Skin				Red Skin			
	Incidence	%	Onset		Incidence	%	Onset	
			Range (Day)	Average (week)			Range (Day)	Average (week)
0	1/14	7	232	33	8/14	57	13-225	20
10[1]	5/8	63	106-253	25	6/8	75	81-253	22
50	5/8	63	176-241	30	4/8	50	164-218	27
200	8/14	57	106-260	28	12/14	86	81-267	25

[1]One female was humanely euthanized on Study Day 210

Table 3 Incidence of clinical skin findings in the second 39-week study (P019-11-01)

Dose (mg/kg)	Dry Skin				Red Skin			
	Incidence	%	Onset		Incidence	%	Onset	
			Range (Day)	Average (week)			Range (Day)	Average (week)
0	3/12	25	196-240	31	6/12	50	23-260	17
10	3/8	38	196-231	31	4/8	50	44-224	20
35	7/12	58	49-229	17	12/12	100	11-211	11
200	8/12	67	52-229	21	9/12	75	19-110	7

For most treated animals, the skin findings were mild to moderate, were tolerated, and responded to standard veterinary care (cleaning skin areas with chlorhexidine and local application of diaper rash ointment) except for one female animal in a 10 mg/kg dose group in study PDL.Dac- 04.006/ TR07185_3 where they became adverse resulting in an indeterminate NOAEL for this study.

The skin lesions had microscopic correlates of dermal inflammation and epidermal thickening due to acanthosis/hyperkeratosis. Other less common microscopic skin findings were sebaceous gland atrophy, epidermal crusts, and epidermal spongiosis (intercellular edema) with microvesiculation. In the second 39-week study (P019-11-01), in addition to the standard skin samples taken as part of the routine histopathology assessment collected at necropsy, skin biopsies were also collected throughout the study. The additional punch biopsy specimens had the same findings as the routine terminal skin sections taken at necropsy. The etiology of skin findings observed in the chronic (39-Week) repeat dose studies is unclear, but could potentially be related to daclizumab-mediated modulation of IL-2 signaling by immune cell subsets, particularly $CD56^{bright}$ NK cells or regulatory T-cells. Consistent with the hypothesized role of IL-2 modulation contributing to the etiology of the skin findings in monkeys, it is recognized that $CD56^{bright}$ NK cells and regulatory T-cells are involved in a number of skin conditions, including atopic dermatitis [Luci 2012; von Bubnoff 2010; Ilkovitch 2011], psoriasis [Ottaviani 2006; Luci 2012; von Bubnoff 2010; Keijsers 2013], allergic contact dermatitis [Carbone 2010; Lehtimaki 2012].

Skin effects have also been reported in humans administered daclizumab, both in clinical trials with daclizumab (Zinbryta), and with daclizumab (Zenapax) [Oh 2014; Milo 2014]. While the nonclinical studies did not identify a NOAEL for the daclizumab-related skin findings, changes in the skin findings are readily monitorable and manageable in the clinic.

Daclizumab-related CNS findings consisted of microglial aggregates (minimal) in the brain and spinal cord at doses of ≥ 35 mg/kg.

Table 4 Incidence of daclizumab-related microglial aggregates in the brains of cynomolgus monkeys

Study	Dose (mg/kg)	Main Necropsy Males	Main Necropsy Females	Recovery Necropsy Males	Recovery Necropsy Females
Acute Toxicity Study P019-08-01		n=4		n=3	
Single Dose	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	3[a]	NA	1	NA
Two-Doses	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	3[a]	NA	1	NA
Male Reproductive Toxicology Study PDL.Dac-05.001 (5 biweekly doses)		n=5		n=3	
	0	0	NA	0	NA
	10	0	NA	--	NA
	50	2[b]	NA	--	NA
	200	5	NA	0	NA
		n=3	n=3	n=3	n=3
13-Week Toxicity Study PDL.Dac-04.005 (7 biweekly doses)	0	0	0	0[c]	0
	5	0	0	--	--
	50	0	1	--	--
	125	2	2	0	0
	200	2	1	0	0[c]
		n=4	n=4	n=3	n=3
39-Week Toxicity Study PDL.Dac-04.006 (20 biweekly doses)	0	0	0	0	0
	10	0	0[c]	--	--
	50	2	0	--	--
	200	3[b,c]	4[b]	0	1
		n=4	n=4	n=2	n=2
39-Week Toxicity Study P019-11-01 (20 biweekly doses)	0	0	0	0	0
	10	0[d]	0	--	--
	35	0	2	1[b]	1
	200	3[a,c]	3[b]	0	0

[a]Additional microglial aggregate(s) noted in the spinal cord of 2 listed animals.
[b]Additional microglial aggregate(s) noted in the spinal cord of 1 listed animal.
[c]One animal (not listed) had microglial aggregate(s) only in the spinal cord.
[d]A single microglial aggregate in one animal was considered consistent with background occurrence and not test article-related.

Microglial aggregates were observed as small accumulations of cells randomly distributed throughout the grey and white matter of the brain and spinal cord including the cerebral cortex, cerebellum, midbrain and pons, without a preference for a particular site, and all were considered to be of minimal severity. Minimal microhemorrhage was rarely observed associated with the microglial aggregates in animals dosed at 200 mg/kg. A small amount of brown pigment consistent with hemosiderin was observed associated with a microglial aggregate at the recovery necropsy in one 35 mg/kg animal from one of the 39-week studies, suggesting resolution of a previous microhemorrhage. The random distribution of the microglial aggregates does not seem consistent with a neurotoxic effect, and that is in line with de evidence discussed by the applicant. Daclizumab-related CNS findings were not observed at the lowest dose of 10 mg/kg, which provides 7-fold exposure relative to the 150 mg clinical dose.

Table 5 Cynomolgus monkey brain histopathology from toxicity studies with Daclizumab: incidence of microhemorrhage

Study	Dose (mg/kg)	Main Necropsy		Recovery Necropsy	
		Males	Females	Males	Females
Acute Toxicity Study P019-08-01		n=4		n=3	
Single Dose	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	2	NA	0	NA
Two-Doses	0	0	NA	0	NA
	10	0	NA	--	NA
	35	0	NA	0	NA
	200	1	NA	0[1]	NA
39-Week Toxicity Study PDL.Dac-04.006 (20 biweekly doses)		n=4	n=4	n=3	n=3
	0	0	0	0	0
	10	0	0	--	--
	50	0	0	--	--
	200	1	1	0	0
39-Week Toxicity Study P019-11-01 (20 biweekly doses)		n=4	n=4	n=2	n=2
	0	0	0	0	0
	10	0	0	--	--
	35	0	0	0	0[1]
	200	0	1	0	0

[1]A small amount of brown pigment (consistent with hemosiderin) associated with microglial aggregates, suggesting resolution of previous hemorrhage.

To assess the significance of microglial aggregates the applicant pursued different approaches, including:
(1) performing a detailed and dedicated CNS acute neurotoxicity and neurobehavioral study;
(2) review of data from the chronic toxicology studies focusing on expanded histopathology evaluation of CNS tissues and neurobehavioral observations; and,
(3) forming an Expert Pathology Working Group to assess the histologic findings from representative studies.

To assist in the characterization of the CNS findings, an Expert Pathology Working Group (PWG) composed of 6 Board Certified Veterinary Pathologists (Diplomate American College of Veterinary Pathologists, DACVP) was convened to review the CNS data from the 13-week study and the first 39-week study. The PWG concluded that the cellular foci observed in the brain and spinal cords represented aggregates of microglial cells characterized as focal accumulations of mononuclear cells, most of which appeared to be microglial cells within varying regions of the brain parenchyma including the cerebral cortex, cerebellum, midbrain and pons, without a preference for a particular site. They also concluded that the random distribution of the microglial aggregates appear to be inconsistent with a neurotoxic effect and that there was no histologic evidence of neuronal degeneration, axonal fragmentation, or demyelination in association with the microglial aggregates.

The applicant further proposed an understanding of the etiology of the increased microglial aggregates observed in cynomolgus monkeys treated with daclizumab (Zinbryta). In vitro studies were conducted in both human fetal and cynomolgus monkey primary microglial cells to characterize IL-2 receptor expression and daclizumab effects on IL-2 mediated proliferation. These studies demonstrated that cynomolgus and fetal human microglial cell primary cultures express functional intermediate IL- 2 receptors (CD122/CD132), but do not express CD25, the alpha subunit of the high-affinity IL- 2 receptor (R&D/13/953, R&D/13/970). Consistent with the expression of intermediate IL-2 receptors and lack of CD25 expression, primary fetal human and cynomolgus monkey microglial cells signaled in response to

IL-2, but the IL-2 signaling was not affected by blocking CD25, suggesting that microglial aggregates are not a direct consequence of daclizumab binding or a response to injury, but are potentially an indirect effect attributable to increases in IL-2 bioavailability resulting from daclizumabsaturation of CD25 on cells (other than microglial cells) within in the CNS.

The no effect level for daclizumab-related CNS findings (10 mg/kg) provides 7-fold exposure relative to the 150 mg clinical dose, which from a toxicological point of view is acceptable taking into consideration the rationale previously provided.

While effects on liver function tests (LFTs) have been observed in the clinical trials with daclizumab, no clear daclizumab-related effects on the liver were observed in cynomolgus monkeys. This may be due to the low incidence of liver findings in the clinical studies (< 1%).

Genotoxicity and carcinogenicity studies were not conducted with daclizumab. Monoclonal antibodies are not expected to cause genotoxicity by direct interaction with DNA or affect chromosomal structure as tested in the in vitro and in vivo genotoxicity battery, making these types of studies not applicable. There is also no reason to believe that the pharmacological MOA would be associated with an increased risk for carcinogenicity. In fact, blocking the CD25 pathway has been demonstrated to be anti-tumorigenic in mouse tumor models and has been tested as a cancer immunotherapy in humans [Fecci 2006; Sampson 2012; Wainwright 2013; Wang 2012]. Finally, in the clinical experience thus far, the incidence of malignancies was <1% and balanced across the treatment groups, without any specific pattern of malignancies. Taking all of these factors into consideration, it was concluded that daclizumabwould have low risk for carcinogenicity with chronic treatment in humans.

Daclizumabalso poses a low risk for reproductive and developmental toxicity, as there were no adverse effects observed for fertility, embryo-fetal and pre- and post-natal development. Given that daclizumab had no effects on male and female fertility and fetal development and is not expected to alter the immunostasis of pregnancy, it is not anticipated that it will have any generational fertility effects when administered during pregnancy.

Table 6 Reproductive and developmental toxicity studies conducted with daclizumab

Study TR Number; Study Report Number	Type of Study	Duration of Dosing	Doses (mg/kg)	NOAEL[1]	Multiple of Human Exposure[3]
TR07135_2; PDL.Dac-05.001	Male Fertility and Early Embryonic Development[2]	9-Weeks (approximately 60 days to cover all stages of spermatogenesis)	0, 10, 50, 200	200	102
TR06121; PDL.Dac-05.002	Female Fertility and Early Embryonic Development	9-Weeks (approximately 2 menstrual cycles)	0, 10, 50, 200	200	85
TR07122; PDL.Dac-04.003	Pilot Embryo-Fetal Development (Non GLP)	GD 20 – GD 50	200	No maternal or fetal findings	NA
TR07123; PDL.Dac-04.004	Embryo-Fetal Development	GD 20 – GD 50	0, 10, 50, 200	200	140
TC11-033	Pre- and Post-Natal Development	GD 50 – Parturition GD 160 ± 10	0, 50	50	55

NA = Not applicable
[1]Reproductive and Developmental Toxicity NOAEL
[2]Microglial aggregates were observed at ≥ 50 mg/kg
[3] Based on human exposure ($AUC_{0\text{-}28\ days}$; mg*hr/mL) in Clinical Study 205MS302

There were no adverse immunomodulatory effects observed for any of the parameters evaluated. Immunotoxicity was not apparent in repeat dose study findings and in reproductive toxicity studies. While effects on the $CD4^+$ $CD127^{low}$ $FoxP3^+$ T-regulatory cell population have been observed in the clinic this effect has not been observed in cynomolgus monkeys. In normal cynomolgus monkeys, $CD4+/CD127^{low}/-/FoxP3^+$ T-regulatory are rare and only make up approximately 56 to 180 cells/mL [Clark 2010], therefore the lack of an apparent daclizumab-related effect in this cell population may have been related to the limited sampling, cohort sizes and assay sensitivity.

2.3.5. Ecotoxicity / environmental risk assessment

According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*),the environmental risk assessment for proteins may consist of a justification for not submitting ERA studies as they are unlikely to result in significant risk to the environment. The active substance daclizumab is a monoclonal antibody and, therefore, is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The nonclinical characterization of daclizumab included:

a) Pharmacologic characterization of a novel mechanism of action of daclizumab through binding to CD25 and effects on; 1) inhibition of IL-2 induced cell proliferation; 2) inhibition of cytokine secretion by activated T cells; 3) down-modulation of CD25 expression on T cells; 4) in vitro antibody-dependent cellular cytotoxicity (ADCC) and; 5) complement-dependent cytotoxicity (CDC).

b) Detailed pharmacokinetic characterization demonstrating a molecule with consistent and linear pharmacokinetic profile across studies with minimal impact of immunogenicity.

c) Detailed characterization of the safety profile (general, immunological, and developmental and reproductive toxicity) in a comprehensive battery of in vitro investigative and GLP toxicity studies in cynomolgus monkeys.

The target organs identified in the repeat dose toxicity studies are the skin and CNS. Chronic treatment with daclizumab resulted in an increase in skin findings characterized grossly as red, dry, scaly areas with a microscopic correlate of acanthosis/hyperkeratosis and/or inflammation.

While these lesions were also present in controls, their incidence and severity was increased in daclizumab treated animals. There is no safety margin for the daclizumab-related skin findings, but this risk is offset in the clinical setting as skin findings can be appropriately monitored and managed as part of clinical practice.

The daclizumab-related increase in microglial aggregates was characterized across several studies. Evidence from investigative studies indicated that they might not represent a neurotoxic response but rather a physiological response due to increases in IL-2 concentrations that occur when daclizumabDAC HYP saturates CD25 expressing tissues within the CNS of cynomolgus monkeys at exposures which are 27-fold greater than the clinical exposure.

2.3.7. Conclusion on the non-clinical aspects

The nonclinical pharmacology, pharmacokinetics, and toxicology studies described provide the required justification for the use of daclizumab when administered SC to MS patients monthly at doses of 150 mg.

2.4. Clinical aspects

2.4.1. Introduction

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling. This application was submitted to support the approval of Daclizumab High Yield Process (DAC HYP), also known as Zinbryta, a new form of daclizumab, as a disease-modifying therapy (DMT) for the treatment of patients with relapsing forms of multiple sclerosis (RMS).

Daclizumab (DAC-Nutley) was first approved as Zenapax 5 mg/ml concentrate for solution for infusion for the prophylaxis of acute organ rejection in *de novo* allogenic renal transplantation; this medicinal product is no longer authorised. The posology in adult and paediatric patients was 1 mg/kg with the dose added to 50 ml of sterile 0.9% saline solution to be administered intravenously over 15 minutes.

Biogen Idec has evaluated daclizumab High Yield Process for use in relapsing forms of multiple sclerosis in a single Phase 2 study (205MS201) and one Phase 3 studies (205MS301), both with extension studies and a number of clinical pharmacology studies.

- The Overview of the Clinical Development of Daclizumab (Zinbryta) in MS is presented in the below chart:

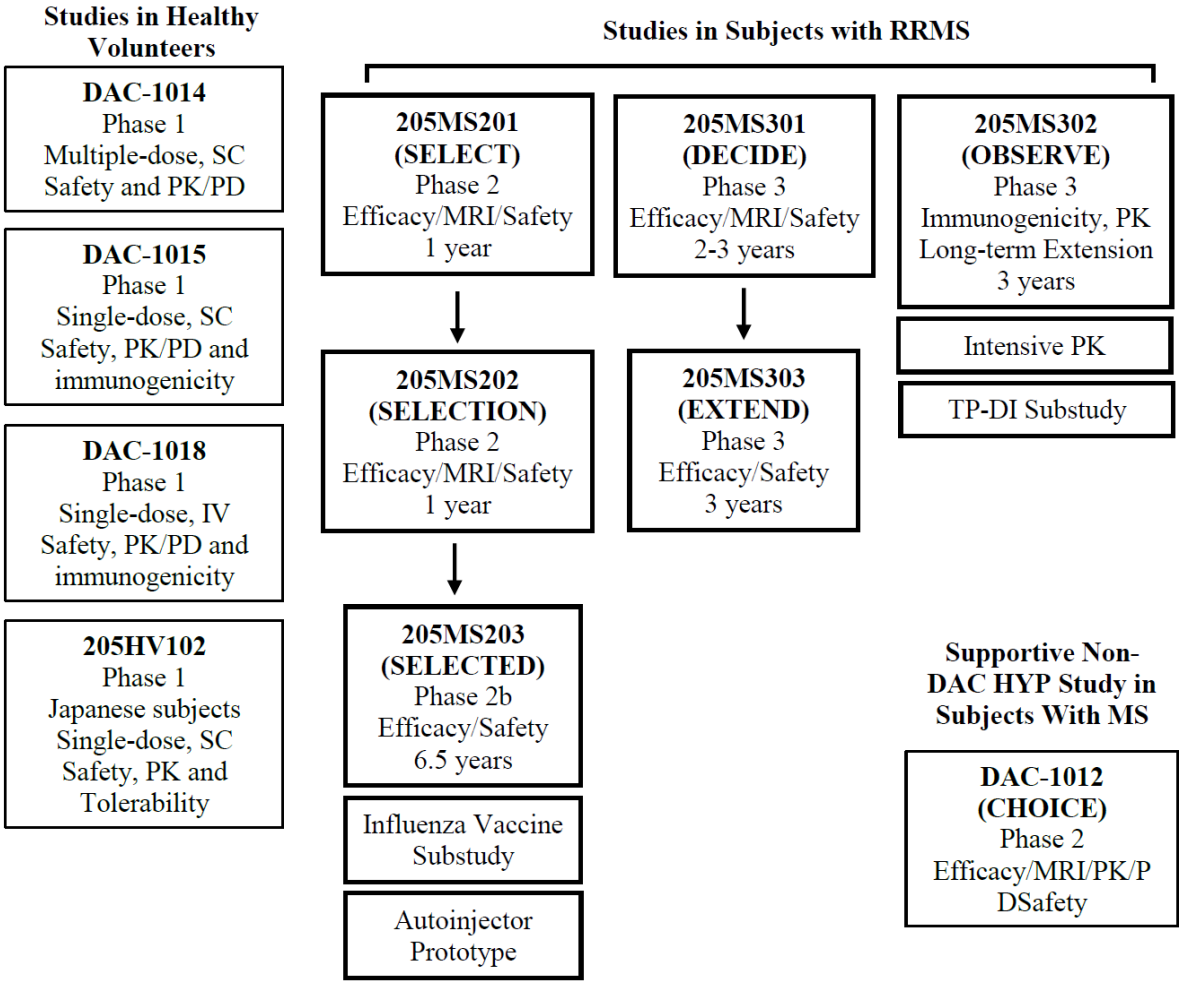


Figure 1 Overview of the Clinical Development of daclizumab (Zinbryta).

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

- Tabular overview of clinical studies

Table 7 Overview of studies

Study No.	Study Description	Number in the Safety Population			Objective
		Placebo	DAC HYP	IFN β-1a	
Placebo-Controlled Study					
205MS201	Double-blind, placebo-controlled, dose-ranging study in RRMS subjects DAC HYP 150 mg or 300 mg SC or Placebo, 1 dose every 4 weeks for 52 weeks	204	417	--	Evaluation of the safety and efficacy
Active-Controlled Study					
205MS301	Double-blind, parallel group, active-controlled study in RRMS subjects DAC HYP 150 mg SC once every 4 weeks for 96 to 144 weeks IFN β-1a IM 30 µg once weekly for 96 to 144 weeks	--	919	922	Evaluation of the safety and efficacy
Dose-Blinded Study					
205MS202	Double-blind extension study of 205MS201 Placebo subjects in 205MS201 were assigned to either DAC HYP 150 mg or DAC HYP 300 mg SC once every 4 weeks for 52 weeks DAC HYP subjects in 205MS201 were assigned to either continue at their current dose of DAC HYP (150 mg or 300 mg) or receive 5 doses of placebo during a washout period, followed by 8 DAC HYP doses (150 mg or 300 mg)	--	517 (170 new exposures)	--	Evaluation of the efficacy safety and immunogenicity of extended treatment with DAC HYP
Uncontrolled Studies					
205MS203	Single-arm, open-label extension study of 205MS202 DAC HYP 150 mg SC every 4 weeks for up to 6.5 years in subjects who completed treatment in 205MS202	--	410 (no new exposures)	--	Evaluation of long-term safety and efficacy
205MS302	Single-arm, open-label study DAC HYP injections were given using the PFS every 4 weeks over an initial 24-week treatment period (for a total of 6 doses), followed by a 20-week washout period After completion of the washout period, eligible subjects had the option to resume open-label treatment with DAC HYP 150 mg every 4 weeks for up to 3 years (or subjects could elect to complete the study through Week 44 only)	--	133 (n=113 in the main study phase)	--	Evaluation of the immunogenicity of DAC HYP using a PFS

Table 8 Overview of studies (ctd.)

205MS303	Single-arm, open-label extension study of 205MS301 DAC HYP 150 mg SC once every 4 weeks for 33 mean cumulative doses	--	308 (146 new exposures)	--	Evaluation of long-term safety and efficacy
Substudies[a]					
205MS203	Open-label substudy comparing the use of the PFS and autoinjector DAC HYP 150 mg SC once every 4 weeks for 4 doses using autoinjector, and once every 4 weeks using PFS or autoinjector for approximately 16 weeks	--	60	--	Assessment of the PK of the single-use autoinjector compared with the PFS
205MS203	Open-label substudy evaluating the immune response to the trivalent influenza vaccine DAC HYP 150 mg SC once every 4 weeks 2013-2014 trivalent influenza vaccine, 1 dose	--	91 (90 received vaccine)	--	Assessment of the impact of DAC HYP treatment on response to the seasonal influenza vaccine
205MS302	Open-label substudy evaluating the PK and PD from the PFS Intensive PK sampling was performed after doses 1 and 6.	--	26	--	--
205MS302	Open-label therapeutic protein-drug interaction (TP-DI) substudy evaluating the PK of probe drugs for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A). DAC HYP 150 mg SC once every 4 weeks for 6 doses	--	20	--	--
Subjects in the Safety Population for DAC HYP MS Studies[b]		204	1785[c]	922	--

Source: CSRs 205MS201, 205MS301, 205MS202, 205MS203, 205MS302, 205MS303; Appendix Table 14.
CSR = clinical study report; CYP = cytochrome P450; DAC HYP = daclizumab high yield process; IFN β-1a = interferon beta-1a; IV = intravenous; IM = intramuscular; MS = multiple sclerosis; PD = pharmacodynamics; PFS = prefilled syringe; PK = pharmacokinetics; RRMS = relapsing-remitting multiple sclerosis
[a] Substudy subjects are counted in the substudy as well as the parent study.
[b] Subjects are counted in more than 1 column as appropriate.
[c] Total subjects in pooled safety population.

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of daclizumab have been characterized utilizing intensive/serial sampling from 4 Phase 1 studies in healthy volunteers (HVs) and 1 immunogenicity study in subjects with multiple sclerosis (MS), and using sparse sampling from Phase 2 and 3 studies in subjects with MS. In addition, the therapeutic protein-drug interaction (TP-DI) potential for daclizumab was investigated in subjects with MS (see Table 9 and Table 10).

Table 9 Summary of Daclizumab (Zinbryta) Clinical Pharmacology studies (healthy volunteers)

Study Identifier	Study Objectives	Study Design	Test Product; Dosage Regimen; Route of Administration	Planned Treatment Period	Number of Subjects Enrolled; Completed	Planned Age range
PK/PD Studies in Healthy Volunteers						
DAC-1015	To determine the safety, tolerability, PK, PD, and immunogenicity of SC DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 50 mg SC (n = 7) 150 mg SC (n = 8) 300 mg SC (n = 8) Placebo SC (n = 10)[a]	Single dose	34 enrolled; 32 completed	18 to 75 years, inclusive
DAC-1014	To determine the safety, tolerability, PK, PD, and immunogenicity of multiple doses of DAC HYP administered by SC injection	Multiple-dose, randomized, double-blind, placebo-controlled	DAC HYP, multiple dose 200 mg SC every 2 weeks × 9 doses (n = 12) 200 mg SC loading dose + 100 mg SC every 2 weeks × 8 doses (n = 12) Placebo SC 9 doses (n = 8)	16 weeks	32 enrolled; 27 completed[b]	18 to 65 years, inclusive
DAC-1018	To determine the safety, tolerability, PK, PD, and immunogenicity of IV DAC HYP	Single-dose, double-blind, placebo-controlled, dose-escalating	DAC HYP, single dose 200 mg IV (n = 12) 400 mg IV (n = 12) Placebo IV (n = 7)	Single dose	31 enrolled; 30 completed	18 to 65 years
205HV102	To evaluate the PK, safety, and tolerability of DAC HYP administered as a single SC dose in Japanese and Caucasian adult HVs	Single-dose, single-blind	DAC HYP, single dose 75 mg SC (n = 28; 14 per ethnic group) 150 mg SC (n = 28; 14 per ethnic group)	Single dose	56 enrolled; 56 completed	18 to 55 years, inclusive

Table 10 Summary of daclizumab (Zinbryta) Clinical Pharmacology studies (MS patients)

Study Identifier	Study Objectives	Study Design	Test Product; Dosage Regimen; Route of Administration	Planned Treatment Period	Number of Subjects Enrolled; Completed	Planned Age range
PK and PD Studies in MS Subjects						
205MS203 *Autoinjector PK Substudy*	To compare the systemic exposure of daclizumab following SC administration of 150 mg DAC HYP using the single-use autoinjector (PFP) to the systemic exposure following manual PFS injection	Open-label, parallel design	DAC HYP 150 mg SC from a PFS by either manual injection or by autoinjector every 4 weeks for 4 doses	16 weeks	60 enrolled; 60 completed	18 to 55 years, inclusive
205MS302 *Intensive PK Substudy*	To characterize the PK of DAC HYP following single and multiple doses of SC DAC HYP administered by the PFS in a subset of subjects with RRMS	Single-arm, open-label	DAC HYP 150 mg SC by PFS every 4 weeks for 6 doses	24 weeks	26 enrolled; 25 completed	18 to 65 years, inclusive
205MS302 *TP-DI Substudy*	To evaluate the effect of DAC HYP on the PK of probe substrates for CYP isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A) in MS subjects	Single-arm, open-label study)	DAC HYP 150 mg SC by PFS every 4 weeks for 3 doses	12 weeks	20 enrolled; 20 completed	18 to 65 years, inclusive

CYP=cytochrome P450; DAC HYP=Daclizumab High-Yield Process; HV = healthy volunteer; IV=intravenous; MS=multiple sclerosis; PD=pharmacodynamic; PFS=prefilled syringe; PK=pharmacokinetic; RRMS=relapsing-remitting multiple sclerosis; SC=subcutaneous; TP-DI=therapeutic protein-drug interaction

[a]One subject was assigned to placebo but had measurable daclizumab concentrations in the PK samples at every timepoint. Therefore, this subject is not counted as a placebo subject.

[b]Twenty-seven of 32 subjects completed the 16-week treatment period, but none of these subjects received all of the planned doses because of a temporary suspension of dosing for a safety evaluation.

Pharmacokinetic Properties of Daclizumab (Zinbryta)

Daclizumab exhibits PK characteristics of a typical IgG1 mAb. Following SC administration, daclizumab absorption is believed to be mediated primarily via the lymphatic system with an observed Tmax of approximately 1 week. Daclizumab disposition is well characterized by a 2-compartment model with a first-order absorption and elimination. Linear PK was observed for doses greater than 100 mg, with the estimated absolute bioavailability for subcutaneous administration of 90%. A small volume of distribution was observed, indicating daclizumab is largely confined to the vascular and interstitial spaces. Daclizumab is not expected to undergo metabolism by hepatic enzymes such as CYP isoenzymes or renal elimination. A low systemic clearance and long elimination half-life (approximately 3 weeks) were observed. Steady state was achieved by Week 16 dosing daclizumab 150 mg SC every 4 weeks, with the resulting mean steady-state peak-to-trough concentration ratio of approximately 2 and an AUC accumulation ratio of approximately 2.5.

Single-Dose Pharmacokinetics of Daclizumab (Zinbryta)

A single-dose IV study was conducted in HVs at daclizumab doses of 200 mg and 400 mg (Study DAC-1018). Following a 30-minute IV infusion, daclizumab exhibited a low clearance (mean CL 10 mL/h), a low steady-state volume of distribution (mean Vss values from 5.89 to 6.53 L), and long elimination half-life (mean t1/2 values from 18 to 20 days). Dose-proportional increase in exposure was observed between 200 mg and 400 mg. Single-dose SC studies were performed in HVs at daclizumab doses of 50 mg, 75 mg, 150 mg, and 300 mg. Median Tmax was 6 to 7 days. Mean Cmax and AUC0-inf values increased more than dose proportionally between 50 and 150 mg and dose proportionally between 150 and 300 mg. A relatively long elimination half-life (mean t1/2 values from 17.2 to 24.9 days) was observed.

Multiple-Dose Pharmacokinetics of Daclizumab (Zinbryta)

Multiple-dose PK of DAC HYP was evaluated in HVs (DAC-1014) for 2 different dosing regimens: 200 mg SC every 2 weeks, and a 200 mg SC loading dose followed by 100 mg every 2 weeks. A total of 9 SC administrations over 16 weeks were planned for both regimens. However, dosing during the study was interrupted because of a temporary treatment suspension. As a result, none of the 24 daclizumab subjects received all 9 planned doses; 17 of 24 of daclizumab subjects received 7 or 8 doses. The daclizumab PK profile after multiple SC administrations showed a slow absorption (Tmax approximately 7 days after the first dose) and a long elimination half-life (approximately 15 days). Steady-state AUCtau values were estimated to be 8 mg.h/mL (100 mg every 2 weeks) and 16 mg.h/mL (200 mg every 2 weeks). Multiple-dose PK in MS subjects was characterized for daclizumab 150 mg SC every 4 weeks by PFS in 2 studies (302 and 203). PK parameters determined from these studies were comparable. Daclizumab PK following multiple SC administrations showed a slow absorption profile, with a median Tmax of approximately 5 days and a long elimination half-life (t1/2) of approximately 22 days. Daclizumab pre-dose concentrations in Study 302 revealed that steady state was reached by Week 16 of dosing (or Dose 4), which is consistent with the half-life. Repeated dosing of daclizumab every 4 weeks resulted in an approximately 2.5-fold drug accumulation at steady state.

Daclizumab (Zinbryta) Population Pharmacokinetics

Population PK of daclizumab were characterized using data from the Phase 1 studies in HVs who received daclizumab 50 to 300 mg SC (Study DAC-1014, Study DAC-1015) or 200 and 400 mg IV (Study DAC-1018), and from the Phase 2 and 3 studies in MS subjects who received 150 or 300 mg SC every 4 weeks (Study 201, Study 202, Study 302, and Study 301).

Population PK modelling was conducted using NONMEM 7 (version 2.0) with first-order conditional estimation with interaction (FOCEI) method. Perl Speaks NONMEM (PsN, Version 3.5.3) was used to conduct bootstrap and a visual predictive check (VPC) for model qualification. The program Xpose4 (version 4.3.2, Pharmacometrics Research Group, Uppsala University, Sweden), a module written for the statistical program R, was used to assist diagnostics.

Model development was performed in 2 stages: The initial model was developed without data from Study 301, and the final model was updated with data from Study 301 to obtain the final parameter estimates. Covariate modelling was performed in a stepwise forward addition and backward elimination manner. Examined covariates included body weight, age, sex, dose group, NAb, non-NAb, baseline percentages of CD4+ T cells staining positive for CD25, and baseline absolute CD25+CD4+ T cell counts. Race was not tested because of the limited sample size for races other than White.

A 2-compartment model with first-order absorption and elimination described the daclizumab PK well in both HVs and MS subjects. The point estimates from the final model and the median parameter estimates from the bootstrap datasets were similar.

For a typical subject with a body weight of 68 kg, clearance was 0.212 L/day, central and peripheral volumes of distribution (V2 and V3) were 3.92 L and 2.42 L, respectively, with a moderate IIV between 27% and 51%. The SC absorption half-life was 5 days with an absorption lag time of 1.61 hours, and SC bioavailability was 88% for the 100 to 300 mg dose levels and 55% for the 50 mg dose level. The terminal half-life was 21.4 days. Due to the low number of subjects with PK data usable to quantify the IOV of daclizumab, a model development with the full dataset was not possible. As such, the applicant provided an evaluation of the IOV in a subset of 26 subjects from the intensive PK subgroup in OBSERVE study. In this subset, IOV variability in CL and V2 (around 20%) was lower than the IIV.

Statistically significant covariates for daclizumab PK included body weight and the presence of NAbs. Body weight was a significant covariate for CL and V2, with exponents of 0.87 and 1.12, respectively, thereby explaining 37% and 27% of the IIV for CL and V2, respectively. Time-varying NAb-positive status increased daclizumab CL by 19%. The impact of these 2 covariate effects does not appear to be clinically relevant based on the following observations. In Study 301, no meaningful differences in safety or efficacy were observed among the subgroups by body weight quartile. There was no discernible impact of immunogenicity status (ADA or NAb) on the efficacy or safety profile of daclizumab.

Factors Influencing Pharmacokinetics and Special Populations

Daclizumab is not expected to undergo metabolism by hepatic enzymes or renal elimination. Therefore, no studies were conducted to evaluate daclizumab PK in patients with hepatic or renal impairment. However, the effect of ALT (similarly for AST) elevation on the pharmacokinetics of daclizumab (clearance, CL) was tested as a time-varying covariate within the context of the population PK model developed for daclizumab. According to these analyses, liver enzyme elevation was estimated to minimally increase clearance of daclizumab (~10%). This does not seem to be physiologically meaningful because in general, an adverse effect on the liver is expected to impair drug clearance instead of enhancing it. Given the small magnitude of estimated effect and almost no reduction in the overall inter-subject variability in clearance, it can be concluded that liver enzyme elevation is unlikely to have any clinically meaningful detrimental effect on the clearance of daclizumab. No apparent PK differences were observed between Japanese and Caucasian subjects following a single-dose administration of daclizumab 75 mg or 150 mg SC. Population PK analysis indicated that the PK parameters of daclizumab were not influenced by age (range 18 to 66 years) or sex of adult subjects. Population PK analysis showed that body weight was a significant covariate for daclizumabCL and central volume of distribution, explaining 37% and 27%, respectively, of the estimated IIV for these two parameters. Time-varying

NAb-positive status increased daclizumab CL by 19% on average. However, the impact of these 2 covariate effects on daclizumab exposure does not appear to be clinically relevant.

Overall, the pharmacokinetics of daclizumab are well characterized, and well described in the SmPC.

2.4.3. Pharmacodynamics

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling that is important for lymphocyte activation.

The immunogenicity of daclizumab was characterized as follows:

The incidence of immunogenicity to daclizumab 150 mg after multiple dosing of MS subjects with daclizumab showed the following results:

- Treatment-emergent ADAs were observed in 4% and 19% of evaluable subjects during the study in Study 201 and Study 301, respectively. Treatment-emergent neutralizing antibodies (NAbs) were observed in 3% and 8% of evaluable subjects in Study 201 and Study 301, respectively. The differences in the incidences of immunogenicity between the 2 studies appeared to be due primarily to more frequent immunogenicity testing at early timepoints and to a more sensitive assay being used in Study 301 than in Study 201;

- Pre-existing ADA reactivity at Baseline was observed in 4% and 6% of evaluable subjects in Study 201 and Study 301, respectively;
- The majority of ADA reactivity to daclizumab occurred early during treatment, and this reactivity decreased with continuing daclizumab treatment. ADA titers observed were generally low with only 3 persistent subjects in Study 301 reaching a titer of >1920 (highest titer observed in the transient category);
- The majority of subjects that exhibited immunogenicity showed transient responses;
- There was increased detection of observed immunogenicity during the washout of daclizumab;
- The immunogenicity profile of daclizumab administered by SC injection using the PFS was comparable to daclizumab administered from vials;
- Time-varying NAb status increased daclizumab clearance by 19% on average. However, the impact does not appear to be clinically relevant since there was no discernible impact of immunogenicity status on the efficacy, safety, or PD profile of daclizumab.

No relationship has been established between daclizumab plasma concentrations and the efficacy parameters use in the clinical studies, whether for relapses or MRI imaging. No relationship could be found either between daclizumab exposure and safety. No specific difference was seen with regards to PD depending on race.

2.4.4. Discussion and conclusions on clinical pharmacology.

Daclizumab is a humanized monoclonal antibody (mAb) of the immunoglobulin G1 (IgG1) isotype that binds to CD25, the alpha subunit of the high-affinity interleukin-2 receptor (IL-2R), and modulates IL-2 signalling that is important for lymphocyte activation.

Generally the PK and PD of daclizumab were well described and no additional measures are considered necessary.

2.5. Clinical efficacy

The clinical efficacy of daclizumab in the proposed indication was evaluated in three clinical trial:

- DAC-1012 a 6-month Phase 2 dose ranging study with DAC Penzberg
- Study 205MS201 a 1 year phase 2 Efficacy/MRI/safety study with DAC-HYP 150 mg and 300 mg SC every 4 weeks, with one year extension (study 202)
- Study 301, a Phase 3 study over 3 years with DAC-HYP 150mg SC every 4 weeks

In addition there were two extension studies form Study 205MS201, i.e. Study 202 (one year extension, completed) and Study 203, extension to Study 202, ongoing.

2.5.1. Dose response study(ies) and Main study(ies)

2.5.1.1. DAC-1012

DAC-1012 was a Phase 2 randomized, double-blind, placebo-controlled, multi-center, proof-of-concept, dose-ranging, parallel-design study comparing daclizumab and placebo in subjects receiving concurrent IFN β therapy for active, relapsing forms of MS. In this study, 2 regimens of DAC Penzberg (an investigational form of daclizumab) administered SC over a 24-week period (20 weeks plus 4 weeks follow-up) were compared to placebo; follow-up duration was 48 weeks.

DAC Penzberg is a different form of daclizumab with a different glycation; it was developed before daclizumab.

Patient population

Males or females, 18 to 55 years of age, inclusive; diagnosis of MS by McDonald criteria; score of ≤5.0 on the EDSS; taking a stable IFN-beta regimen (defined as at least 6 months on the same dose of the same drug product); had at least one MS relapse while taking stable IFN-beta regimen, or had a qualifying MRI, showing at least one confirmed Gd-CEL of the brain or spinal cord while taking stable IFN-beta regimen.

DAC-1012 was conducted in 51 investigational sites in the US, Canada and the European Union (Germany, Italy and Spain).

288 patients were screened and 230 were randomized; 214 (93%) completed 24 weeks of treatment and 194 (84%) completed follow-up through Week 72.

Treatment

The 2 DAC Penzberg regimens were 2 mg/kg every 2 weeks for a total of 11 doses (high dose) and 1 mg/kg every 4 weeks for a total of 6 doses (low dose). The study consisted of a 24-week treatment period, followed by a 48-week washout period, during which study drug was not administered, but continued on IFN-beta therapy for at least 5 months of the 48 weeks).

The doses of 1 mg/kg and 2 mg/kg were extrapolated from animal and clinical data.

Objectives: The primary objective was to evaluate the efficacy of daclizumab in patients who had active, relapsing forms of multiple sclerosis (MS) and were concurrently on interferon-beta (IFN-beta) therapy.

The secondary objectives were safety, PK and PD and immunogenicity (i.e., development of antibodies to daclizumab).

The primary efficacy endpoint was the total number of new or enlarged gadolinium contrast enhancing lesions (Gd-CELs) on monthly brain magnetic resonance imaging (MRI) collected between Weeks 8 to 24 in daclizumab versus placebo-treated patients. An enlarged lesion was defined as a greater than 50% increase if the lesion was <5 mm in diameter, and a 20% increase if the lesion was ≥5 mm in diameter; the enlargement was estimated visually and by the judgment of the reader.

Compared with placebo the effect of DAC Penzberg on reducing new Gd-enhancing lesions, the primary endpoint of Study DAC-1012, was robust and statistically significant in the high-dose arm 2 mg/kg every 2 weeks (p=0.0038), but was marginal and not statistically significant in the low-dose arm 1 mg/kg every 4 weeks (p=0.5138). Safety was similar between the low-dose and high-dose regimens.

Based on the results of Study DAC-1012, two daclizumab dosing regimens (150 mg and 300 mg SC every 4 weeks) were selected for further evaluation in Study 205MS201 based on the following considerations:

- The low-dose regimen from Study DAC-1012, which is approximately equivalent to a fixed-dose regimen of 75 mg SC every 4 weeks, was considered to be below the lowest efficacious dose. Furthermore, this regimen showed no evidence for an improved safety profile compared to the high-dose regimen. Therefore, daclizumab doses that were expected to provide similar exposures were not evaluated further.
- Daclizumab 300 mg SC every 4 weeks was projected to be approximately equal to the highest efficacious dose (2 mg/kg SC every 2 weeks) evaluated in Study DAC-1012.
- Daclizumab150 mg SC every 4 weeks was projected to be a lowest efficacious dose since it was between the low-dose and high-dose arms in Study DAC-1012.

2.5.1.2. Studies 205MS201 and 205MS301

Study 205MS201 was a double-blind, placebo-controlled, dose-ranging study to determine the safety and efficacy of daclizumab as a monotherapy treatment in subjects with RRMS. Two daclizumab dose regimens were studied: daclizumab 150 mg and 300 mg administered by SC injection once every 4 weeks. The study consisted of a 52-week (Weeks 0 through 52), double-blind, placebo-controlled, safety and efficacy treatment phase; and a 20-week (Weeks 52 through 72), double-blind, follow-up phase for subjects who did not enter the extension study (Study 202). The primary endpoint of Study 205MS201 was the annualized relapse rate between baseline and Week 52.

Upon completion of the 12-month treatment period in Study 205MS201, subjects were eligible to complete up to an additional 12 months of treatment with daclizumab in a double-blind extension (Study 205MS202 referred to as 202), which was completed in 2012. Study 202 also assessed the effects of daclizumab washout in some subjects who were treated with daclizumab in Study 205MS201. Subjects completing Study 202 could continue long-term therapy with open-label daclizumabin the ongoing extension Study 203, which is evaluating the long-term safety and efficacy of daclizumab monotherapy for an additional 6.5 years.

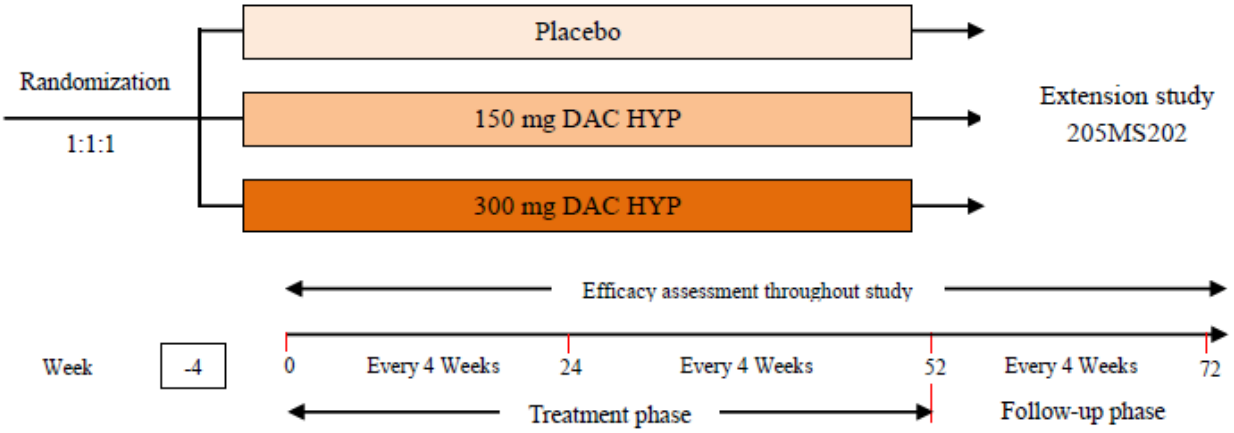


Figure 2 Design of study 205MS201

Study 205MS301 was a double-blind, randomized, parallel-group, monotherapy, active-control study to determine the efficacy and safety of daclizumab versus interferon beta-1a (IFN β-1a) in patients with RRMS. Two treatment groups were studied: Daclizumab 150 mg SC once every 4 weeks for 96 to 144 weeks and IFN β-1a 30 µg intramuscular (IM) injection once weekly for 96 to 144 weeks. Subjects were treated in this study for at least 96 weeks but no more than 144 weeks.

The primary efficacy endpoint of the study was the annualized relapse rate. Subjects who completed the treatment period and who met study entry criteria were eligible to enrol in the open-label extension (Study 303) to either continue (subjects treated with daclizumab in Study 301) or start (subjects treated with IFN β-1a in Study 301) dosing with daclizumab. Those subjects who did not enrol in the open-label extension study remained in a 24-week, blinded, post-dosing, safety follow-up period.

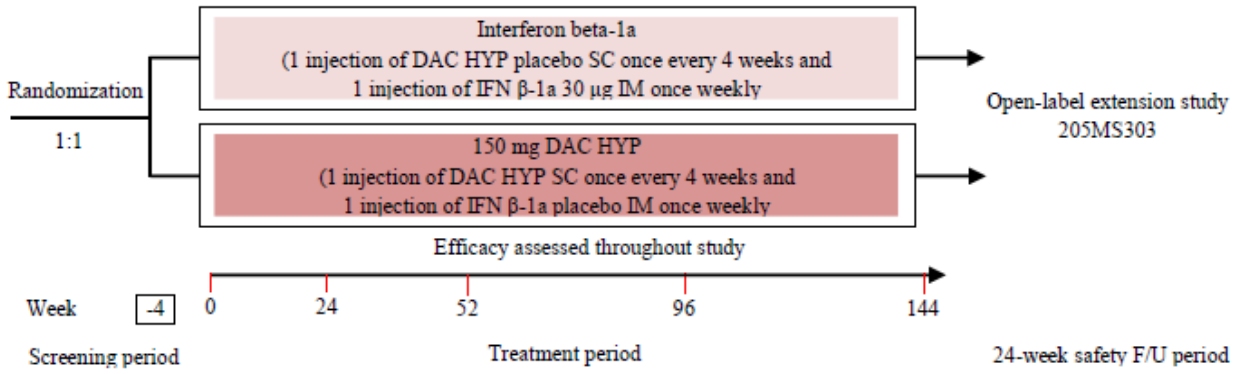


Figure 3 Design of Study 205MS301

- The following tables summarize the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment sections.

Table 11 Summary of efficacy for trial 205MS201

Title: Multicenter, Double-Blind, Placebo-Controlled, Dose-Ranging Study to Determine the Safety and Efficacy of Daclizumab (DAC HYP/Zinbryta) as a Monotherapy Treatment in Subjects with Relapsing-Remitting Multiple Sclerosis			
Study identifier	205MS201		
Design	Multicenter, Randomized, Double-blind, Placebo-controlled, Dose-ranging		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		1 year not applicable 1 year (205MS202) + up to 6.5 years (205MS203)
Hypothesis	Superiority		
Treatments groups	Placebo		Placebo SC every 4 weeks, for 1 year, 204 pts
	Daclizumab150mg		Daclizumab150 mg SC every 4 weeks, for 1 year, 208 pts
	Daclizumab300mg		Daclizumab300 mg SC every 4 weeks, for 1 year, 209 pts
Endpoints and definitions	Primary endpoint	Annualized relapse rate	Annualized relapse rate
	Secondary endpoint	new Gd+ lesions	Number of new Gd+ lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 in a subset of subjects
	Secondary endpoint	newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions at Week 52
	Secondary endpoint	% relapsing subjects	Proportion of relapsing subjects between baseline and Week 52
	Secondary endpoint	Change in MSIS-29 physical score	Change in MSIS-29 physical score at Week 52 compared to baseline
Database lock	04 November 2011		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat 52 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Daclizumab150mg	Daclizumab300mg
	Number of subject	196	201	203
	Primary endpoint			
	Primary endpoint Annualized relapse rate (adjusted)	0.458	0.211	0.230
	(95% CI)	(0.370-0.566)	(0.155-0.287)	(0.172-0.308)
	Secondary endpoints			

	Adjusted mean number of new Gd lesions (week 8 to 24)	4.79	1.46	1.03
	(95% CI)	(3.56, 6.43)	(1.05, 2.03)	(0.73, 1,46)
	New or Newly Enlarging T2 Hyperintense Lesions at Weeks 52 (Adjusted mean)	8.13	2.42	1.73
	(95% CI)	(6.65, 9.94)	(1.96, 2.99)	(1.39-2.15)
	Estimated proportion of subjects relapsed by 52 weeks	0.36	0.19	0.20
	Unadjusted Mean change from baseline in MSIS-29 physical score at week 52 (SD)	3.0 (13.52)	-1.0 (11.80)	1.4 (13.53)
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 52	0.133	0.059	0.078
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 52	0.111	0.026	0.068

Effect estimate per comparison	Annualized relapse rate	Comparison groups	Placebo vs. Daclizumab 150 mg
		ARR ratio	0.461
		95% CI	(0.318 0.668)
		P-value	P< 0.0001
	Adjusted mean number of new Gd lesions (week 8 to 24)		Placebo vs. Daclizumab150 mg
		Lesion mean ratio	0.305
		95% CI	0.196, 0.476
		P-value	P < 0.0001
	New or Newly Enlarging T2 Hyperintense Lesions at Weeks 52 (Adjusted mean)		Placebo vs. Daclizumab 150 mg
		Lesion mean ratio	0.298
		95% CI	(0.221, 0.409)
		P-value	P <0.0001
	Estimated proportion of subjects relapsed	Comparison groups	Placebo vs. Daclizumab 150 mg
		Hazard ratio	0.45

	by 52 weeks	95% CI	(0.30, 0.67)
		P-value	P< 0.0001
	Unadjusted Mean change from baseline in MSIS-29 physical score at week 52	Comparison groups	Placebo vs. Daclizumab 150 mg
		Relative mean change	-4.27
			-6.76, -1.78
			0.0008
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 52	Comparison groups	Daclizumab 150mg vs. placebo
		Hazard ratio	0.43
		95% CI	(0.21, 0.88)
		P-value	P=0.0211
		Comparison groups	Daclizumab 300mg vs. placebo
		Hazard ratio	0.57
		95% CI	(0.30, 1.09)
		P-value	p=0.0905
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 52	Comparison groups	Daclizumab 150mg vs. placebo
		Hazard ratio	0.24
		95% CI	(0.09, 0.63)
		P-value	P=0.0037
		Comparison groups	Daclizumab 300mg vs. placebo
		Hazard ratio	0.60
		95% CI	(0.30, 1.20)
		P-value	p=0.1487

Table 12 Summary of efficacy for trial 205MS301

Title: Multicenter, Double-blind, Randomized, Parallel-group, Monotherapy, Active-control Study to Determine the Efficacy and Safety of Daclizumab High Yield Process (DAC HYP) versus Avonex® (Interferon β-1a) in Patients with Relapsing-Remitting Multiple Sclerosis			
Study identifier	205MS301		
Design	Multicenter, double-blind, randomized, parallel-group, monotherapy, active-control study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		96-144 weeks not applicable Up to 5 years (205MS303)
Hypothesis	Superiority		
Treatments groups	IFN β-1a 30 µg		IFN β-1a 30 µg IM every week, for96-144 weeks, 922 pts
	DAC HYP 150 mg		Daclizumab150 mg SC every 4 weeks, for96-144 weeks, 919 pts
Endpoints and definitions	Primary endpoint	Annualized relapse rate	Annualized relapse rate
	Secondary endpoint	newly enlarging T2 hyperintense lesions	Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks
	Secondary endpoint	% confirmed disability progression	Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from baseline EDSS ≥1.0 that is sustained for 12 weeks or at least a 1.5-point increase on the EDSS from baseline EDSS = 0 that is sustained for 12 weeks
	Secondary endpoint	% relapse-free	Proportion of subjects who are relapse-free
	Secondary endpoint	% of subjects with a significant worsening the MSIS-29 Physical Impact score	Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks
Database lock	16 September 2014		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat – all patients randomised and treated		
Descriptive statistics and estimate variability	Treatment group	IFN β-1a 30 µg	Daclizumab 150 mg
	Number of subject	922	919

	Primary endpoint		
	Annualized relapse rate (adjusted)	0.393	0.216
	(95% CI)	(0.353, 0.438)	(0.191, 0.244)
	Secondary endpoints		
	Adjusted mean number of new or newly Enlarging T2 Hyperintense Lesions at Week 96	9.44	4.31
	(95% CI)	(8.46, 10.54)	(3.85, 4.81)
	Estimated proportion progressed (sustained increase in EDSS for 12 weeks) at week 96	0.143	0.120
	Estimated proportion of subjects relapse free at week 96	0.585	0.729
	% of patients with clinically meaningful worsening in MSIS-29 Physical Impact score	23	19
	Tertiary endpoint		
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks) at week 96	0.121	0.092

Effect estimate per comparison	Annualized relapse rate	Comparison groups	(% reduction Daclizumab 150 mg vs. IFN β-1a)
		ARR ratio	0,550
		95% CI	(0.469, 0.645)
		P-value	P<0.0001
	Adjusted mean number of new or newly Enlarging T2 Hyperintense Lesions at Weeks 96	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Lesion mean ratio	0.46
		95% CI	(0.39, 0.53)
		P-value	P<0.0001
	Estimated proportion progressed (sustained	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.84
		95% CI	(0.66, 1.07)

	increase in EDSS for 12 weeks)	P-value	P=0.1575
	Estimated proportion of subjects relapse free	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.59
		95% CI	(0.50, 0.69)
		P-value	P<0.0001
	% of patients with clinically meaningful worsening in MSIS-29 Physical Impact score	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Odds ratio	0.76
		95% CI	(0.60, 0.95)
		P-value	P= 0.0176
	Estimated proportion progressed (sustained increase in EDSS for 24 weeks)	Comparison groups	Daclizumab 150 mg vs. IFN β-1a
		Hazard ratio*	0.73
		95% CI	(0.55, 0.98)
		P-value	p=0.0332
Notes	* calculated over the treatment period up to 144 weeks.		

2.5.1.2.1. Study 205MS201

Methods

- **Treatments**

Subjects were randomized in a 1:1:1 ratio to receive 1 of the following doses:

- Group 1: placebo (3 SC injections every 4 weeks for a total of 13 doses)
- Group 2: 150 mg daclizumab (3 SC injections every 4 weeks for a total of 13 doses)
- Group 3: 300 mg daclizumab (3 SC injections every 4 weeks for a total of 13 doses)

Concomitant therapies

Symptomatic therapy, such as treatment for spasticity, depression, or fatigue were not restricted, but were optimized as early as possible during screening in an attempt to maintain consistent treatment for the duration of the study.

Subjects were instructed not to start taking any new medications, including non-prescribed drugs, unless they received permission from the Investigator.

Disallowed therapies

Any alternative drug treatments directed towards the treatment of MS, such as chronic immunosuppressant therapy or other immunomodulatory treatments, with the exception of acute management of a protocol-defined relapse.

Any investigational product, including investigational symptomatic therapies for MS and investigational therapies for non-MS indications. Any monoclonal antibodies other than daclizumab IV Ig, cladribine, plasmapheresis or cytapheresis, total lymphoid irradiation, or T-cell or T-cell receptor vaccination

Any systemic steroid therapy including, but not limited to, oral corticosteroids (e.g., prednisone) or periodic (e.g., monthly) treatment with IV methylprednisolone (IVMP), except for protocol-defined

treatment of relapses. Steroids that were administered by non-systemic routes (e.g., topical, inhaled) were allowed.

- **Objectives**

Primary objective

The primary objective of this study was to determine whether daclizumab, when compared to placebo, is effective in reducing the rate of relapses between baseline and Week 52. The primary endpoint was the change in annualized relapse rate between baseline and Week 52.

Secondary Objectives

The secondary objectives were to determine whether daclizumab is effective in:

- Reducing the number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects
- Reducing the number of new or newly enlarging T2 hyperintense lesions at Week 52
- Reducing the proportion of relapsing subjects between baseline and Week 52
- Improving quality of life as measured by the MSIS-29 physical score at Week 52 compared to baseline

Tertiary Objectives

There were a number of tertiary objectives including:

- slowing the progression of disability as measured 12 weeks, reduction in the number of new or newly enlarging T2 hyperintense lesions at Week 24 compared to baseline
- MRI: reduction of the number of Gd-enhancing lesions at Week 52 compared to baseline, reduction of the volume of new T1 hypointense lesions at Week 24 and Week 52 compared to baseline, reduction of the total lesion volume of new and newly enlarging T2 hyperintense lesions at Week 24 and Week 52 compared to baseline and at Week 52, reduction of the volume of non-Gd enhancing T1 hypointense ("blackholes") lesions at Week 24 and week 52 compared to baseline and at Week 52, efficacy in reducing brain atrophy on MRI at Week 24 over the 52-week treatment period, the efficacy of daclizumab in reducing the total lesion volume of T2 hyperintense lesions over the 52-week treatment period
- safety and tolerability
- time to relapse and disability progression from baseline to Week 52
- efficacy the subject's global impression of well-being as measured by a Visual Analogue Scale (VAS)
- efficacy on quality of life as measured by the MSIS-29 psychological scale, the SF-12, and the EQ-5D

- **Outcomes/endpoints**

Clinical Efficacy variables

Relapses

Definition of relapse

Relapses were defined as new or recurrent neurologic symptoms not associated with fever or infection, lasting at least 24 hours, and accompanied by new objective neurological findings upon examination by the examining neurologist. New or recurrent neurologic symptoms that evolved gradually over months

were considered disease progression, not an acute relapse. New or recurrent neurologic symptoms that occurred less than 30 days following the onset of a protocol-defined relapse were considered part of the same relapse.

Evaluation of relapse cases by INEC

Independent Neurology Evaluation Committee (INEC): The INEC was established for the purpose of obtaining a consistent and independent blinded determination of whether a subject had experienced an MS relapse as defined by the protocol. The INEC included 5 members, all of whom were neurologists with expertise in MS.

Note: INEC-confirmed relapses were the primary way to define relapse in efficacy analyses. In sensitivity analyses of relapse outcomes, all relapses determined by the Investigator to meet the protocol definition of relapse were evaluated regardless of whether they were INEC-confirmed. In addition, all MS relapses as determined by the Investigator were captured as AEs of MS relapse and reported in safety tabulations regardless of whether they met the protocol definition of relapse or whether they were INEC-confirmed.

Disability Progression

Disability progression was assessed using the EDSS, an ordinal scale used to measure neurological impairment and disability [Kurtzke 1983]. Functional Scores (FS) scores were determined using the Neurostatus scoring worksheet and definitions (Version 12/05). The FS and the furthest distance the subject was able to walk without aid or rest were recorded along with the EDSS score on the CRF.

In this study, tentative EDSS progression was defined as a minimum change (i.e., at least a 1.0 point increase on the EDSS from baseline EDSS 1.0 or at least a 1.5 point increase on the EDSS from baseline EDSS = 0) that was present on a scheduled or unscheduled study visit. EDSS progression was considered confirmed when this minimum EDSS change was present on the next study visit occurring after 74 days from the initial observation.

Progression had to start prior to the end of the Week 52 treatment period but could have been confirmed either during the 205MS201 follow-up period or during the 205MS202 extension study. Progression was not confirmed at a visit where a relapse was also occurring.

MRI imaging

The MRI assessments were conducted at baseline (any time from screening to the baseline visit) and at Weeks 24, 36, and 52. In this MRI-intensive cohort (the first 307 subjects enrolled in the study), MRIs were also performed every 4 weeks between baseline and Week 24.

Professor Radue in Basel, Switzerland was selected by Biogen Idec to read and interpret all MRIs for this study.

DaclizumabPD Assessments

- Pharmacodynamic assessments
- The assessment of cell-mediated immunity using Cylex® Immunknow™ assay
- The assessment of CD25 expression on peripheral T cells (CD25 assay)
- Expanded lymphocyte phenotyping addressing T and cluster of differentiation (CD)56+ natural killer (NK) cells.
- Whole blood samples were collected and frozen for possible future ribonucleic acid (RNA) and DNA transcription profiling and genotyping, respectively

- Identification and/or analysis of serum biomarkers that may relate to daclizumab efficacy or MS disease activity such as soluble CD25 level. Serum collected for other assessments could have also been used for biomarker analysis.

• **Sample size**

It was assumed that if subjects were not allowed to add IFN-β during the study, the annualized relapse rate in the placebo group would be 0.50. However, because subjects were permitted to add IFN-β as a treatment for relapse, the annualized relapse rate in the placebo group would be reduced to 0.476 while the rate in the daclizumab group would stay the same. In this setting, a sample size of 198 subjects per treatment group would have approximately 90% power to detect a 50% reduction in the annualized relapse rate between a daclizumabtreatment group and placebo. Power was estimated from simulations assuming a negative binomial distribution, a 10% drop out rate, and a 5% type 1 error rate. Based on these assumptions, a sample size of 594 subjects would be required for the study.

• **Randomisation**

Subjects were randomized to receive daclizumab at doses of 150 mg or 300 mg every 4 weeks or placebo, with equal randomization (1:1:1) into each of the 3 treatment groups.

Randomization took place across all study sites using a centralized interactive voice response system (IVRS). The randomization was not stratified.

• **Blinding (masking)**

This study was double-blind. Treatment assignments were generated and assigned centrally through the IVRS system.

Except for the pharmacist (or designee) who was responsible for preparing the study treatment, all study staff and subjects were blinded to treatment. The Pharmacist did not have any interaction with the subjects and was strictly instructed not to communicate any information that could potentially unblind study personnel or the Sponsor to treatment assignment.

To further protect the blind during the study, a separate Treating Neurologist and Examining Neurologist were designated at each investigational site. The Treating Neurologist functioned as the primary treating physician during the study. The Examining Neurologist conducted all EDSS evaluations and relapse assessments but was not involved in any other aspect of subject care and was instructed to limit all interactions with subjects to the minimum necessary to perform the required neurologic examinations.

• **Statistical methods**

Analysis Populations

All analysis populations were defined and documented prior to database lock and were as follows:

Intent-to-treat (ITT) Population: The ITT population was defined as all randomized subjects who received at least 1 dose of study treatment. Subjects from 1 site (Site 903) were prospectively excluded from the ITT population after it was found that there was systematic misdosing by the unblinded pharmacist at the site. Subjects were analyzed according to the treatment to which they were randomized. Efficacy endpoints were evaluated using the ITT population. The efficacy analyses performed on the ITT population were considered the primary analyses.

Efficacy Evaluable Population: The efficacy-evaluable population was defined as all subjects in the ITT population who (1) had no missing MRI data from Weeks 8, 12, 16, 20, and 24 and (2) did not take prohibited alternative MS medications. MRI scans for these subjects were to be performed within $\pm$14

days of the target study day. The number of new Gd-enhancing lesions was evaluated using the efficacy evaluable population. The analyses based on the efficacy-evaluable population were considered supportive analyses.

Safety Population: The safety population included all subjects who received at least 1 dose of study treatment and had at least 1 post-baseline assessment of the safety parameter being analyzed. The safety population was used to analyze safety data.

Subjects Excluded From Analyses

Site 903 - was closed for misconduct and closure of Site 903 produced an ITT population of 196 subjects in the placebo group, 201 subjects in the Daclizumab 150 mg group, and 203 subjects in the Daclizumab 300 mg group. However, the 21 subjects excluded from the efficacy analyses were included in the safety analyses, and sensitivity analyses were performed to assess any effects their inclusion may have had on safety and efficacy analyses.

Efficacy analyses

Control of Type I Error Rate

Statistical testing for efficacy endpoints was performed between the Daclizumab 300 mg group and placebo and the Daclizumab 150 mg group and placebo separately. A sequential, closed testing procedure was used to control the overall type I error rate that might result from multiple comparisons. If the first comparison (300 mg versus placebo) was statistically significant ($p \leq 0.05$), then the second comparison (150 mg versus placebo) was tested at the $\alpha = 0.05$ significance level. However, if the first comparison was not statistically significant, then the second comparison was not considered statistically significant.

In order to control for a type I error for the secondary endpoints, the sequential closed testing procedure included both the order of the secondary endpoints and the order of testing of the dose groups. Specifically, for each of the secondary endpoints, a sequential closed testing procedure was used, with the first comparison (the Daclizumab 300 mg group versus placebo) and the second comparison (the Daclizumab 150 mg group versus placebo). Secondary endpoints were rank prioritized, in the following order:

1. The number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects
2. The number of new or newly enlarging T2 hyperintense lesions at Week 52
3. The proportion of relapsing subjects between baseline and Week 52
4. The change in MSIS-29 physical score at Week 52 compared to baseline

Tertiary supportive analyses did not include adjustments made for multiple comparisons and endpoints.

Model Characteristics

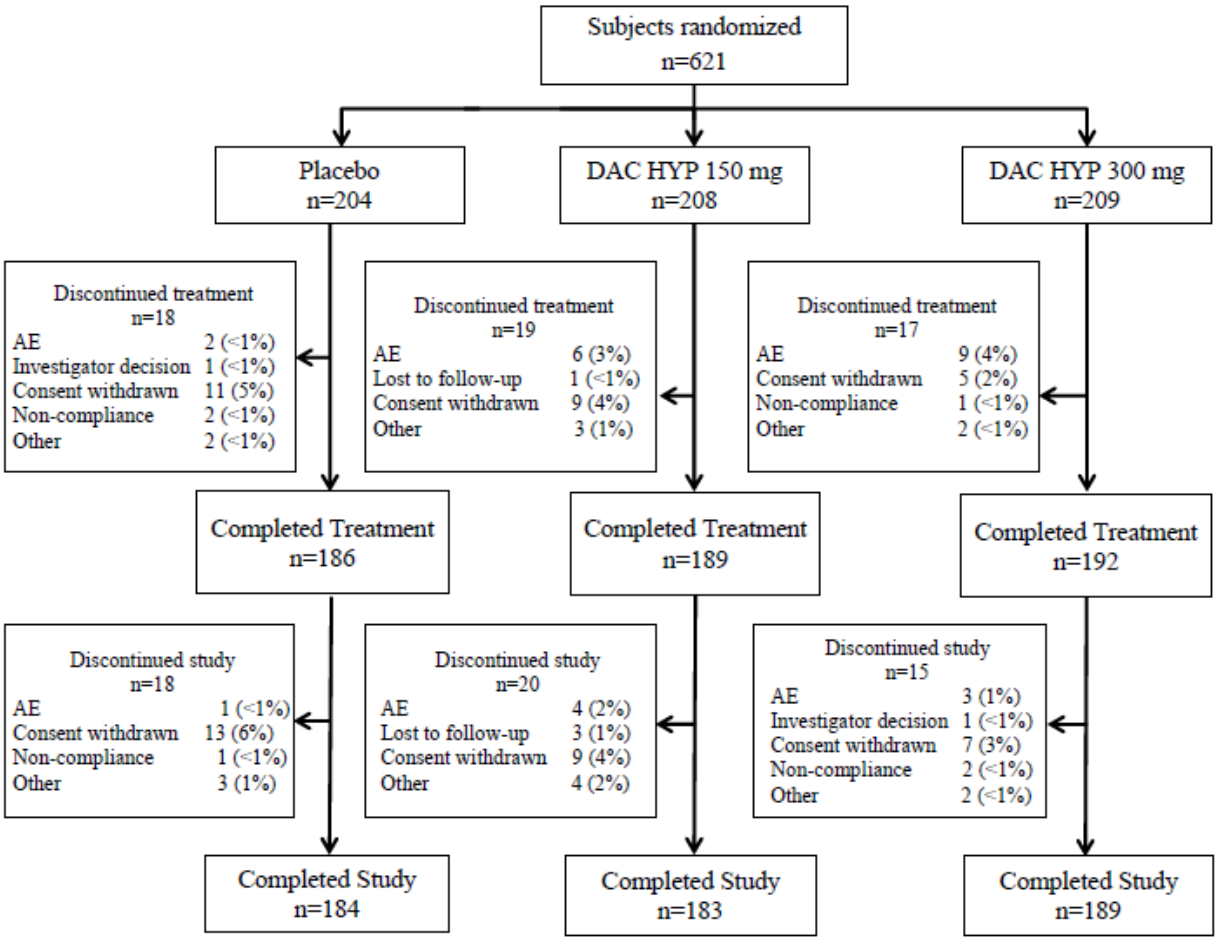
For the relapse endpoints (annualized relapse rate and proportion of relapsing subjects), the analysis models were adjusted for the number of relapses in the 1-year prior to study entry, baseline EDSS (EDSS 2.5 versus EDSS >2.5), and baseline age (age 35 versus age >35 years). For the disability progression endpoint, the model included a term for baseline EDSS (EDSS 2.5 versus EDSS >2.5) and baseline age (age 35 versus age >35 years). Other secondary and tertiary analyses included a term for treatment group and the baseline factor only.

All statistical tests were 2-sided with an overall Type I error rate of 0.05%.

RESULTS

- **Participant flow**

A total of 621 subjects (204 placebo; 208 Daclizumab 150 mg; 209 Daclizumab 300 mg) were randomized at 78 investigational sites in the Czech Republic, Germany, Hungary, India, Poland, Russia, Turkey, the Ukraine, and the United Kingdom. Evidence of deliberate misdosing was detected at 1 site during study monitoring, prompting the prospective exclusion of 21 subjects from the efficacy analysis prior to study completion, resulting in an ITT population of 196 subjects in the placebo group, 201 subjects in the Daclizumab 150 mg group, and 203 subjects in the Daclizumab 300 mg group. The 21 excluded subjects were included in the safety analysis.



Subjects who withdrew during the Study 201 follow-up period to enroll in the extension study were excluded from the total number of subjects who completed the study.
Source: CSR 205MS201, Table 14.

Figure 4 Study 205MS201- Subject Disposition

- **Recruitment**

The study started on 15 February 2008, with end of study date of 30 August 2011.

Clinical study report is dated 15 February 2013.

- **Conduct of the study**

The original protocol included one placebo group and three active groups, i.e. 25 mg, 100mg and 200mg. Doses of 150 mg and 300 mg were ultimately selected based on the fact that a minimum plasma concentration of 51 µg/ml would be need for the saturation of the CD25 receptor. Sample size was updated as a result.

- **Baseline data**

Demographic data

Table 13 Demographic data

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Age (yrs)				
18-19	1 (<1)	4 (2)	5 (2)	10 (2)
20-29	46 (23)	55 (26)	53 (25)	154 (25)
30-39	79 (39)	73 (35)	90 (43)	242 (39)
40-49	60 (29)	67 (32)	49 (23)	176 (28)
50-55	18 (9)	9 (4)	12 (6)	39 (6)
n	204	208	209	621
Mean	36.6	35.3	35.2	35.7
SD	9.02	8.94	8.67	8.88
Median	37.0	36.0	35.0	35.0
Min, Max	19, 55	18, 54	18, 55	18, 55
Sex				
Female	128 (63)	140 (67)	134 (64)	402 (65)
Male	76 (37)	68 (33)	75 (36)	219 (35)
Race				
White	197 (97)	202 (97)	200 (96)	599 (96)
Asian	7 (3)	6 (3)	9 (4)	22 (4)
Black or African American	0	0	0	0
American Indian or Alaska native	0	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0	0
Other	0	0	0	0
Height (cm)				
n	204	207	209	620
Mean	169.54	169.93	169.33	169.60
SD	9.424	9.805	9.879	9.694
Median	169.00	168.00	168.00	168.00
Min, Max	140.0, 202.0	149.0, 198.0	150.0, 196.0	140.0, 202.0

Weight (kg)				
n	203	207	209	619
Mean	69.99	68.31	68.20	68.82
SD	14.443	15.878	15.195	15.185
Median	68.00	64.00	66.50	66.30
Min, Max	40.0, 141.0	38.2, 130.0	33.0, 118.0	33.0, 141.0
Body mass index (kg/m^2)				
n	203	207	209	619
Mean	24.30	23.53	23.63	23.82
SD	4.566	4.474	4.129	4.398
Median	23.57	22.79	23.01	23.05
Min, Max	17.3, 52.4	15.7, 40.3	13.1, 39.9	13.1, 52.4
Body surface area (m^2)				
n	203	207	209	619
Mean	1.81	1.79	1.78	1.79
SD	0.212	0.239	0.235	0.229
Median	1.78	1.73	1.77	1.76
Min, Max	1.3, 2.5	1.3, 2.7	1.2, 2.4	1.2, 2.7

NOTE: Numbers in parentheses are percentages.

SOURCE: DACMS/205MS201/CSR/T-DM-DEMOG.SAS DATE: 27DEC2011

According to the data patients had 2.4 relapses in the past 3 years, with 1.4 relapses in the past 12 months alone and with a time lapse of 5.5 months on average since the last relapse.

The maximum EDSS score at entry into the study was 5. Patients presented with a mean EDSS score of 2.7, which complies with the characteristics for most patients enrolled in clinical trials for MS. Most patients presented with McDonald criterion 1, i.e. 2 or more relapses and 2 or more objective lesions. It should be noted that patients in the low daclizumab group had a slightly higher median EDSS score (3.0 instead of 2.5 in the other groups).

Baseline MRI (main)

Patients had a mean number of T2 lesions of 39.5, 44.6 and 35.9 respectively in the placebo, 150 mg Daclizumab and 300 mg Daclizumab. The difference between the two daclizumab groups is important, corresponding to a 40% increase in volume.

The mean volume of T1 hypointense lesions was largely comparable between pplacebo and active, with 2238.0, 2738.4 and 2030.5 mm3 in the placebo, the 150mg Daclizumab and the 300mg Daclizumab groups respectively. The difference between the two active groups is nevertheless notable.

The number of Gd-enhancing lesions was similar between the placebo and the Daclizumab 150mg (2.0 and 2.1 respectively) but was only 1.4 in the 300 mg Daclizumab group.

There was no notable difference between groups for the normalised brain volume.

Altogether the 300mg Daclizumab group presented with a lesser burden of T2 lesions accompanied by a lesser volume of T1 hypointense lesions as compared to placebo and especially to the 150 mg Daclizumab group.

Prior MS therapy

Table 14 Prior use of approved MS therapy

	Placebo	150 mg DAC HYP	300 mg DAC HYP	Total
Number of subjects randomized	204 (100)	208 (100)	209 (100)	621 (100)
Number of subjects with prior use of approved RRMS treatments	26 (13)	41 (20)	31 (15)	98 (16)
INTERFERON BETA-1B	8 (4)	20 (10)	16 (8)	44 (7)
INTERFERON BETA-1A	10 (5)	15 (7)	11 (5)	36 (6)
GLATIRAMER	8 (4)	9 (4)	9 (4)	26 (4)
NATALIZUMAB	0	2 (<1)	0	2 (<1)
MITOXANTRONE	1 (<1)	0	0	1 (<1)

NOTE 1: Numbers in parentheses are percentages.
2: Prior use of approved RRMS treatments INTERFERON BETA-1A, INTERFERON BETA-1B, NATALIZUMAB, GLATIRAMER and MITOXANTRONE were included in this table.

SOURCE: DACMS/205MS201/CSR/T-CM-PREVMS-EXCL-CORT1.SAS DATE: 09AUG2012

20% of patients in the in the 150mg Daclizumab group had prior treatment for MS (mainly Interferon) as compared to 13% in the placebo group and 15% in the 300mg group.

Concomitant medication

Concomitant medication during Study 205MS201 was similar between groups with a higher frequency of patients receiving methylprednisolone in the placebo group; time on treatment was comparable between groups.

To note IFN-β was taken as a protocol-allowed concomitant medication after Month 6 in subjects experiencing a relapse by 7 subjects in the study (5 in the placebo group and 1 each in the Daclizumab 150 mg and Daclizumab 300 mg groups).

- **Numbers analysed**

ITT population**:** The ITT population includes all randomized subjects who received at least 1 dose of study medication, excluding 21 subjects from Site 903. Subjects were analyzed according to the treatment group to which they were randomized (196 subjects in the placebo group, 201 subjects in the Daclizumab150 mg group, and 203 subjects in the Daclizumab 300 mg group).

Efficacy-evaluable population**:** The efficacy-evaluable population includes subjects in the ITT population with non-missing MRI data from Weeks 8, 12, 16, 20, and 24 who did not take prohibited alternative MS medications during the treatment period and who had their baseline MRI scan prior to their first dose of study treatment.

Subjects must have had their MRI scans carried out within 14 days of the target study day as indicated on the study activities chart.

- **Outcomes and estimation**

Primary efficacy endpoint analysis

The primary analysis of the annualized relapse rate was based on INEC-confirmed relapses and it included data from all subjects in the ITT population until either the end of the treatment period, a switch to alternative MS medication, or withdrawal from the study. Treatment group differences were compared

using a negative binomial regression model adjusted for the number of relapses in the 1 year prior to study entry, baseline EDSS (2.5 vs. >2.5), and age (35 vs. >35 years).

The adjusted annualized relapse rate in the placebo group was 0.458 [95% CI: 0.370, 0.566], compared to 0.211 [95% CI: 0.155, 0.287] in the Daclizumab 150 mg group and 0.230 [95% CI: 0.172, 0.308] in the Daclizumab 300 mg group. The annualized relapse rate ratio was 0.461 (95% CI: 0.318, 0.668) for Daclizumab 150 mg versus placebo and 0.503 (95% CI: 0.352, 0.721) for Daclizumab 300 mg versus placebo, indicating that the annualized relapse rate was reduced by 54% in the Daclizumab 150 mg group ($p<0.0001$) and by 50% ($p = 0.0002$) in the Daclizumab 300 mg group, compared with placebo (Table 15).

Table 15 Primary analysis - Annualized Relapse Rate between Baseline and Week 52 - Negative Binomial Regression

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Number of relapses			
0	127 (65)	163 (81)	163 (80)
1	52 (27)	33 (16)	34 (17)
2	15 (8)	5 (2)	5 (2)
3	2 (1)	0	1 (<1)
>= 4	0	0	0
Total number of relapses	88	43	47
Total subject-years followed	190.39	193.90	197.51
Unadjusted annualized relapse rate (a)	0.462	0.222	0.238
Adjusted relapse rate (95% CI) (b)	0.458 (0.370,0.566)	0.211 (0.155,0.287)	0.230 (0.172,0.308)
Rate ratio (95% CI)(b)		0.461 (0.318,0.668)	0.503 (0.352,0.721)
p-value vs placebo		<0.0001	0.0002
Subject relapse rate (c)			
n	196	201	203
Mean	0.484	0.229	0.250
SD	0.7958	0.5419	0.6024
Median	0.000	0.000	0.000
25th, 75th percentile	0.000, 1.001	0.000, 0.000	0.000, 0.000
Min, Max	0.00, 4.96	0.00, 4.20	0.00, 4.94

Note 1: Numbers in parentheses are percentages.
2: Data after subjects switched to alternative MS medications are excluded.
(a) Total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.
(b) Estimated from a negative binomial regression model adjusted for the number of relapses in the 1 year prior to study entry (p= 0.005), baseline EDSS (<= 2.5 vs > 2.5, p= 0.411), and age (<= 35 vs > 35, p= 0.063).
(c) Number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics are presented.

SOURCE: DACMS/205MS201/CSR/T-ARR-BS-NB.SAS DATE: 27DEC2011

The primary endpoint has been met for both dose groups. The benefit seemed similar in the two dose groups, with a 50% reduction in relapse rates in the 300mg group (as evidenced by the rate ratio of 0.50) and a 54% reduction in the 150mg group (from the 0.46 rate ratio). Both results were highly statistically significant, with the upper bound of the confidence interval for the rate ratio being well below 1.00.

Even without formal statistical analysis the benefit is clear, with approximately twice as many relapses in the placebo group compared to both active groups, the number of patients reporting 0 relapses about

15% higher in the active groups compared to placebo, and the placebo group having more patients in all of the 1, 2 and 3 relapse categories.

Sensitivity analyses

Multiple sensitivity analyses were performed to assess the robustness of the primary analysis. Alterations were made to the regression model parameters used to assess treatment effects on the annualized relapse rate:

b) using a Poisson regression model instead of a negative binomial regression model

c) excluding time and relapses that occurred after stopping study treatment (c)

d) including time on study and relapses that occurred after starting alternative MS medications

e) excluding relapses and follow-up time that occurred after starting protocol allowed concomitant use of IFN-

f) adjusting the analysis only for the number of relapses in the 1 year prior to study entry

g) including all relapses that met the protocol-defined objective relapse criteria (INEC confirmed or not)

h) including the 21 subjects from Site 903 who had been prospectively excluded from the ITT population

The results of these sensitivity analyses were all supportive and similar to the primary analysis presented above, indicating that the primary result was robust to a range of factors, including modelling assumptions, use of concomitant therapies that can affect annualized relapse rate, and the exclusion of subjects from 1 site from the ITT population.

Subgroup analyses

Predefined subgroups were evaluated for the primary efficacy endpoint (annualized relapse rate). The predefined subgroups included the following and the Daclizumab 150 and Daclizumab300 were combined:

- gender (male vs. female)
- age (>35 vs. ≤ 35 years)
- weight (≥ median vs. < median)
- number of relapses in the past 12 months (≤ 1 vs. >1)
- baseline EDSS (>2.5 vs. ≤ 2.5)
- baseline Gd lesions (present vs. absent)
- baseline CD25 (≥ median vs. < median)
- soluble CD25 (≥ median vs. < median)
- CD25 SNP rs2104286 (CC+TC vs. TT)

In addition as a post-hoc analysis:

- subjects who received prior MS medication (yes vs. no)
- disease activity at baseline (high vs. low)

High disease activity at baseline was defined as ≥ 2 relapses in year prior to randomization and ≥ 1 Gd-enhancing lesion at baseline.

Subgroup analyses demonstrated that daclizumab was effective across all demographic and baseline characteristic subgroups. While there was minor variation in treatment effect estimates across the multiple subgroups analyzed, some subgroups involved small numbers of patients and results appeared consistent with sampling variability. Subgroups for which point estimates of daclizumab treatment effect were stronger for the annualized relapse rate endpoint did not show concordant findings when using the MRI endpoints, and overall there was no convincing evidence for effect modification by any of the characteristics analysed.

Secondary Endpoints

1. Number of new Gd-enhancing lesions over 5 brain MRI scans at Weeks 8, 12, 16, 20, and 24 (calculated as the sum of these 5 MRIs) in a subset of subjects

The adjusted mean numbers of new lesions from Weeks 8 to 24 after adjustment were 4.79 lesions for placebo, 1.46 lesions for Daclizumab 150 mg, and 1.03 lesions for Daclizumab 300 mg. This result indicated that treatment with Daclizumab 150 mg and 300 mg reduced the number of new Gd-enhancing lesions between Weeks 8 and 24 after initiation of treatment by 69% ($p<0.0001$) and 78.4% ($p<0.0001$), respectively.

When the data for new Gd-enhancing lesions were analyzed by visit in the MRI-intensive population, the number of Gd-enhancing lesions in both daclizumab dose groups was significantly lower than that in the placebo group at all post-treatment time points beginning at the Week 4 MRI after adjustment for the baseline number of Gd+ lesions. This effect over time was also evident in the ITT population when examining new Gd-enhancing lesions at Weeks 24, 36, and 52.

Table 16 Number of New Gd-Enhancing Lesions between Week 8 and Week 24 - MRI Intensive Population – Primary Analysis

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in MRI intensive population	105	101	103
Number of subjects in MRI intensive population in the analysis (a)	104 (100)	101 (100)	102 (100)
Number of new Gd-enhancing lesions			
n	104	101	102
Mean	5.7	3.1	1.4
SD	9.98	9.21	2.99
Median	2.0	0.0	0.0
Min, Max	0, 78	0, 67	0, 17
0	29 (28)	54 (53)	70 (69)
1	18 (17)	16 (16)	12 (12)
2	9 (9)	8 (8)	2 (2)
3	6 (6)	5 (5)	3 (3)
>=4	42 (40)	18 (18)	15 (15)
Adjusted mean number of new Gd lesions (b)	4.79	1.46	1.03
95% CI (b)	3.56, 6.43	1.05, 2.03	0.73, 1.46
Percent reduction (b)		69.47	78.44
95% CI (b)		52.40, 80.41	65.97, 86.35
p-value vs placebo		<0.0001	<0.0001

NOTE 1: Numbers in parentheses are percentages.
2: For subjects with missing data the last valid non baseline measurement was carried forward if the subject was missing only 1 or 2 consecutive post-baseline scans. Otherwise the mean based on treatment group and visit was used as the imputed value.
(a) Number of subjects in MRI intensive populations with non-missing baseline values
(b) Estimated from a negative binomial model adjusted for the baseline number of Gd-enhancing lesions.

SOURCE: DACMS/205MS201/CSR/T-GD824-ITT.SAS DATE: 27DEC2011

Multiple sensitivity analyses were performed to evaluate the robustness of the primary analysis. In 2 sensitivity analyses, modifications were made to the analysis population: a) analysis restricted to the efficacy-evaluable population; b) MRI-intensive population excluding subjects who did not receive all assigned study doses. In 2 sensitivity analyses, modifications were made to the MRI scans that were eligible for inclusion in the analysis: analysis including the Week 4 MRI scan (new Gd-enhancing lesions between Weeks 4-24) and c) analysis excluding any MRI scans taken within 24 days of steroid treatment. One additional sensitivity analysis was performed to assess the statistical model and effect of outliers: d) analysis with new lesion number truncated at 30.

The results of these sensitivity analyses were all supportive and similar to the primary analysis.

2. Number of new or newly enlarging T2 hyperintense lesions at Week 52

The number of new or newly enlarging T2 hyperintense lesions at Week 52 was evaluated using the baseline MRI scan as a reference. Treatment effects on the number of new T2 lesions at Week 52 were analyzed using a negative binomial regression model adjusting for the baseline number of T2 lesions.

The adjusted mean number of new or newly enlarging T2 hyperintense lesions at Week 52 was 8.13 (95% CI: 6.65, 9.94) in the placebo group, 2.42 (95% CI: 1.96, 2.99; p<0.0001) in the Daclizumab 150 mg group, and 1.73 (95% CI: 1.39, 2.15; p<0.0001) in the Daclizumab 300 mg group. This result indicated

that Daclizumab150 mg reduced the number of new or newly enlarging T2 lesions by 70% (p<0.0001) and Daclizumab 300 mg reduced it by 79% (p<0.0001), respectively compared to placebo.

In the placebo group, 19% of subjects had no new or newly enlarging T2 lesions at Week 52 compared to 46% in the Daclizumab 150 mg group and 52% in the Daclizumab 300 mg group.

Table 17 Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196	201	203
Number of subjects in ITT population in the analysis (a)	195 (100)	199 (100)	200 (100)
Number of new or newly enlarging T2 hyperintense lesions at 52 weeks			
n	195	199	200
Mean	8.2	3.4	2.1
SD	9.34	8.15	5.19
Median	6.0	1.0	0.0
Min, Max	0, 56	0, 86	0, 53
0	38 (19)	91 (46)	104 (52)
1	16 (8)	25 (13)	24 (12)
2	14 (7)	15 (8)	35 (18)
3	9 (5)	27 (14)	8 (4)
>=4	118 (61)	41 (21)	29 (15)
Adjusted mean number of new or newly enlarging T2 hyperintense lesions	8.13	2.42	1.73
95% CI (b)	6.65, 9.94	1.96, 2.99	1.39, 2.15
Percent reduction (b)		70.23	78.73
95% CI (b)		59.94, 77.88	71.33, 84.22
p-value vs placebo (c)		<0.0001	<0.0001

NOTE 1: Number in parentheses are percentages.
2: Missing data is imputed using the mean within each treatment group.
(a) Number of subjects in ITT population with a non-missing baseline value.
(b) Estimated from a negative binomial model adjusted for the baseline number of T2 lesions.
(c) P-value for comparison between the treated and placebo groups based on negative binomial regression adjusted for baseline number of T2 lesions.

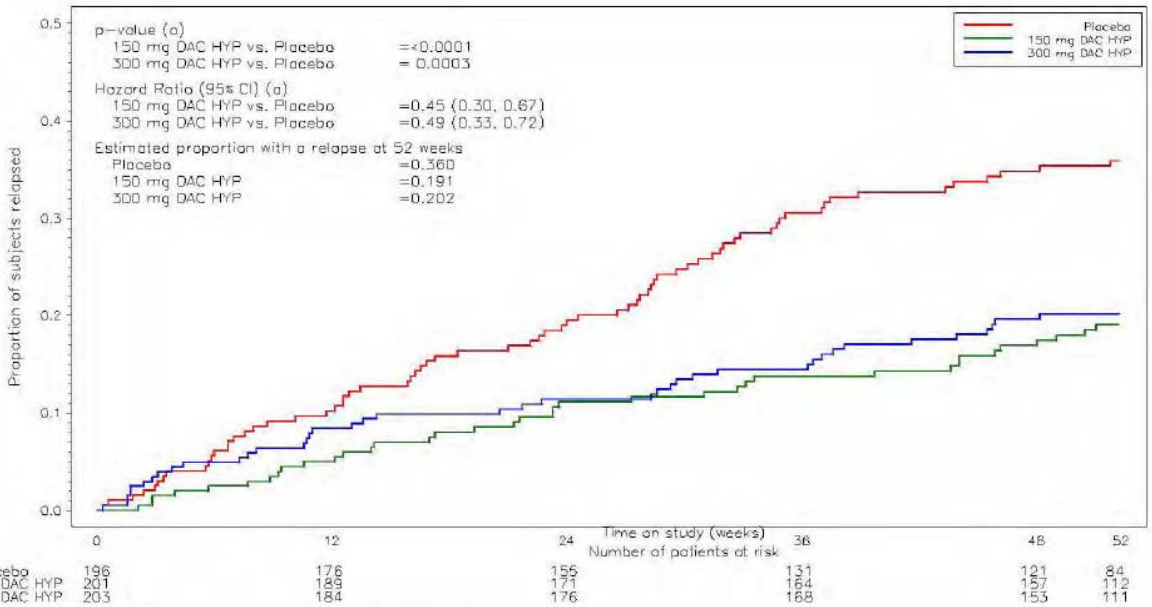
3. Proportion of relapsing subjects between baseline and Week 52

The Kaplan-Meier estimate for the proportion of subjects who relapsed at Week 52 was 36% in the placebo group compared to 19% in the Daclizumab150 mg and 20% in the Daclizumab300 mg group. The hazard ratio was 0.45 (95% CI: 0.30, 0.67) in the Daclizumab150 mg group compared to placebo and 0.49 (95% CI: 0.33, 0.72) in the DAC 300 mg group compared to placebo. These results indicate that the proportion of relapsing subjects was reduced by 55% in the Daclizumab 150 mg group (p<0.0001) and 51% (p = 0.0003) in the Daclizumab 300 mg group, compared to placebo.

Table 18 Proportion of Relapsing Subjects between Baseline and Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196	201	203
Subject status at 52 weeks			
Relapsed	69 (35)	38 (19)	40 (20)
Censored	127 (65)	163 (81)	163 (80)
Reason for censoring			
Completed treatment period	118 (60)	152 (76)	153 (75)
Early withdrawal from study	8 (4)	11 (5)	10 (5)
Alternative MS medication	1 (<1)	0	0
Estimated cumulative proportion of subjects relapsed at (a)			
12 weeks	0.10	0.05	0.08
24 weeks	0.20	0.11	0.11
36 weeks	0.31	0.14	0.14
48 weeks	0.35	0.17	0.20
52 weeks	0.36	0.19	0.20
Time (wk) relapse (a)			
10th percentile	11.7	23.3	20.6
25th percentile	30.1	NA	NA
50th percentile (Median)	NA	NA	NA
Hazard Ratio and 95% CI (b)		0.45 (0.30-0.67)	0.49 (0.33-0.72)
p-value vs placebo (b)		<0.0001	0.0003

NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored.
(a) Based on the Kaplan-Meier product limit method.
(b) Estimated from the Cox proportional hazards model. Covariates included were number of relapses in the 1 year prior to study entry (p=0.001), baseline EDSS (<=2.5 versus >2.5, p=0.449), and age (<=35 versus >35, p=0.026).



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawal from study are censored.
(a) P-value and hazard ratio are based on Cox proportional hazards model, adjusted for number of relapses in the 1 year prior to study entry, baseline EDSS (<=2.5 vs. >2.5), and age (<=35 vs. >35).

Figure 5 Time to first relapse (INEC confirmed relapses)

4. Change in MSIS-29 physical score at Week 52

The analysis of this endpoint demonstrated a nominally statistically significant benefit in the Daclizumab 150 mg group compared to placebo but not in the Daclizumab 300 mg group. The mean ± SD change in the MSIS-29 physical score from baseline to Week 52 was 3.0 ± 13.52 in the placebo group, - 1.0 ± 11.80 in the Daclizumab 150 mg group (p = 0.0008 vs. placebo), and 1.4 ± 13.53% in the Daclizumab 300 mg group (p = 0.1284 vs. placebo). The difference for Daclizumab 150 mg versus placebo was not considered statistically significant per the sequential closed testing procedure because the procedure required that the 300 mg dose group be tested first and achieve statistical significance before the 150 mg dose group could be tested.

Table 19 Change in MSIS-29 Physical Score at Week 52

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Change from Week 0 to Week 52			
n	196	201	203
Mean	3.0	-1.0	1.4
SD	13.52	11.80	13.53
Median	2.5	0.0	0.0
Min, Max	-56, 65	-39, 38	-43, 47
p-value vs placebo (a)		0.0008	0.1284
Relative mean change (95% CI) (a)		-4.27 (-6.76,-1.78)	-1.93 (-4.42,0.56)

NOTE: If the subject is missing data for less than 10 of the 20 items that make up the physical score, the mean of the non-missing items will be used for the missing items. If the subject is missing data for 10 or more items, the score was imputed using a mixed effects model (including visit week, treatment group, and their interaction, with random intercept and slope for each subject).
(a) Analysis of variance for difference between treatment groups, controlling for baseline score.

Tertiary Endpoints

- Disability progression

The risk of 12-week sustained disability progression at 52 weeks as measured by increase on the EDSS was reduced in the Daclizumab 150 mg group by 57% (hazard ratio (HR) = 0.43; 95% CI, 0.21 to 0.88; p = 0.0211) and in the Daclizumab 300 mg group by 43% (hazard ratio = 0.57; 95% CI, 0.30 to 1.09; p = 0.0905).

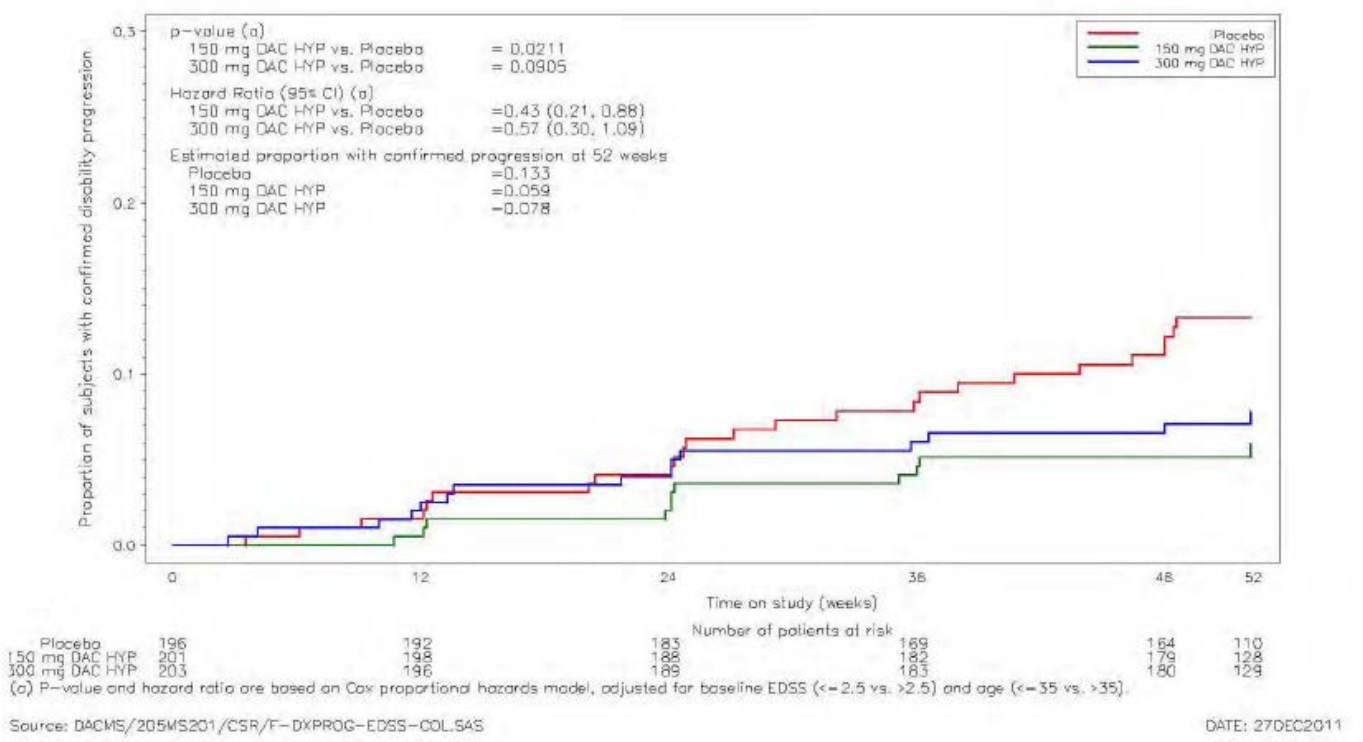


Figure 6 Time to Sustained Progression of Disability as Measured by Increase in EDSS

As in the protocol-defined analysis, the risk of 24-week sustained disability progression on EDSS was significantly reduced in the Daclizumab 150 mg group (p = 0.0037) but not in the Daclizumab 300 mg group (p = 0.1487) compared with placebo. The hazard ratios relative to placebo were 0.24 (95% CI: 0.09, 0.63) for Daclizumab 150 mg and 0.60 (95% CI: 0.30, 1.20) for Daclizumab 300 mg.

Table 20 Summary of time to 24 –week sustained progression of disability measured by increase in EDSS

Summary of time to 24-week sustained progression of disability measured by increase in EDSS

	Placebo	150 mg DAC HYP	300 mg DAC HYP
Number of subjects in ITT population	196 (100)	201 (100)	203 (100)
Number of subjects who progressed	21 (11)	5 (2)	13 (6)
Time (wk) to progression (a)			
25th percentile	NA	NA	NA
50th percentile	NA	NA	NA
Estimated proportion of subjects with progression at 52 weeks (a)	0.111	0.026	0.068
Hazard ratio and 95% CI (b)		0.24 (0.09-0.63)	0.60 (0.30-1.20)
p-value vs placebo (b)		0.0037	0.1487

NOTE: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks.
(a) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.
(b) Hazard ratio and p-value assessing the difference between the treatment groups were estimated from a Cox proportional hazards model. Covariates included were baseline EDSS (<=2.5 versus >2.5, p= 0.037), and age (<=35 versus >35, p= 0.047).

SOURCE: DACMS/205MS201/CSR/T-DXPROG-EDSS-24WK.SAS DATE: 12DEC2012

2.5.1.2.2. Study 205MS301

Methods

- **Treatments**

All subjects received study treatment (either daclizumab or Avonex or their respective matching placebos) starting at Week 0 (Baseline Visit) and ending at Week 144 or when the last subject enrolled had completed the Week 96 Visit, whichever was sooner.

- Subjects randomized to Group 1 received an injection of Daclizumab 150 mg SC once every 4 weeks plus A-PLC IM once weekly for 96 to 144 weeks.
- Subjects randomized to Group 2 received IFN β-1a 30 µg IM once weekly plus D-PLC SC once every 4 weeks for 96 to 144 weeks.

Treatment of relapses

Subjects who experienced a suspected MS relapse could be treated with intravenous methylprednisone (IVMP) 1000 mg/day for 3 to 5 days. Methylprednisolone could be given once a day or in divided doses.

Objectives

Primary Objective

The primary study objective was to test the superiority of daclizumab compared with IFN β-1a in preventing MS relapse in subjects with RRMS.

Secondary Objectives

The secondary study objectives were to test the superiority of daclizumab compared with IFN β-1a in slowing functional decline and disability progression and maintaining quality of life in this subject population.

Additional/Exploratory Objectives

Additional objectives of this study were to monitor the safety and tolerability of daclizumab; to measure DAC HYP trough levels; to monitor immunogenicity; to determine the efficacy of daclizumabversus IFN β-1a in slowing cognitive, visual, and physical decline and reducing brain atrophy; and to evaluate pharmacodynamic (PD) parameters that may be associated with treatment response in this subject population.

- **Outcomes/endpoints**

Primary endpoint

The primary endpoint was the annualized relapse Rate (ARR).

Secondary endpoints (ranked ordered)

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks
- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that was sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks
- Proportion of subjects who were relapse free

- Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact

Tertiary endpoints

- Safety and tolerability as measured by physical and neurological examinations, vital signs, clinical laboratory assessments (hematology, blood chemistry, thyroid function panel [thyroid-stimulating hormone (TSH) and thyroxine (T4)], urinalysis), electrocardiograms (ECGs), Beck Depression Inventory, Second Edition (BDI-II), drug trough levels and immunogenicity assessments, injection site assessments, and AE and concomitant medication monitoring
- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the Expanded Disability Status Scale (EDSS) from a baseline EDSS ≥1.0 that was sustained for 24 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 24 weeks
- Visual function as measured by the visual function test (VFT)
- Change in Multiple Sclerosis Functional Composite (MSFC) score
- Change in Timed 25-Foot Walk (T25FW), 9-Hole Peg Test (9HPT), and 3-Second Paced Auditory Serial Addition Test (PASAT 3) scores
- Change in oral Symbol Digit Modalities Test (SDMT)
- Change in EDSS score
- Proportion of subjects who are free of disease activity
- Change in quality of life on the European Quality of Life, 5 dimensions (EQ-5D and EQ-VAS), MSIS-29 Psychological Impact score, and MSIS-29 Physical Impact score
- Brain atrophy
- Total number and volume of new T1 hypointense lesions, T2 hyperintense lesions, and Gd+ lesions on brain MRI scans
- Change in CD56bright NK cells, CD4+ T cells, and Fox P3+ regulatory T cells
- Healthcare Resource Utilization (HRU)

Sample size

A sample size of 900 subjects per treatment group would have approximately 90% power to detect a 24% reduction in the ARR between the IFN β-1a treatment group and the daclizumab treatment group based on a negative binomial regression model with a 5% type 1 error rate. Power was estimated from simulations assuming a 21% drop-out rate, an average of 2.4 years of follow-up, and an ARR of 0.27 in the IFN β-1a group. Approximately 1800 subjects were required for this study. The actual number of subjects randomised (1841) was in line with the planned sample size of 1800.

Randomisation

Subjects were randomized to receive either Daclizumab 150 mg SC once every 4 weeks plus A-PLC IM once weekly or IFN β-1a 30 μg IM once weekly plus D-PLC SC once every 4 weeks in a 1:1 ratio.

Randomization took place using a centralized centralized interactive voice response system (IVRS). Randomization was stratified by site and prior use of IFN-β using permuted block randomization.

- **Blinding (masking)**

This study was double-blind. Treatment assignments were generated and assigned centrally through the IVRS system. No code-breaking supplies to break the blind were provided to the study sites.

Statistical methods

Analysis Populations

All analysis populations were defined and documented prior to database lock and were as follows:

Intent-to-treat (ITT) Population: The ITT population included all randomized subjects who received at least 1 dose of any study treatment. Subjects were analyzed in the group to which they were randomized. In general, efficacy endpoints were analyzed using the ITT population as the primary analysis, although subjects with missing data for baseline covariates were excluded.

The main analysis of the number of new or newly enlarging T2 lesions at Week 96 was evaluated in the subset of subjects with non-missing post baseline scan data; sensitivity analyses of this endpoint included all subjects.

Per-protocol population: The per-protocol population was defined as subjects from the ITT population who satisfied the following conditions:

- Met both inclusion criteria related to MS-specific disease activity:
    - Had a confirmed diagnosis of RRMS according to McDonald criteria 1-4 and a cranial MRI demonstrating lesion(s) consistent with MS.
    - Had a baseline EDSS between 0.0 and 5.0, inclusive.
- Compliant with study treatment: $\geq$ 90% of daclizumab or Avonex doses up to Week 96.
- Did not permanently discontinue study treatment prior to Week 96.

The primary and secondary endpoints were evaluated on the per-protocol population as supportive analyses.

Safety Population: The safety population was defined as all subjects who received at least 1 dose of any study treatment. All safety analyses were based on the safety population.

Subjects Excluded From Analyses

There were no centres or subjects excluded from the analysis.

Efficacy analyses

Control of Type I Error Rate

Statistical testing for efficacy endpoints was performed between the Daclizumab 150 mg group and the Avonex (IFN β-1a) 30 μg group. The secondary endpoints are listed in the order of importance. In order to control for inflation of type I error due to multiple treatment comparisons for the secondary endpoints, a sequential closed testing procedure was employed with the sequence of endpoints defined as follows:

The secondary endpoints (rank ordered) for this study were:

- Number of new or newly enlarging T2 hyperintense lesions on brain MRI over 96 weeks

- Proportion of subjects with confirmed disability progression defined by at least a 1.0-point increase on the EDSS from a baseline EDSS ≥1.0 that was sustained for 12 weeks or at least a 1.5-point increase on the EDSS from a baseline EDSS = 0 that was sustained for 12 weeks
- Proportion of subjects who were relapse free
- Proportion of subjects with a ≥7.5-point worsening from baseline in the MSIS-29 Physical Impact score at 96 weeks

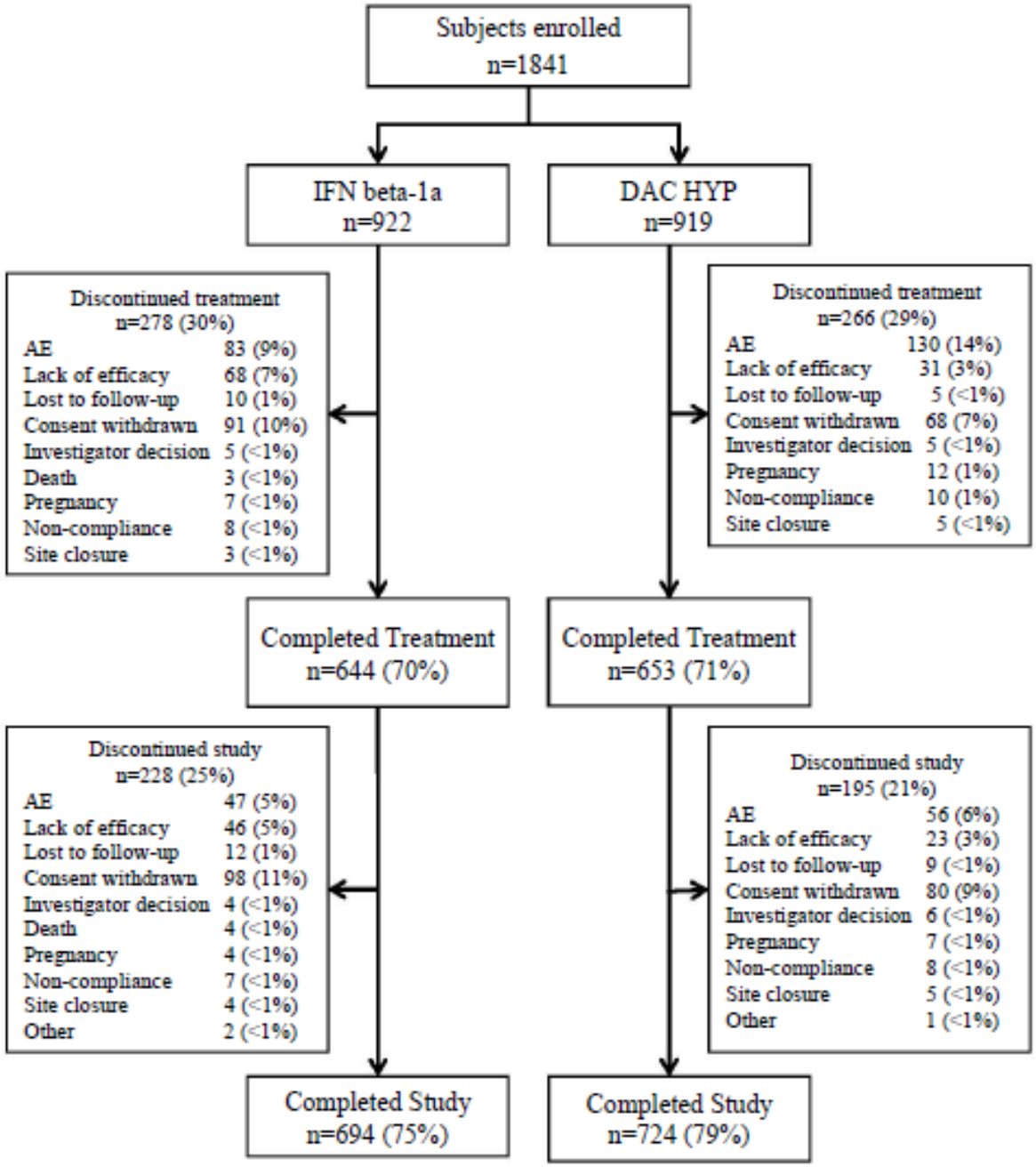
If the first comparison (number of new or newly enlarging T2 hyperintense lesions over 96 weeks) was statistically significant ($p<0.05$), the second comparison (disability progression) was then tested at the 0.05 significance level. However, if the first (or any subsequent) comparison was not statistically significant, then all endpoint(s) of a lower rank were not considered statistically significant.

Tertiary supportive analyses did not include adjustments made for the multiple comparisons for endpoints.

Results

- **Participant flow**

A total of 1841 subjects were randomized to treatment at 246 investigational sites in 28 countries worldwide. All 1841 subjects randomized received at least 1 dose of study treatment. The highest enrolling countries were Poland (451 subjects), United States (217 subjects), Russian Federation (198 subjects), Ukraine (129 subjects), and Serbia (111 subjects). All other countries each enrolled fewer than 100 subjects.



Source: Table 17.

Figure 7 Study 301 - Subject Disposition

Outcomes and estimation

1. **Primary efficacy endpoint analysis**

The primary analysis of the annualized relapse rate was based on INEC-confirmed relapses and it included data from all subjects in the ITT population between the first dosing date and the subject's end of treatment period visit or a switch to alternative MS medication. Treatment group differences were compared using a negative binomial regression model adjusted for the baseline relapse rate (number of relapses in the 3 years prior to study entry divided by 3), history of prior IFN β-1a use, baseline EDSS score (≤2.5 vs. >2.5), and age (≤35 vs. >35 years).

In the primary analysis, the adjusted ARRs were 0.393 (95% CI: 0.353, 0.438) in the IFN β-1a treatment group and 0.216 (95% CI: 0.191, 0.244) in the daclizumab treatment group. The adjusted ARR ratio (daclizumab/IFN β-1a) was 0.550 (95% CI: 0.469, 0.645), indicating that daclizumab reduced the ARR by 45% (95% CI: 35, 53%) compared with IFN β-1a (p <0.0001).

Table 21 Primary analysis: Annualised relapse rate

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects with a relapse	392 (43)	260 (28)
Number of relapses per subject		
0	530 (57)	659 (72)
1	227 (25)	174 (19)
2	109 (12)	51 (6)
3	36 (4)	20 (2)
>= 4	20 (2)	15 (2)
Total number of relapses	643	402
Total number of subject-years followed	1822.92	1897.57
Unadjusted annualized relapse rate (a)	0.353	0.212
Adjusted annualized relapse rate (95% CI) (b)	0.393 (0.353, 0.438)	0.216 (0.191, 0.244)
Rate ratio (DAC HYP/IFN beta-1a) (95% CI) (b)		0.550 (0.469, 0.645)
p-value vs IFN beta-1a (b)		<0.0001
Subject relapse rate (c)		
n	922	919
Mean	0.50	0.32
SD	1.110	2.467
Median	0.00	0.00
Min, Max	0.0, 12.6	0.0, 73.1

NOTE 1: Only relapses confirmed by INEC are included in this analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) Total number of relapses that occurred during the study divided by the total number of subject-years followed in the study.
(b) Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35).
(c) Number of relapses for each subject divided by the number of years followed in the study for that subject. Summary statistics across all subjects are presented.

The primary endpoint has been met, showing a highly statistically significant advantage for daclizumab 150mg over IFN β-1a. the absolute rate reduction was 0.177 and a 45% reduction in the relapse rate was seen (as evidence by the relapse ratio of 0.55) and the upper bound of the 95% confidence interval was well below 1.00.

The clinical study report notes that there was a 38% reduction in the rate of severe or serious relapses in the daclizumab group compared with the IFN β-1a group (p=0.0021).

Sensitivity analyses

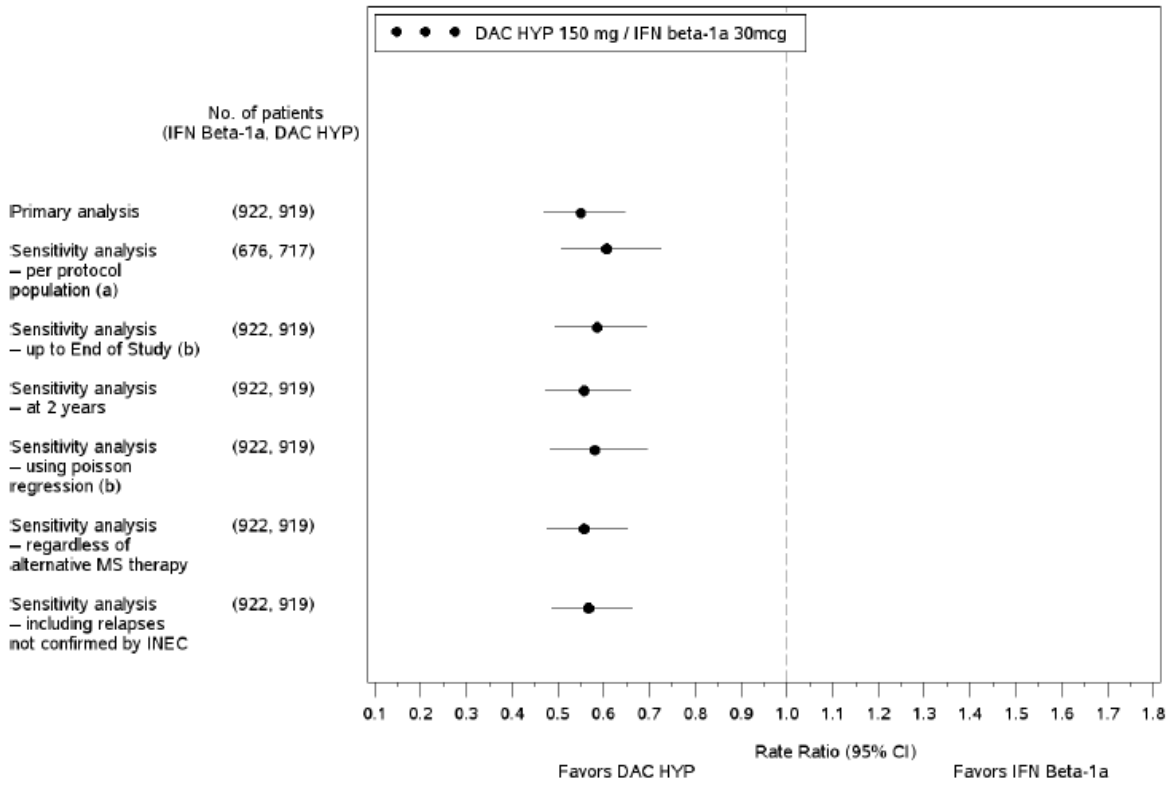
Multiple sensitivity analyses were performed to assess the robustness of the primary analysis. Alterations were made to the regression model parameters used to assess treatment effects on the annualized relapse rate:

- Using the per-protocol population instead of the ITT population

- using a Poisson regression model instead of a negative binomial regression model including all data until the end of study instead of the End of Treatment Period Visit
- censoring all subjects at the earliest of (1) the start of alternative MS medications, (2) end of treatment period visit date, or (3) 96 weeks after the first dosing date
- using a Poisson regression model instead of a negative binomial regression model. Adjusting the analysis only for the number of relapses in the 1 year prior to study entry
- including all INEC-confirmed relapses and follow-up time that occurred after the start of alternative MS medication
- including all protocol-defined relapses as assessed by the Investigator (whether or not INEC confirmed)

The results of these sensitivity analyses were all supportive and similar to the primary analysis presented above, indicating that the primary result was robust to a range of factors, including modelling assumptions and use of concomitant therapies that can affect annualized relapse rate.

Table 22 Annualised relapse rate – Summary of primary and sensitivity analysis results



(a) Estimated from a negative binomial regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35).
(b) Estimated from a poisson regression model adjusted for the baseline relapse rate, history of prior IFN beta use, baseline EDSS (<=2.5 vs >2.5) and baseline age (<=35 vs >35). The model was adjusted for over-dispersion.

Subgroup analyses

Pre-specified subgroup analysis was performed for the primary and secondary efficacy endpoints. The subgroups were defined by the following demographic and baseline MS characteristics.

- gender
- age at baseline (≤ 35 years versus >35 years)

- geographic region
- weight (below median versus above median)
- number of relapses in the past 12 months (≤ 1 versus ≥ 2)
- number of relapses in the past 3 years (≤ 2 versus ≥ 3)
- baseline EDSS (EDSS ≤ 2.5 versus EDSS >2.5)
- baseline presence of Gd+ lesions (lesions present versus lesions absent)
- prior IFN-β use (yes versus no)
- prior immunomodulatory MS treatment excluding steroids (yes versus no)
- disease activity (high [≥ 2 relapses in the year prior to randomization and ≥ 1 Gd lesion at baseline MRI] versus low)

The definition of region was based not only on geography but also on the type of health care system and access to health care in each country and was defined as follows:

- Region 1: United States and Canada
- Region 2: Western European countries (Denmark, Finland, France, Germany, Greece, Ireland, Italy, Spain, Sweden, Switzerland, and United Kingdom), Australia, and Israel
- Region 3: Eastern European countries (Czech Republic, Georgia, Hungary, Moldova, Poland, Romania, Russia, Serbia, and Ukraine), Argentina, Brazil, India, and Mexico

The trend was in favour of daclizumab in all sub-groups with positive effect seen in various age groups or disease activity. As opposed to Study 205MS201 there was little difference according to prior MS treatment. Effect was also similar in patients with high or low disease activity (> 2 relapses in the last year and ≥ 1 Gd-enhancing lesion), with a point estimate actually lower in patients with high disease activity at baseline, and in patients with high or lower T2 lesion volume or with longer disease duration at baseline.

- **Secondary efficacy endpoints**

New or Newly Enlarging T2 Hyperintense Lesions at week 96

The adjusted mean number of new or newly enlarging T2 hyperintense lesions at Week 96 was 9.44 (95% CI: 8.46, 10.54) in the IFN β-1a treatment group and 4.31 (95% CI: 3.85, 4.81) in the daclizumab treatment group. Relative to IFN β-1a, daclizumab reduced the number of new or newly enlarging T2 lesions by 54.4% (95% CI: 46.9%, 60.8%; p<0.0001) at Week 96. The reductions in the number of new or newly enlarging T2 lesions at Week 96 were robust and consistent across all pre-specified subgroups.

Table 23 Number of New or Newly Enlarging T2 Hyperintense Lesions at Week 96

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	841	864
Adjusted mean number of lesions at Week 96 (95% CI) (b)	9.44 (8.46, 10.54)	4.31 (3.85, 4.81)
Lesion mean ratio (compared to IFN beta-1a) (95% CI) (b)		0.46 (0.39, 0.53)
Percent reduction (compared to IFN beta-1a) (95% CI) (b)		54.4 (46.9, 60.8)
p-value vs IFN beta-1a (b)		<0.0001

NOTE: Observed data after subjects switched to alternative MS medications are excluded. Missing data are not imputed. Only observed new or newly enlarging T2 lesions at the last visit of the subject up to Week 96 visit is used in this analysis. 245 subjects with last new or newly enlarging T2 MRI observations taken prior to Week 96 assessment, and 1460 subjects with last new or newly enlarging T2 MRI observations taken at Week 96 assessment are included in the analysis.
(a) Subjects with baseline and at least one post-baseline MRI measurement are included in this analysis.
(b) Estimated from a negative binomial regression model, adjusted for baseline volume of T2 hyperintense lesions, history of prior IFN beta use and baseline age (<=35 vs >35). To account for the timing of the MRI measurement, the logarithmic transformation of the scan number of the MRI assessment will be included in the model as the 'offset' parameter.

Progression of Disability as Measured by EDSS Score

Confirmed disability progression was defined as a ≥ 1.0-point increase on the EDSS from a baseline EDSS ≥ 1.0 that was sustained for 12 weeks, or a ≥ 1.5-point increase on the EDSS from a baseline EDSS of 0 that was sustained for 12 weeks. The difference between treatment groups in confirmed disability progression was assessed using a Cox proportional hazards model, adjusted for baseline EDSS (EDSS ≤ 2.5 vs. EDSS >2.5), history of prior IFN β use, and baseline age (age ≤ 35 versus age >35 years).

In the primary analysis, the hazard ratio for daclizumab/IFN β-1a was 0.84 (95% CI: 0.66, 1.07), indicating daclizumab reduced the risk of disability progression by 16% (p=0.1575) compared with IFN β-1a.

Table 24 Summary of Time to 3-Month Sustained Disability Progression Measured by Increase in EDSS

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects progressed	140 (15)	121 (13)
Time (weeks) to progression (a)		
10th percentile	60.1	72.6
25th percentile	NA	NA
50th percentile	NA	NA
Estimated proportion progressed (a)		
24 weeks	0.036	0.035
48 weeks	0.081	0.064
72 weeks	0.114	0.095
96 weeks	0.143	0.120
120 weeks	0.161	0.148
144 weeks	0.203	0.162
Hazard ratio (DAC HYP/ IFN beta-1a) and 95% CI (b)		0.84 (0.66, 1.07)
p-value vs IFN beta-1a (b)		0.1575

NOTE 1: Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 12 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 12 weeks.
2: Subjects are censored at the time of withdrawal/switch if they withdrew from study or switched to alternative MS medication without a progression.
3: Subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment are censored at their last EDSS assessment.
4: For baseline EDSS assessment, the value obtained at Screening was used for 5 subjects (2 for the IFN beta-1a group and 3 for DAC HYP 150 mg group) and Week 12 for subject 3010125 in IFN beta-1a group.
(a) Estimated time to progression and proportion of subjects with progression based on the Kaplan-Meier product limit method.
(b) Based on Cox Proportional Hazards model, adjusted by baseline EDSS values as continuous variable, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

In the primary analysis of 12-week confirmed disability progression, all subjects who had a tentative disability progression and did not have an available confirmatory assessment were assumed to be nonprogressors and were censored at the time of the last assessment. A prespecified sensitivity analysis of 12-week confirmed disability progression was performed based on the alternative assumption that confirmed disability progression would occur at a similar rate as that for subjects who completed the confirmatory assessment in the trial (after adjustment for treatment group, baseline EDSS, change in EDSS at time of tentative progression, and presence of a relapse within the 29 days prior to the tentative progression. In this analysis, daclizumab reduced the risk of 12-week confirmed disability progression by 21% as compared with the IFN β-1a group (hazard ratio [daclizumab/IFN β-1a] of 0.79 [95% CI: 0.62, 1.00; p=0.0469]). An additional prespecified sensitivity analysis was carried out in which all tentative progressions with no confirmation assessment were assumed to be confirmed. In this analysis,

daclizumab also significantly reduced the risk of 12-week confirmed progression by 24% compared with the IFN β-1a group (hazard ratio [daclizumab/IFN β-1a] of 0.76 [95% CI: 0.61, 0.95; p=0.0157]).

Proportion of Subjects Free From Relapse

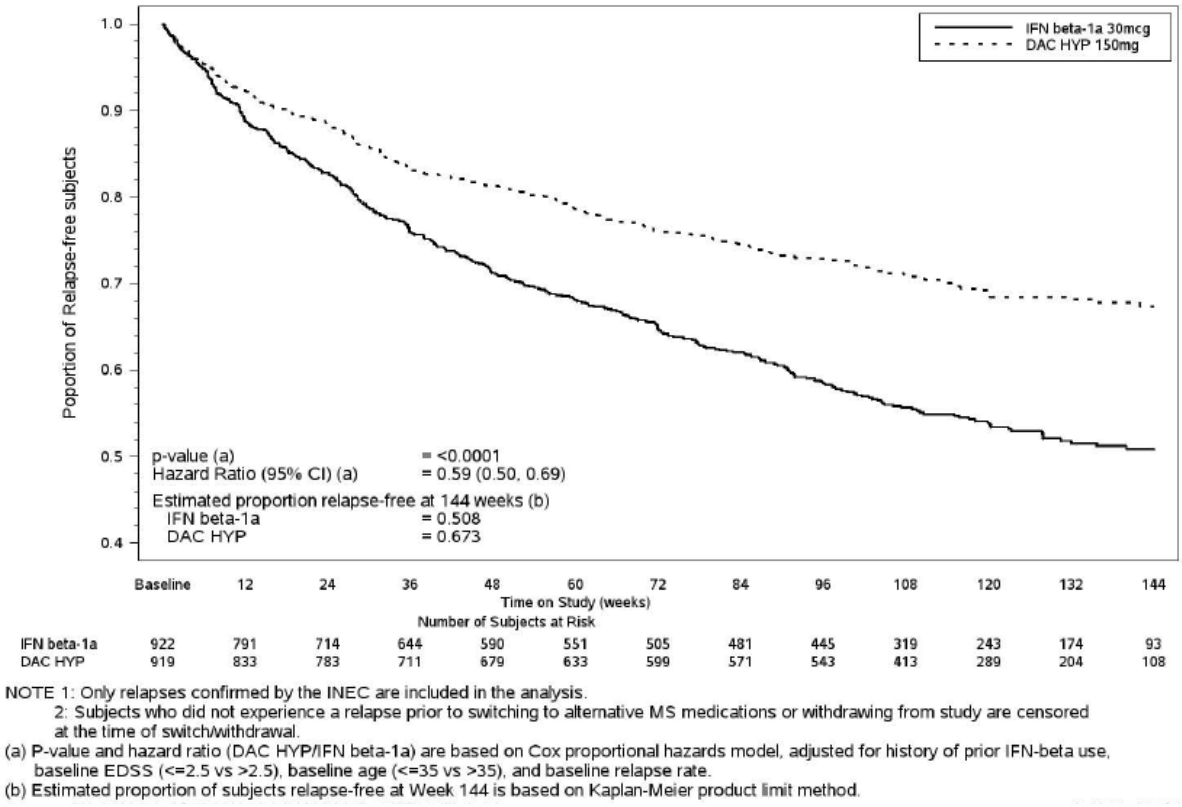
The primary analysis of this endpoint was based on INEC-confirmed relapses and included data from all subjects in the ITT population between the first dosing date and the subject's End of Treatment Period Visit or time of receiving alternative medication. No data were imputed.

Across the treatment period, 392 subjects (43%) in the IFN β-1a group and 260 subjects (28%) in the daclizumab group had an INEC-confirmed relapse. The Kaplan-Meier estimate for relapse-free subjects in the IFN β-1a and daclizumab groups was 71.2% and 81.2%, respectively, at 48 weeks; 58.5% and 72.9% at 96 weeks; and 50.8% and 67.3% at 144 weeks. The hazard ratio (daclizumab/IFN β-1a) for the risk of relapse was 0.59 (95% CI: 0.50, 0.69; p<0.0001), indicating that the risk of relapse was reduced by 41% in the daclizumab group compared to IFN β-1a.

Table 25 Proportion of Subjects Relapse Free

	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922 (100)	919 (100)
Number of subjects		
Relapsed	392 (43)	260 (28)
Relapse-free (a)	530 (57)	659 (72)
Estimated proportion of subjects relapse-free at (b)		
0 weeks	1.000	1.000
24 weeks	0.828	0.883
48 weeks	0.712	0.812
72 weeks	0.646	0.760
96 weeks	0.585	0.729
120 weeks	0.539	0.687
144 weeks	0.508	0.673
Time (weeks) to first relapse (b)		
10th percentile	11.1	18.1
25th percentile	39.0	80.4
50th percentile	145.4	NA
Hazard ratio for risk of relapse (DAC HYP/IFN beta-1a)		0.59
(95% CI) (c)		(0.50, 0.69)
p-value vs IFN beta-1a (c)		<0.0001

NOTE 1: Only relapses confirmed by INEC are included in this analysis.
2: Data after subjects switched to alternative MS medications are excluded.
3: Numbers in parentheses are percentages.
(a) Subjects who did not have a relapse.
(b) Based on the Kaplan-Meier product limit method.
(c) Based on Cox proportional hazards model, adjusted for baseline relapse rate, history of prior IFN beta use, baseline EDSS (EDSS <= 2.5 vs EDSS > 2.5) and baseline age (<=35 vs >35).



NOTE 1: Only relapses confirmed by the INEC are included in the analysis.
2: Subjects who did not experience a relapse prior to switching to alternative MS medications or withdrawing from study are censored at the time of switch/withdrawal.
(a) P-value and hazard ratio (DAC HYP/IFN beta-1a) are based on Cox proportional hazards model, adjusted for history of prior IFN-beta use, baseline EDSS (<=2.5 vs >2.5), baseline age (<=35 vs >35), and baseline relapse rate.
(b) Estimated proportion of subjects relapse-free at Week 144 is based on Kaplan-Meier product limit method.

Figure 8 Time to first relapse (INEC confirmed relapses) – Study 205MS301

Change in MSIS-29 Physical Score at Week 52

The MSIS-29 includes 2 scales that examine the impact of MS from a subject's perspective: the 20-item Physical Impact scale and the 9-item Psychological Impact scale. Increased scores on these scales represent worsening from baseline and decreased scores represent improvement; a change of ≥ 7.5 points is considered clinically meaningful. The treatment effect on the proportion of subjects with a ≥ 7.5-point worsening from baseline in the MSIS-29 Physical Impact score was analyzed using a logistic regression model and adjusting for the baseline Physical Impact score, baseline BDI, history of prior IFN β use, and baseline age (age ≤ 35 versus age >35 years). Week 96 data were imputed for 202 subjects in the IFN β-1a group and 169 subjects in the daclizumab group.

At 96 weeks, 213 subjects (23%) in the IFN β-1a group had a ≥ 7.5-point worsening from baseline compared with 171 subjects (19%) in the daclizumab treatment group. The odds ratio (daclizumab/IFN-β 1a) was 0.76 (95% CI: 0.60, 0.95; p=0.0176), indicating that the risk of a clinically meaningful worsening on the subject-reported physical impact of MS was reduced by 24% in the daclizumab group compared with the IFN β-1a group.

The proportion of subjects with a ≥ 7.5-point worsening on the MSIS-29 Physical Impact score was lower in the daclizumab group than in the IFN β-1a group at each visit up to and including Week 96. Throughout the study, 14% to 19% of subjects in the daclizumab group and 19% to 23% of subjects in the IFN β-1a group had a ≥ 7.5-point worsening on MSIS-29 Physical Impact score.

Table 26 Proportion of Subjects With a ≥7.5-Point Worsening From Baseline in the Multiple Sclerosis Impact Scale (MSIS-29) Physical Impact Score at Week 96

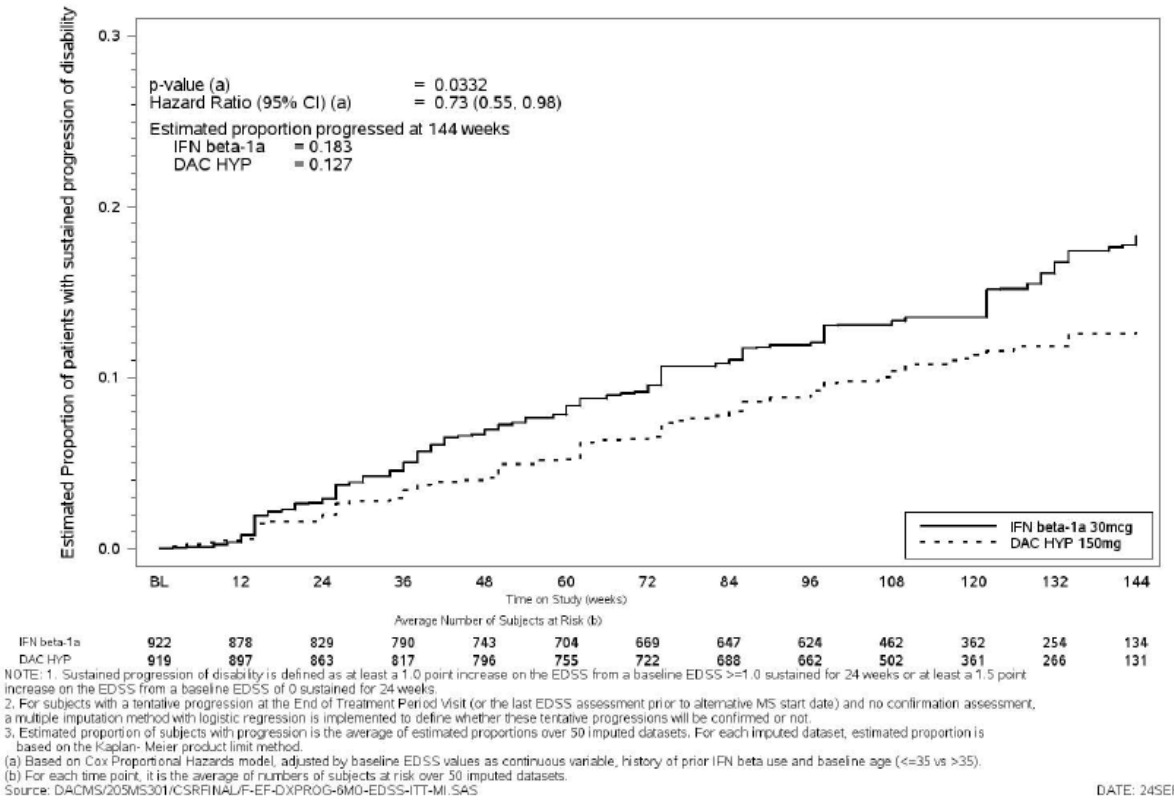
	IFN beta-1a 30 mcg	DAC HYP 150 mg
Number of subjects in the ITT population	922	919
Number of subjects included in analysis (a)	912 (100)	906 (100)
Number of subjects with worsening MSIS-29 physical score at Week 96		
No	699 (77)	735 (81)
Yes	213 (23)	171 (19)
Odds ratio (DAC HYP/ IFN beta-1a) (95% CI) (b)		0.76 (0.60, 0.95)
p-value vs IFN beta-1a (b)		0.0176

NOTE 1: If a subject is missing data for less than 10 of the 20 items that make up the physical score, then the mean of the non-missing items will be used for the missing items. The number of subjects with imputed data was 3 for the IFN beta-1a group.
2: If the subject was missing 10 or more of the 20 items that make up the physical score, or missing the questionnaire entirely, or if the questionnaire was completed after the subject switched to alternative MS medication, a random effects model was used to estimate the MSIS-29 physical score. The number of subjects with imputed data was 202, 169 for the IFN beta-1a and DAC HYP 150 mg groups, respectively.
3: Numbers in parentheses are percentages.
(a) Subjects with available baseline assessments will be included in this analysis.
(b) Based on logistic regression model, adjusted for baseline MSIS-29 physical score, baseline BDI score, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

- **Tertiary endpoints**

- **24-week sustained disability progression**

Results of the protocol-specified analysis of 24-week confirmed disability progression show that daclizumab reduced the risk of 24-week confirmed disability progression by 27% compared with IFN β-1a (hazard ratio of 0.73 [95% CI: 0.55, 0.98]; p=0.0332).



NOTE: 1. Sustained progression of disability is defined as at least a 1.0 point increase on the EDSS from a baseline EDSS >=1.0 sustained for 24 weeks or at least a 1.5 point increase on the EDSS from a baseline EDSS of 0 sustained for 24 weeks.
2. For subjects with a tentative progression at the End of Treatment Period Visit (or the last EDSS assessment prior to alternative MS start date) and no confirmation assessment, a multiple imputation method with logistic regression is implemented to define whether these tentative progressions will be confirmed or not.
3. Estimated proportion of subjects with progression is the average of estimated proportions over 50 imputed datasets. For each imputed dataset, estimated proportion is based on the Kaplan- Meier product limit method.
(a) Based on Cox Proportional Hazards model, adjusted by baseline EDSS values as continuous variable, history of prior IFN beta use and baseline age (<=35 vs >35).
(b) For each time point, it is the average of numbers of subjects at risk over 50 imputed datasets.
Source: DACMS/205MS301/CSRFINAL/F-EF-DXPROG-6M0-EDSS-ITT-MI.SAS
DATE: 24SEP2014

Figure 9 Time to 6-Month Sustained Progression of Disability Measured by Increase in EDSS Using Multiple Imputation

The protocol-specified analysis of 24-week confirmed progression was performed using the same methodology that was used as a sensitivity analysis for 12-week confirmed progression. Overall, the same pattern of results was observed in the analysis of 24-week confirmed progression as for 12-week confirmed progression: when it was assumed that disability progression occurred in censored subjects at a similar rate as subjects who completed the confirmatory visit (after adjustment for baseline EDSS, change in EDSS at the time of tentative progression, treatment group, and the occurrence of recent MS relapse), the effect estimate favoring daclizumab over IFN β-1a was statistically significant. Furthermore, in an analysis in which all tentative progressions with no confirmation assessment are assumed to be confirmed, daclizumab reduced the risk of 24-week confirmed disability progression by 30% compared to IFN β-1a (hazard ratio of 0.70 [95% CI: 0.56, 0.89]; p=0.0034). When it was assumed that disability progression did not occur in any subject who was censored after a tentative progression, the risk of 24-week confirmed disability progression was reduced by 21% with daclizumab compared to IFN β-1a (hazard ratio of 0.79 [95% CI: 0.59, 1.06]; p=0.1186).

- **Change in EDSS score and change from baseline**

At Week 96, the median (minimum, maximum) scores were 2.00 (0.0, 7.0) and 2.00 (0.0, 6.5) respectively, in the IFN β-1a and daclizumab groups, representing median (minimum, maximum) changes of 0.0 (-3.0, 3.5) and 0.0 (-2.5, 4.0), respectively. The median (minimum, maximum) change at Week 144 was 0.00 (-3.0, 4.0) in the IFN β-1a group and 0.0 (-3.5, 3.5) in the daclizumab group.

- **Sustained Improvement in Disability as Measured by EDSS Score in Subjects With Baseline EDSS Score of ≥2**

Sustained improvement in disability was defined as at least a 1.0-point decrease on the EDSS from baseline EDSS assessment ≥2.0 that was sustained for 12 weeks. Among the subjects with a baseline EDSS score of ≥2, a similar proportion of subjects in both treatment groups experienced an improvement in disability: 105 subjects (17%) in the IFN β-1a group and 108 subjects (17%) in the daclizumab group

- **Change in Multiple Sclerosis Functional Composite (MSFC) score over 48 and 96 weeks**

At Week 96, the median increases (indicating improvement) from baseline in the MSFC composite z-score were 0.055 and 0.091 in the IFN β-1a and daclizumab groups, respectively (p=0.0007), indicating greater improvement in the daclizumab group relative to IFN β-1a. The increases at each 12-week timepoint up to Week 96 were all greater in the daclizumab group compared with the IFN β-1a group. At Week 48, the median increase from baseline in the MSFC composite z-score was 0.058 in the IFN β-1 group and 0.071 in the daclizumab group (p=0.0461).

Results for the MSFC component z-scores (T25FW, 9HPT, PASAT 3) also indicated greater improvement in ambulation, dexterity, and cognition in the daclizumab group compared to the IFN β-1a group. The median changes at Week 96 were as follows:

- T25FW: Median change (25th, 75th percentile) of -0.017 (-0.124, 0.075) in the IFN β-1a group and 0.00 (-0.099, 0.083) in the daclizumab group (p=0.0060)
- 9HPT: Median change (25th, 75th percentile) of 0.017 (-0.273, 0.291) in the IFN β-1a group and 0.063 (-0.195, 0.356) in the daclizumab group (p=0.0016)

PASAT 3: Median change (25th, 75th percentile) of 0.177 (-0.088, 0.442) in the IFN β-1a group and 0.177 (-0.088, 0.530) in the daclizumab group (p=0.0411)

- **Visual Function Test (VFT)**

VFT scores are expressed as the number of letters correctly identified on the low-contrast Sloan letter chart at 100%, 2.5%, and 1.25% contrast. In the prespecified analysis, the mean change at Week 96 for 1.25% contrast was evaluated using an analysis of covariance (ANCOVA) model after imputing missing data using LOCF. In this analysis, the mean change from baseline at Week 96 was -1.51 in the IFN β-1a group and -1.34 in the daclizumab group (p=0.5712).

- **Change in oral Symbol Digit Modalities Test (SDMT)**

The prespecified approach was an ANCOVA model on the change from baseline after imputing missing data using an LOCF approach. In this analysis, the mean change from baseline at Week 96 was 2.96 in the IFN β-1a group and 3.42 in the daclizumab group (p=0.1552).

- **Proportion of subjects who are free of disease activity**

Subjects were considered free of disease activity if they were without clinical or radiological activity. Clinical activity included an assessment of relapses and of disease progression, and radiological activity included an assessment of Gd+ lesions and new or enlarging T2 lesions. A greater proportion of subjects in the daclizumab group (198 subjects [22%]) remained free of disease activity as compared with the IFN β-1a group (116 subjects [13%]). The odds ratio (daclizumab/IFN β-1a) was 2.009 (95% CI: 1.554, 2.598; p<0.0001).

- **Change in quality of life on the European Quality of Life, 5 dimensions (EQ-5D and EQ-VAS), MSIS-29 Psychological Impact score, and MSIS-29 Physical Impact score**

-EQ-5D VAS: Numerically greater improvement relative to IFN β-1a was observed in the daclizumab group at Week 48. Scores increased over time in the daclizumab group and remained relatively unchanged in the IFN β-1a group. At Week 72, mean changes were 1.25 and 2.60 in the IFN β-1a and daclizumab groups, respectively (p=0.02200; by Week 96, mean changes were 0.33 and 2.69 (p= 0.0006).

-The results of the EQ-5D index score reflected improved health status in the daclizumab group as compared with the IFN β-1a group, with greater improvement at Weeks 48 and 96 (Table 147). By Week 96, the mean increases in the EQ-5D index scores were 0.004 and 0.028 in the IFN β-1a and daclizumab groups, respectively (p=0.0048).

-The differences in the MSIS-29 Physical Impact scores between the daclizumab and IFN β-1a groups were evident as early as 24 weeks (p=0.0322) and persisted up to Week 96. The mean ± SD change in the MSIS-29 Physical Impact score from Baseline to Week 96 was a worsening of 1.15 ± 14.064 points in the IFN β-1a group and an improvement of 0.84 ± 14.156 points in the daclizumab group (p = 0.0008).

- **Whole brain volume**

The annualized Percent Brain Volume Change (PBVC) was reduced in the daclizumab group compared with the IFN β-1a group during the 2 prespecified time periods of baseline to Week 24 (median annualized PBVC of -0.745 for IFN β-1a versus -0.674 for daclizumab; p=0. 0325) and Week 24 to Week 96, (median annualized PBVC -0.549 for IFN β-1a vs. -0.511 for daclizumab; p<0.0001).

- **Total number and volume of new T1 hypointense lesions, T2 hyperintense lesions, and Gd+ lesions on brain MRI scans**

Reductions in the tertiary MRI endpoints of brain atrophy and T2, T1, and Gd+ lesion count and volume were also consistent with the effect on new or enlarging T2 lesions. The treatment effect of daclizumab on new or enlarging T2 lesions and other MRI endpoints was detectable by Week 24 (p<0.0001) and was

sustained through to the Week 96 MRI at a similar magnitude. Daclizumab produced treatment-related reductions in brain atrophy (p<0.0001).

- **MRI variables over 24, 48 and 96 weeks**

Statistical significant difference was noted for the number of new non enhancing T1 Hypointense lesions at Weeks 24, 96, and 144 (p<0.0001), and at week 24 for the number of Gd-Enhancing lesions or Number of New or Newly Enlarging T2 Hyperintense Lesions; similar results were seen for the volume of these lesions. Of note the median decrease in T2 hyperintense lesion volume with IFN β-1a and daclizumabwas 0.27% and 1.44%, respectively (p=0.0188) at week 24 and the median T2 lesion volume increase from baseline to week 96 was 3.76% and 0.20%, respectively (p<0.0001).

- **Ancillary analyses**

Subgroup analyses demonstrated that the effect of daclizumab on the primary endpoint was evidenced across all prespecified demographic and baseline characteristic subgroups. There was minor variation in treatment effect estimates across the multiple subgroups; however, the point estimates for all endpoints and subgroups favoured daclizumab, and there was no convincing evidence for effect modification by any of the prespecified characteristics that were analyzed. An ad hoc analysis of ARR by body weight quartiles demonstrated a consistent treatment effect favoring daclizumab over IFN β-1a across all quartiles.

2.5.1.2.3. Effect on disability progression in all forms of RMS

In order to gain the full RMS indication the applicant was asked to demonstrate a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided in the response to the CHMP query, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects and was considered sufficient to support an indication for “relapsing forms of MS.”

As shown in the following tables (see Table 27 and Table 28), data and analyses were provided showing evidence for the efficacy of daclizumab compared to IFN β-1a for the prevention of confirmed neurologic worsening independent of relapse activity and in the relapse-free population in the trial. The efficacy results demonstrated consistent and meaningful trends favoring daclizumab over IFN β-1a across the range of baseline EDSS categories including ≥3.5, ≥4.0, and ≥4.5, indicating that the benefit was not confined to subjects with lower baseline EDSS scores. The hazard ratios (daclizumab/IFN β-1a) demonstrate that the risk of worsening in neurologic function based on the composite of all 3 endpoints was reduced by approximately 25% in the daclizumab arm relative to IFN β-1a in all baseline EDSS categories. Overall, the evidence of benefit was strongest on preventing the 6-month confirmed 20% decline on the T25FW gait measure, with an approximate 40% reduction in the risk of worsening in the daclizumab group compared to IFN β- 1a. This result is particularly relevant to the relapsing SPMS population, as decline in gait is typically the strongest contributor to EDSS decline in the early SPMS period.

Finally, the efficacy results were also consistent in the relapse-free population, providing additional confidence that the benefits on disease progression were not related to the effect of daclizumab on the prevention of clinical relapses. These data can support the indication of Daclizumab 150 mg for relapsing forms of MS with added information to be provided in section 5.1 of the SmPC regarding the effect in relapse-free patients with EDSS ≥3.5

Table 27 Summary of Confirmed Progression Independent of Relapse in Study 301

Proportion subjects with confirmed progression at 144 weeks independent of relapse

EDSS range	Outcome	IFN beta-1a 30 mcg	DAC HYP 150 mg	HR (95% CI) (b)
>=3.5	Number of subjects evaluated	291	260	
	Composite	0.331	0.236	0.73 (0.51, 1.04)
	Timed 25-Foot Walk	0.241	0.153	0.66 (0.43, 1.01)
	Nine-Hole Peg (a)	0.078	0.070	0.92 (0.46, 1.83)
	EDSS	0.153	0.127	0.86 (0.52, 1.43)
>=4.0	Number of subjects evaluated	179	159	
	Composite	0.391	0.285	0.73 (0.48, 1.11)
	Timed 25-Foot Walk	0.275	0.182	0.66 (0.40, 1.10)
	Nine-Hole Peg (a)	0.101	0.085	0.79 (0.36, 1.75)
	EDSS	0.193	0.157	0.84 (0.47, 1.49)
>=4.5	Number of subjects evaluated	97	84	
	Composite	0.445	0.344	0.77 (0.44, 1.33)
	Timed 25-Foot Walk	0.297	0.173	0.58 (0.29, 1.15)
	Nine-Hole Peg (a)	0.094	0.085	0.85 (0.28, 2.54)
	EDSS	0.281	0.237	0.91 (0.47, 1.76)

Note: Estimated proportion of subjects with confirmation is based on the Kaplan Meier product limit method.
(a) Analysis excludes subjects with missing baseline data for Nine-Hole Peg Test.
(b) Based on Cox Proportional Hazards model, adjusted by baseline value of the corresponding MSFC component or EDSS, history of prior IFN beta use, and baseline age (age <= 35 vs age >35). Analysis on composite adjusted for baseline EDSS, baseline Timed 25-Foot Walk Test, baseline Nine-Hole Peg Test, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

Table 28 Summary of Confirmed Progression in Relapse-free Population in Study 301

Proportion subjects with confirmed progression at 144 weeks and relapse free

EDSS range	Outcome	IFN beta-1a 30 mcg	DAC HYP 150 mg	HR (95% CI) (b)
>=3.5	Number of subjects evaluated	163	154	
	Composite	0.234	0.143	0.67 (0.36, 1.22)
	Timed 25-Foot Walk	0.164	0.091	0.49 (0.23, 1.03)
	Nine-Hole Peg (a)	0.064	0.031	0.50 (0.15, 1.67)
	EDSS	0.087	0.072	1.16 (0.46, 2.93)
>=4.0	Number of subjects evaluated	101	88	
	Composite	0.284	0.134	0.50 (0.22, 1.15)
	Timed 25-Foot Walk	0.189	0.074	0.34 (0.12, 0.97)
	Nine-Hole Peg (a)	0.066	0.000	NA
	EDSS	0.153	0.092	0.76 (0.27, 2.18)
>=4.5	Number of subjects evaluated	56	45	
	Composite	0.392	0.172	0.49 (0.17, 1.39)
	Timed 25-Foot Walk	0.221	0.056	0.23 (0.05, 1.13)
	Nine-Hole Peg (a)	0.095	0.000	NA
	EDSS	0.290	0.145	0.62 (0.20, 1.98)

Note: Estimated proportion of subjects with confirmation is based on the Kaplan Meier product limit method.
(a) Analysis excludes subjects with missing baseline data for Nine-Hole Peg Test.
(b) Based on Cox Proportional Hazards model, adjusted by baseline value of the corresponding MSFC component or EDSS, history of prior IFN beta use, and baseline age (age <= 35 vs age >35). Analysis on composite adjusted for baseline EDSS, baseline Timed 25-Foot Walk Test, baseline Nine-Hole Peg Test, history of prior IFN beta use, and baseline age (age <= 35 vs age >35).

2.5.1.2.4. Clinical studies in special populations

MS is a disease predominantly affecting young adult females, and therefore, age and gender were preselected as principal patient demographics for evaluation. Because MS is encountered mostly among individuals of Caucasian, Northern European descent, only a small proportion of non-white subjects enrolled in Studies 201 and 301, and subgroup analyses by race were not conducted. Lastly, several baseline disease characteristics have been identified that are predictive of a potentially more aggressive versus less aggressive clinical course, including evidence of established neurological disability on the EDSS, early versus longer duration of RRMS disease, relapse activity over the 12 months prior to entering study, exposure to previous DMT versus treatment naïve, presence versus absence of T1 Gd+ lesions, and total disease burden on T2 lesion volume. Therefore, subgroups defined by these baseline disease characteristics were also included in the analyses in both clinical studies.

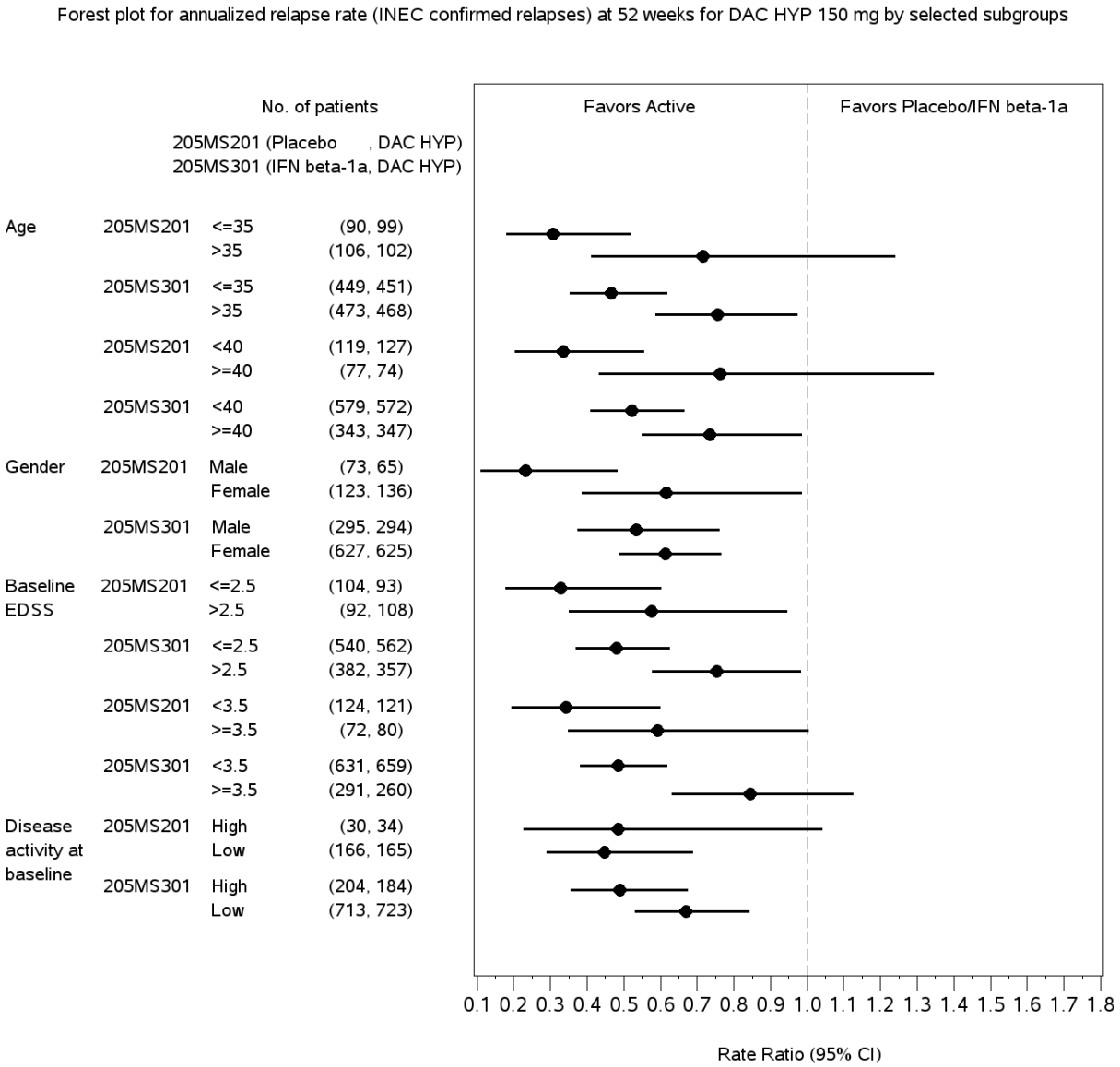
The endpoints for the subgroup analyses consisted of the primary clinical efficacy parameter of annualized relapse rate and the supportive neuroimaging parameters of change from baseline in new or newly enlarging T2 lesions and new Gd lesions. The endpoints of the proportion of subjects with relapse, confirmed disability progression (Study 301 only), and the proportion of subjects with worsening on the MSIS-29 (Study 301 only) were also evaluated.

In both pivotal studies, a greater treatment effect was observed for Daclizumab 150 mg relative to control across all prespecified demographic and baseline characteristic subgroups for each of the efficacy endpoints analyzed (Figure below). A pooled analysis of annualized relapse rate over 1 year was conducted in which data for subjects in the Daclizumab 150 mg dose groups of Studies 201 and 301 were pooled and compared to the results for the placebo group in Study 201 and the IFN β-1a group of Study 301.

The results of the pooled analysis favored daclizumab treatment over control for all subgroups and show that the annualized relapse rate for daclizumab-treated subjects was consistent across the prespecified demographic and disease characteristics subgroups. The results demonstrate that the daclizumab efficacy observed in the ITT analyses for Studies 201 and 301 was not driven disproportionately by particular RRMS patient subgroups. In addition, daclizumab effectively reduced disease activity in every subgroup across the spectrum of RRMS patients. Based on the cross-study population PK analysis, body weight accounted for less than 40% of the inter-subject variability in daclizumab clearance. The impact of body weight on daclizumab exposure does not appear to be clinically relevant as the ARRs in Study 301 were similar across subgroups based on body weight quartiles.

Consistent with the impact seen on clinical MS relapses across the prespecified subgroups in Studies 201 and 301, daclizumab treatment also demonstrated a robust and substantial effect compared to placebo or active comparator treatment on reducing focal areas of inflammation and tissue destruction defined by the MRI endpoints of the number of new or newly enlarging T2 lesions and the number of new Gd+ lesions.

Figure 10 Forest Plot for Annualized Relapse Rate (INEC-Confirmed Relapses) at 52 Weeks for Daclizumab 150 mg by Selected Subgroups



NOTE: Rate ratios and 95% CI are estimated from a negative binomial (NB) or Poisson (if NB failed to estimate) regression adjusted for baseline EDSS (<=2.5 vs. >2.5), baseline age (<=35 vs. >35) and number of relapses in the 1 year prior to study entry for 205MS201, and adjusted for the baseline relapse rate (number of relapses in the 3-years prior to study entry divided by 3), history of prior IFN beta-1a use (yes/no), baseline EDSS (EDSS <= 2.5 versus EDSS > 2.5) and baseline age (age <= 35 versus age >35) for 205MS301.

SOURCE: DACMS/BLA/BLA/F-ISE-ARR-FOREST-TRT.SAS DATE: 30SEP2014

Efficacy by Antibody Status

The impact of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) on efficacy has been explored by summarizing key efficacy endpoints by AB status.

Treatment-emergent ADAs to Daclizumab150 mg were observed in 4% and 19% of evaluable subjects in Studies 201 and 301, respectively. The majority (12% [110/913]) of the treatment emergent ADA responses in Study 301 were transient (defined as positive evaluations other than final evaluations that are non-consecutive or are consecutive but <74 days apart), and the minority (7% [65/913]) were persistent. Treatment-emergent NAbs to Daclizumab150 mg were observed in 3% and 8% of evaluable

subjects in Studies 201 and 301, respectively. The majority of ADA and NAb reactivity to daclizumaboccurred early during treatment and decreased with continuing daclizumab treatment.

The impact of ADAs and NAbs on efficacy was explored by summarizing clinical endpoints (relapses) and radiological endpoints. In Study 301, the adjusted annualized relapse rate was comparable for both AB-positive and AB-negative daclizumab-treated subjects. Similarly, there was no detectable impact of ADAs or NAbs on the number of Gd+ lesions or the number of new or newly enlarging T2 hyperintense lesions at Week 24 and Week 96. With the limitations of the low incidence of AB-positive subjects in Study 201, the adjusted annualized relapse rate was similar between daclizumab-treated ADA-positive and ADA-negative subjects. The percentage of subjects that were relapse-free at 1 year was comparable for ADA-positive and ADA-negative groups. Similar results were observed for the Nab positive or Nab-negative subjects.

The mean number of new Gd lesions at 1 year in Study 201 was similar for ADA-positive and ADA-negative daclizumab-treated subjects, and the percentage of subjects with no Gd+ lesions at 1 year on cranial MRI was similar in the ADA-positive and ADA-negative groups. Similar results were observed for the NAb-positive or NAb-negative subjects.

Overall, immunogenicity to daclizumab was typically transient and most often occurred during the first year of treatment. There was no discernible impact of ADAs or NAbs on efficacy during treatment with daclizumab.

Redefined “high disease activity”

The applicant redefined “high disease activity” and this modified definition added a second criterion to the definition used in the applicant’s primary analysis as shown below.

- Subjects with 2 or more relapses in 1 year, and with 1 or more Gd-enhancing lesions on brain MRI, or
- Subjects who failed to respond to a full and adequate course (at least 1 year of treatment) of prior DMT treatment, having had at least 1 relapse in the previous year while on therapy, and at least 9 T2-hyperintense lesions in cranial MRI or at least 1 Gd-enhancing lesion, or having an unchanged or increased relapse rate in the prior year as compared to the previous 2 years

Subjects who did not meet the criteria for high disease activity were classified in our analyses as having low/unknown disease activity.

To facilitate the assessment of benefit/risk based on this new definition of high disease activity, analyses were performed on the data from Study 201 and Study 301 for the following endpoints by baseline disease activity level:

- Overall summary of adverse events (AEs)
- Incidence of maximum values in liver function tests (Study 301 only)
- Annualized relapse rate (using INEC confirmed relapses)
- Number of new or newly enlarging T2 lesions
- 6-month sustained disability progression

Study 201

In Study 201, the overall AE profile was similar for the subjects with high and low/unknown disease activity at baseline. The incidence of AEs and SAEs reported were also similar among subjects with high

disease activity and low/unknown disease activity. Notably the incidence of AEs in the high and low disease activity subgroups of the total daclizumab group was similar for events in the Infections and Infestations SOC (53% and 52%, respectively) and the Skin and Subcutaneous Tissue Disorders SOC (16% and 21%, respectively).

The results of the analyses of annualized relapse rate and new or newly enlarging T2 lesions by baseline disease activity demonstrate the superiority of daclizumab over placebo for both the high and low/unknown disease activity subgroups. The reductions in the annualized relapse rate in the Daclizumab 150 mg group relative to placebo were similar, with a 52% reduction (p=0.0493) in the high disease activity group and a 54% reduction (p=0.0003) in the low/unknown disease activity. In the analysis of new or newly enlarging T2 lesions, the reduction relative to placebo was greater in the high disease activity group (78%, p<0.0001) than in the low/unknown disease activity group (66%, p<0.0001).

In the analyses of disability progression, treatment with Daclizumab 150 mg was associated with a markedly lower rate of 6-month sustained progression compared to placebo in both the high disease activity group (hazard ratio=0.23, p=0.2034) and the low/unknown disease activity group (hazard ratio=0.24, p=0.0093).

Study 301

As was the case in Study 201, there were no notable imbalances in the safety data between the high and low/unknown disease activity groups in Study 301. The incidence of SAEs was greater in subjects with high disease activity as compared to subjects with low disease activity in both treatment groups, suggesting the differences were associated with baseline disease severity and were not indicative of treatment-related differences. In the daclizumab arm, the incidence of AEs was slightly higher in the high disease activity subgroup as compared to the low disease activity subgroup for the Infections and Infestations SOC (70% vs. 62%) and the Skin and Subcutaneous Disorders SOC (41% vs. 62%). However, a similar trend was also seen in the IFN β-1a group, which suggests the differences are primarily a function of greater disease severity in these subjects.

Maximum values for liver function tests were also similar in the high and low/unknown disease activity groups of Study 301. Most subjects in both subgroups had maximum values that were between $\leq 3 \times$ ULN. The incidence of maximum values $\geq 5 \times$ ULN was low and similar between the disease activity subgroups and the daclizumab and IFN β-1a arms.

The results of the analyses of annualized relapse rate and new or newly enlarging T2 lesions by baseline disease activity demonstrate the superiority of daclizumab over IFN β-1a for both the high and low/unknown disease activity subgroups, with highly significant p values (<0.0001). For annualized relapse rate, the effect relative to IFN β-1a was greater in the high disease activity group (rate ratio 0.497: 95% CI 0.397, 0.621) than in the low/unknown disease activity group (rate ratio=0.614: 95% CI 0.490, 0.770). For new or newly enlarging T2 lesions, the results by baseline activity were comparable (reductions of 53.7% and 52.3%, respectively, for high and low/unknown disease activity).

In Study 301, there was a 43% reduction in 6-month sustained disability progression with daclizumab compared to IFN β-1a in the high disease activity subgroup (HR=0.57, p=0.0102). No significant difference was evident between treatment groups in the low/unknown disease activity group (HR=0.89, p=0.5662). The stronger treatment effect in the high disease activity subgroup may be due to a higher rate of disease progression in the IFN β-1a group, which provides more power to detect a treatment benefit. Conversely, the low rate of disease progression in the IFN β-1a arm provides less power to detect a treatment effect in the low disease activity subgroup. A similar pattern has been seen in other MS development programs in which a significant treatment benefit over IFN β-1a has been difficult to establish when there is a low progression rate [Cohen 2012] [Coles 2012]. Nevertheless, the clearly

superior findings of efficacy against disability progression compared to placebo in the low disease activity subgroup of Study 201 provide evidence that daclizumab does have a beneficial effect on disability progression in these subjects.

The results of these analyses demonstrate that the benefit/risk profile of daclizumab seem favourable when high disease activity is redefined based on the amended definition. The overall safety profile of daclizumab is consistent in subjects with low and high disease activity at baseline in both studies. Likewise, daclizumab provides a meaningful and consistent efficacy benefit over placebo and IFN β-1a whether measured in terms of relapses (annualized relapse rate), number of new/newly enlarging T2 lesions, or disability progression in subjects with both high and low disease activity at baseline. The differences between subgroups for some of the safety and efficacy results in both studies were generally observed in both the daclizumab and control groups and were consistent with the greater level of disease activity at baseline.

2.5.1.2.5. Analysis performed across trials (pooled analyses AND meta-analysis)

In both pivotal studies, a greater treatment effect was observed for daclizumab 150 mg relative to control across all pre-specified demographic and baseline characteristic subgroups for each of the efficacy endpoints analysed. A pooled analysis of annualized relapse rate over 1 year was conducted in which data for subjects in the Daclizumab 150 mg dose groups of Studies 201 and 301 were pooled and compared to the results for the placebo group in Study 201 and the IFN β-1a group of Study 301.

The results of the pooled analysis favoured daclizumab treatment over control for all subgroups and show that the annualized relapse rate for daclizumab-treated subjects was consistent across the prespecified demographic and disease characteristics subgroups. The results demonstrate that the daclizumab efficacy observed in the ITT analyses for Studies 201 and 301 was not driven disproportionately by particular RRMS patient subgroups. In addition, daclizumab effectively reduced disease activity in every subgroup across the spectrum of RRMS patients. Based on the cross-study population PK analysis, body weight accounted for less than 40% of the inter-subject variability in daclizumab clearance. The impact of body weight on daclizumab exposure does not appear to be clinically relevant as the ARRs in Study 301 were similar across subgroups based on body weight quartiles.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal studies were designed and carried out with adequate methodology to assess the main objectives. The selected comparator was IFN β-1a and it is considered acceptable, although it is probably the least effective form of IFN β treatment in RRMS.

No significant deviation was observed from current guidelines regarding pivotal trials. The published guidance suggests a 5 year period to assess maintenance of effect on disease progression and although this has not been accomplished the development programme is still quite comprehensive.

Efficacy data and additional analyses

The efficacy of daclizumab has been tested in 2 randomized, double-blind, controlled, pivotal studies. In the first study (Study 201 see 2.5.1.2.1.), the efficacy of daclizumab was compared to placebo, and in the other study (Study 301 see 2.5.1.2.2.), the efficacy of daclizumab was compared to a current standard of MS treatment, IFN β-1a. Both of these studies demonstrated consistent and robust treatment effects of daclizumab across well-validated clinical, radiographic, and patient-reported MS outcome measures. The

effects of daclizumab were apparent after the first dose as defined radiographically and within 3 months as defined by clinical endpoints. The benefits of daclizumab were then sustained over 3 years during continuous treatment.

Both clinical studies were designed to enrol a broad population of RRMS patients who had experienced relapses. The mean age of subjects was approximately 36 years, and the percentage of subjects with highly active MS (defined as having ≥ 2 relapses in the prior year and ≥ 1 Gd+ lesion on baseline MRI) at study entry ranged from 16% to 21%. The two studies enrolled subjects across a broad geographic catchment area, representing a diversity of MS practice patterns and healthcare systems. In both studies, a minority of enrolled subjects had received prior DMT, but the proportion was higher in Study 301 (41%) compared to Study 201 (20%).

The primary endpoint of both Studies 201 and 301 was the annualized relapse rate. Both studies demonstrated a robust effect of daclizumab on the reduction in clinical MS relapses: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301. The effect was consistent for subject-reported relapses, protocol defined relapses, and INEC-confirmed relapses. The observed relapse rate in the daclizumab-treated subjects was highly consistent at common time points across the two studies and was sustained over the duration of therapy: 0.211 over 1 year in Study 201 versus 0.249 over 1 year in Study 301. The annualized relapse rate for severe or serious relapses in the daclizumab arm at 1 year was 0.096 in Study 201 and 0.094 in Study 301, representing a 67% reduction relative to placebo ($p < 0.0001$) in Study 201 and a 34% reduction relative to IFN β-1a ($p = 0.0117$) in Study 301. The results of the analyses of annualized relapse rate in Studies 201 and 301 were supported by analyses of the proportion of subjects who relapsed. The proportion of subjects on daclizumab who relapsed after 1 year of treatment was 19% in both Studies 201 and 301. This represented a 55% reduction in the risk of relapse compared to placebo in Study 201 and a 39% reduction at 1 year compared to IFN β-1a in Study 301.

Consistent with the impact seen on clinical MS relapses, daclizumab demonstrated a robust and substantial effect on reducing focal areas of inflammation and tissue destruction defined by MRI in comparison to placebo and IFN β-1a. daclizumab treatment resulted in a 70% reduction in new or newly enlarging T2 lesions compared to placebo at 1 year in Study 201 and a 54% reduction compared to IFN β-1a at 2 years in Study 301 ($p < 0.0001$ for both comparisons). The number of new or newly enlarging T2 lesions in the Daclizumab 150 mg treatment group was consistent at similar time points in Studies 201/202 when compared to Study 301 (adjusted mean of 1.55 and 2.16 lesions at Week 24 and 2.83 and 4.31 lesions at Week 96). Since Gd enhancement typically lasts for only about 3 weeks, analysis of Gd+ lesions provides an informative way to assess the maintenance of efficacy over time. On this endpoint, the effect of daclizumab was highly consistent across the 2 studies, with a mean of 0.5 Gd+ lesions at Week 24 in both Studies 201 and 301 and 0.3 Gd+ lesions at 2 years in the Studies 201/202 compared to 0.4 Gd+ lesions in Study 301. Analysis of other MRI endpoints across studies such as T2 lesion volume and the number and volume of T1 hypointense black holes across Studies 201/202 and 301 demonstrated a consistent and robust effect of daclizumab that was present by Week 24 and sustained for the duration of daclizumab treatment.

In both pivotal studies, there was evidence that daclizumab reduced the risk of confirmed disability progression. In Study 201, daclizumab reduced the risk of 12-week confirmed disability progression by 57% relative to placebo ($p = 0.0211$) and the risk of 24-week confirmed disability progression by 76% ($p = 0.0037$). In Study 301, daclizumab reduced the risk of 12-week confirmed disability progression by 16% ($p = 0.1575$; not statistically significant) and the risk of 24-week confirmed disability progression by 27% ($p = 0.0332$). The differences in the daclizumab efficacy estimates for disability progression between Studies 201 and 301 are consistent with the established effect of IFN β-1a on confirmed

disability progression compared to placebo (37% vs. placebo in registrational studies). Overall, the magnitude of the treatment effect on confirmed disability progression against IFN β-1a in Study 301 (16% to 27% reduction) is confirmatory of the 57% to 76% reduction in confirmed disability progression against placebo in Study 201, recognizing the effect of IFN β-1a on this endpoint. Furthermore, the observed rates of disability progression during daclizumab treatment were consistent across Studies 201 and 301. In Study 301, confirmed disability progression was common after a tentative disability progression among subjects with at least one tentative disability progression in the trial: 35% for 12-week confirmed progression and 24% for the 24-week confirmed progression. Censoring after a tentative disability progression was nearly twice as common in the IFN β-1a group compared to the daclizumab group (43 vs. 24 for the 12-week confirmed progression), reflecting a proportionally higher number of tentative disability progressions in the IFN β-1a arm of the trial. While the number of subjects censored after a tentative disability progression (n = 67) was small relative to the total number of subjects with a tentative disability progression in the trial (n = 736), assumptions made about disability progression in these censored subjects impacted whether the test of statistical significance for disability progression was above or below the 0.05 significance threshold in Study 301. Pre-specified analyses of disability progression in Study 301 supported a significant treatment effect of daclizumab over IFN β-1a on both 12- and 24-week confirmed disability progression analyses, except when analysed under the assumption that disability progression did not occur in any patient who was censored after a tentative disability progression.

In order to gain the full RMS indication the applicant was asked to demonstrate a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided in the response to the CHMP query, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects and was considered sufficient to support an indication for “relapsing forms of MS.”

Other tertiary efficacy endpoints in Study 301 that are considered close correlates or mediators of disability progression measured by the EDSS also showed evidence of a treatment benefit of daclizumab. In Study 301, daclizumab demonstrated a benefit over IFN β-1a on physical and cognitive performance measures as defined by the MSFC composite score ($p = 0.0007$) and each of its 3 subcomponents: timed 25-foot walk ($p = 0.0060$), 9HPT ($p = 0.0016$), and the PASAT3 ($p = 0.0411$). In addition, in Study 301, daclizumab also improved cognitive function as measured by the change from baseline on the oral SDMT compared to IFN β-1a therapy at 96 weeks ($p = 0.0274$).

Treatment with daclizumab also reduced brain atrophy relative to both placebo and IFN β-1a across Studies 201/202/203 and 301, an important radiographic correlate of disability progression that may account for much of the variability in treatment effects of MS therapies on disability progression across clinical studies. The annualized PBVC in Study 301 was smaller in the daclizumab group than in the IFN β-1a group (indicating a reduction in whole brain volume loss) during baseline to Week 24 ($p = 0.0325$), a period that may reflect pseudoatrophy due to resolution of brain inflammation, as well as Week 24 to Week 96 ($p < 0.0001$), where the long-term neuroprotective effects of an MS treatment may be more accurately measured. The absolute change in whole brain volume was similar in Studies 201 and 301. In daclizumab-treated subjects, the PBVC was -0.7 during Weeks 0 to 24 in Study 301 and was -0.7 during

Weeks 0 to 52 in Study 201. During Weeks 24 to 96, the PBVC was -0.5 in daclizumab-treated subjects in Study 301 as compared to -0.6 in Year 2 in Studies 201/202. Among subjects who received 3 years of daclizumab across Studies 201/202/203, the PBVC was further reduced to -0.3 in Year 3 of daclizumab treatment, a level of whole brain volume change associated with non-MS, healthy controls of similar age.

Across the 2 pivotal studies, there was clear evidence that daclizumab reduced the physical impact of MS from the patient's perspective. The MSIS-29 physical score was assessed in both Studies 201 and 301 and demonstrated a consistent improvement in daclizumab-treated subjects as compared to no change or worsening in control subjects ($p = 0.0008$ vs. placebo in the change at 1 year in Study 201 and $p = 0.0008$ vs. IFN β-1a in the change at 2 years in Study 301). The improvement in daclizumab-treated subjects was detectable at Week 24 and then generally sustained throughout the treatment period. In both pivotal studies, daclizumab reduced the proportion of subjects with a clinically meaningful decline on the MSIS-29 physical score (≥ 7.5-point worsening from baseline). There was a 44% reduction ($p = 0.0125$) in Study 201 and a 24% reduction ($p = 0.0176$) in Study 301 in the odds of a clinically meaningful decline in the MSIS-29 physical score over the treatment period. When the treatment effect of daclizumab was assessed on the MSIS-29 psychological score and on more generic patient-reported outcome measures such as the EQ-5D, similar treatment effects were present in both pivotal studies. Overall, the consistent results on analyses of the MSIS-29 physical score supported the treatment effect of daclizumab on clinician-assessed disability progression measured by the EDSS and provided an important affirmation that the treatment benefits were meaningful to the patients.

In both trials, a sequential closed testing procedure was used to test statistical significance on secondary endpoints to protect against multiple hypothesis testing. In Study 201, lack of statistical significance on the change in the MSIS-29 Physical Impact score in the 300-mg dose group prevented testing of the MSIS-29 Physical Impact score in the 150-mg dose group within this procedure. Similarly, in Study 301, the lack of statistical significance on the 12-week confirmed disability progression analysis prevented testing of lower ranked secondary endpoints within the closed testing procedure. Nevertheless, the magnitude of the observed treatment effects on the other pre-specified secondary endpoints that were not tested as part of the sequential closed testing procedure and the similarity of the daclizumab treatment effects on these endpoints across the 201 and 301 trials make it unlikely that the results were due to chance. The consistency of the efficacy results of the 2 pivotal studies both internally with respect to the magnitude of the clinical and radiographic findings as well as the similarity of outcomes among daclizumab-treated subjects at common timepoints across the 2 studies provides strong evidence for the validity of the efficacy findings in the daclizumab development program. Substantial efforts were made in both studies to achieve and maintain effective blinding of investigators and subjects during the course of the studies. While there was potentially more opportunity for unblinding in Study 301 due to the known side effects of IFN β administration, the efficacy estimates for daclizumab were similar across clinical and radiographic endpoints, IFN-naïve and experienced patients, and those with and without flu-like symptoms during Study 301. The concordance of efficacy findings between Studies 201 and 301 on both clinical and radiologic endpoints provides further support for the integrity of the results. While the absolute rate of treatment completion was lower in the 2- to 3-year treatment period of Study 301 compared to the 1-year treatment period of Study 201, the effects of daclizumab on efficacy endpoints were observed early in treatment when the incidence of dropout was low and were then sustained throughout both studies at a similar magnitude. Sensitivity analyses that included data after treatment had been permanently discontinued and/or alternative MS treatments had been started showed similar results to the primary analyses.

In both pivotal studies, subgroup analyses of efficacy demonstrated that the effect of Daclizumab 150 mg relative to control favoured daclizumab across all key demographic and baseline characteristic subgroups for each of the efficacy endpoints analysed. There was some variation in treatment effect estimates

across the multiple subgroups analysed, but the differences between subgroups were not consistent across related efficacy endpoints. Overall, the benefits of daclizumab over the comparator group were evident in all key subgroups for each of the efficacy endpoints, and there was no convincing evidence for effect modification by any of the characteristics analysed.

2.5.3. Conclusions on the clinical efficacy

The results of the DAC HYPdaclizumab pivotal clinical studies support the following conclusions regarding the efficacy of DAC HYPdaclizumab in the treatment of subjects with relapsing forms of MS:

- Daclizumab 150 mg SC every 4 weeks produced relevant effects on clinical, radiographic, and possibly patient-reported MS outcome measures compared to both placebo and IFN β-1a, a current standard of MS care. These effects include a reduction in the risk of relapse, confirmed disability progression, number of new/newly enlarging T2 lesions, and worsening in the patient-reported physical impact of MS.
- The consistency of the efficacy results of the 2 pivotal studies supports the validity of the efficacy findings within the clinical development program.
- The efficacy of Daclizumab 150 mg was noticed within 1 month for radiographic endpoints such as new Gd-enhancing lesions, within 3 months for endpoints such as relapse, and within 6 months for disability progression.
- The effects of Daclizumab 150 mg that were observed early in treatment were sustained, over 3 years of treatment.
- The benefits of daclizumab over the comparator group were evident across prespecified subgroups defined by demographic factors and MS characteristics. There was no convincing evidence for effect modification by any prespecified characteristic.
- Overall, immunogenicity to daclizumab was typically transient and most often occurred during the first year of treatment. ABs to daclizumab had no discernible effect on clinical efficacy.
- The lowest efficacious dose of Daclizumab is 150 mg once a month by SC injection. The 300-mg dose provided no additional benefit. Doses of daclizumab lower than 150 mg may have lower efficacy and are not expected to improve tolerability based on the results of the supportive Phase 2 dose-finding study using DAC Penzberg (DAC-1012).
- The totality of the efficacy results supports the proposed commercial dose of Daclizumab 150 mg once a month that will provide clinically meaningful treatment benefits to relapsing MS patients in comparison to both placebo and IFN β-1a.

2.6. Clinical safety

The safety profile of Daclizumab has been evaluated in healthy volunteers and in MS subjects who comprise the majority of the safety data.

Safety data from the pivotal placebo-controlled Study 201 and the active-controlled Study 301 provide the best source of information defining the safety profile of daclizumab in the intended population and aid in distinguishing treatment-related events from background events expected in this population. To evaluate the long-term safety of daclizumab, safety data from the controlled studies have been combined with data from the dose-blinded and uncontrolled studies to form an integrated safety database (referred to hereafter as the total daclizumab experience).

For the 6 MS studies, the integrated safety database includes all safety data from the completed controlled and dose-blinded studies (Studies 201, 301, and 202) and safety data for the ongoing long-term extension studies as of their respective data cut-off dates (Study 203, 20 January 2014; Study 302, 03 February 2014; Study 303, 28 February 2014). Any deaths and important SAEs as of 31 October 2014 have also been described.

At the time of the data cut-offs to support the filing, 2133 MS patients have been dosed with daclizumab. Of these subjects, 348 who had previously been treated with IFN β-1a in Study 301 had received their first dose of daclizumab in Study 303 but had not had the first post-dose safety visit; therefore, they are not included in the integrated safety population.

The integrated safety population for the SCS consists of 1785 MS patients who received daclizumab for periods up to 6 years, accounting for approximately 4100 subject-years of exposure. This represents the total daclizumab experience. Of these subjects, 1215 have been exposed for ≥ 2 years and 573 were exposed for ≥ 3 years. This extent of exposure satisfies and exceeds ICH population exposure requirements for assessment of clinical safety (ICH E1).

Study data from 127 healthy volunteers from the 4 Phase 1 studies that support the development program were not integrated, since these studies are different in their design, study population, objectives, daclizumab doses, and dosing regimens. Safety results from these studies are generally consistent with the safety profile seen in the MS subjects.

During the daclizumab clinical development program, the Sponsors instituted thorough safety monitoring. Subjects had clinic visits every 4 weeks throughout the 1- to 3-year pivotal studies and every 4 to 12 weeks during the extension studies. Subjects who discontinued study treatment were encouraged to remain in the studies and to complete all follow-up study assessments, and a minimum of 6-months of safety follow-up.

An independent data safety monitoring board (DSMB) was convened to monitor safety and the overall benefit/risk profile throughout the development program, and received monthly SAE reports from all ongoing daclizumab studies, regardless of the development phase. The DSMB consisted of expert neurologists, statisticians, as well as a hepatologist, infectious disease specialist and rheumatologist/immunologist. The DSMB met regularly and evaluated AEs and SAEs, as well as laboratory data, vital signs and ECG summaries.

An increased incidence of liver transaminases and cutaneous events were observed in daclizumab clinical studies. For both observations, the Sponsor worked closely with independent expert hepatologists and dermatologists to develop detailed procedures and guidances for monitoring and managing the treatment of subjects with transaminase elevations or cutaneous events. These guidances were incorporated into the protocols and specific processes and forms for AEs of special interest were implemented in the studies to collect detailed follow-up information on hepatic and cutaneous events that occurred during treatment, enabling a comprehensive review of these events. To closely monitor the cutaneous events, a blinded, independent dermatologist (referred to hereafter as the central dermatologist) reviewed clinically significant cutaneous AEs from the ongoing studies and provided regular reports to the DSMB. A final assessment of the cutaneous safety profile of daclizumab by the central dermatologist is provided.

During Study 202, 1 subject in the Daclizumab 300 mg/washout/300 mg group died of liver failure due to autoimmune hepatitis. In response to this event and to the observed elevations in liver transaminases, all ongoing studies were updated to include liver function test (LFT) monitoring every 4 weeks during treatment if not already required, to provide additional guidelines on dose interruption and discontinuation, and to limit concomitant treatment with specific medications associated with hepatotoxicity.

An independent committee of hepatologists (the Hepatic Adjudication Committee [HAC]) was convened to better characterize the hepatic risks associated with daclizumab and to review and adjudicate specific events of hepatic injury. A summary of the key safety findings are as follows and, for brevity, are focused on the proposed dose of Daclizumab 150 mg. The safety profile for Daclizumab 150 mg and 300 mg were comparable and are discussed in the main portions of the SCS and the CSR for Study 205MS201.

Statistical Methods

Daclizumab was evaluated in 4 studies of HVs and 6 studies of subjects with MS. Data from all 6 MS studies of daclizumab, including the placebo-controlled, active-controlled, dose-blinded, and open-label studies, were used to assess the overall safety profile of daclizumab in MS subjects.

The safety assessment primarily uses analyses from the 2 pivotal studies (205MS201 and 205MS301). The distinct populations in these studies are referred to as the placebo-controlled experience and the active-controlled experience, and include all daclizumab safety data in a blinded study with a comparator (placebo or active) over a period of 1 to 3 years.

Supportive analyses were based on integrated safety data from subjects dosed with daclizumab in any of the 6 MS studies in order to summarize the overall and long-term safety experience of MS subjects who received daclizumab. This population is referred to as the total daclizumab experience.

Treatment Groups and Pooling Strategy for the Integrated Analysis of Safety

The 4 Phase 1 studies of daclizumab in HVs were neither pooled with the MS studies nor analyzed as a separate integrated group because the designs of these studies varied in the number of doses (single or multiple) and route of administration (SC or IV).

The placebo-controlled experience (Study 205MS201) and active-controlled experience (Study 205MS301) were analyzed separately. These 2 studies were not integrated into a pool of all controlled studies because of differences in treatment duration (1 year versus 2 to 3 years, respectively), uneven sample size in the common treatment 150 mg dose arm (208 vs. 919), and the absence of a common comparator.

The treatment groups in the Placebo-Controlled experience are placebo (n=204), Daclizumab 150 mg (n=208), and Daclizumab 300 mg (n=209). In most analyses of the Placebo-Controlled experience, summary statistics are presented for the combined daclizumab arms (n=417) in addition to the individual treatment groups.

The treatment groups in the Active-Controlled experience are IFN β-1a (n=922) and Daclizumab 150 mg (n=919).

The total daclizumab experience includes integrated data for subjects treated with daclizumab in any of the MS studies. The pooled treatment groups for the safety population in the total daclizumab experience are Daclizumab 150 mg (n=1492) and Daclizumab 300 mg (n=293). In all analyses of the total daclizumab experience, summary statistics are presented for the combined daclizumab arms (n=1785) in addition to the individual pooled treatment groups. Subjects randomized to Daclizumab 300 mg in Study 205MS201 or Study 205MS202 were analyzed in the Daclizumab 300 mg analysis treatment group; all others were included in the Daclizumab 150 mg analysis treatment group. Note that any subject follow-up time in Study 205MS203 for subjects in the Daclizumab 300 mg analysis treatment group remained attributed to the 300 mg dose group, even though all subjects who entered Study 205MS203 were switched to Daclizumab 150 mg at the start of that study.

Patient exposure

The placebo-controlled studies consists of data from 417 patients who received Daclizumab at 150 mg SC (n=208) or 300 mg SC (n=209), and 204 subjects who received placebo for a period of up to 1 year, representing 423 subject-years of overall exposure to Daclizumab, 211 and 212 subject-years on Daclizumab 150 mg and 300 mg, respectively.

In the active-controlled experience, 919 patients received Daclizumab 150 mg and 922 subjects received IFN β-1a for periods of up to 3 years. The mean (median) time on treatment was 100.54 (111.43) weeks for the IFN β-1a group and 102.04 (108.71) weeks for the daclizumab group. The total number of subject-years of exposure was 1872.9 years in the IFN β-1a and 1952.2 years in the daclizumab group.

For the total daclizumab experience, 1785 patients in the safety population were dosed for periods up to 6 years and the total number of subject-years exposed to daclizumab was 4098. Approximately 60% of the subjects in the total daclizumab group were exposed to at least 25 months of daclizumab.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range	Patients with long term* safety data
Placebo-controlled	621	417	208	194
Active -controlled	1841	919	919	839
Open studies	1854	900	816	349
Post marketing	NA			
Compassionate use	NA			

There is a slight difference between the number of pts exposed to the proposed dose (816) and the previous value for pts exposed to the proposed dose range (831) but this may reflect the fact that some pts may have been treated with a near 150 mg dose, without a real 150 mg dose. This was not considered an issue.

Overall, the safety database is robust and sufficient for identifying uncommon risks and may also be able to detect risks with an incidence as low as 1 in 1000 subject-years associated with daclizumab.

Table 29 Treatment Groups and Pooling Strategy

Groups (n=analyzed) [N=dosed]*	Studies (duration)	Treatment regimens in the study	Treatment groups for analysis
Placebo-Controlled Experience (n=621)	Study 201 (1 year)	Placebo (n=204) DAC 150 (n=208) DAC 300 (n=209)	Placebo (n=204) DAC 150 (n=208) DAC 300 (n=209) DAC total (n=417)
Active-Controlled Experience (n=1841)	Study 301 (2-3 years)	DAC 150 (n=919) IFN (n=922)	DAC 150 (n=919) IFN (n=922)
Total DAC HYP Experience (n=1785) [N=2133] (all RRMS subjects who received DAC HYP in a controlled or uncontrolled study)	Studies 201/202/203 (ongoing)	Placebo/DAC 150/150 (n=86) DAC 150/Washout/150 (n=86) DAC 150/150/150 (n=122**) Placebo/DAC 300/150 (n=84) DAC 300/Washout/300/150 (n=88) DAC 300/300/150 (n=121**)	DAC 150 (n=1492) [N=1840] DAC 300 (n=293) DAC total (n=1785)
	Studies 301/303 (ongoing)	DAC 150 (n=919) IFN/DAC 150 (n=146) [N=494]	
	Study 302 (ongoing)	DAC 150/Washout/150 (n=113) DAC 150 (n=20, TP-DI substudy)	

201 = Study 205MS201; 202 = Study 205MS202; 202 = Study 205MS202; 301= Study 205MS301; 302 = Study 205MS302; 303 = Study 205MS303; IFN = interferon; TP-DI = therapeutic protein-drug interaction

* N dosed is displayed if different from analyzed safety population. For subjects receiving DAC HYP for the first time in Study 303, some post-dosing follow-up was required for inclusion in the safety population (see Section 1.1.4.2) prior to the data cut-off. Study 303 was still enrolling at the time of the data cut-off.

** Includes Study 201 DAC HYP subjects who did not enter Study 202.

Adverse events

The safety results in this section are presented for the placebo-controlled daclizumab experience (Study 205MS201, 1 year of exposure), the active-controlled daclizumab experience (Study 205MS301, 2 to 3 years of exposure), and the total daclizumab experience for controlled and uncontrolled studies (up to 6 years of daclizumab exposure). The placebo-controlled, active controlled and total daclizumab analyses included all available information from the first dose of treatment up to 180 days after the last dose of any study treatment in the subject's last study, regardless of whether the subject received alternative MS therapy. All AE analyses in this section are presented according to the principle of treatment emergence.

Placebo-Controlled Experience

- In Study 205MS201, the overall incidence of AEs was similar across groups (79% placebo, 73% and 76% in the Daclizumab 150 mg and 300 mg groups, respectively). The majority of subjects had AEs that were mild or moderate in severity. The incidence of subjects with severe AEs was 3% in the placebo group, 4% in the Daclizumab 150 mg group, and 6% in the Daclizumab 300 mg group. The incidence of subjects with treatment-related AEs was higher in the daclizumab group than in the placebo group (22% placebo, 29% Daclizumab 150 mg, 35% Daclizumab 300 mg).

The incidence of SAEs was higher in the placebo group (26%) than in the Daclizumab groups (15% Daclizumab 150 mg, 17% Daclizumab 300 mg) due to the higher incidence of MS relapse in the placebo group. The incidence of SAEs excluding MS relapse was higher in Daclizumab 300 mg group (9%) and similar in the placebo and Daclizumab 150 mg groups (6% and 7%, respectively). The incidence of AEs leading to treatment discontinuation was higher in the Daclizumab groups (3% Daclizumab 150 mg, 4% Daclizumab 300 mg) compared with placebo (<1%).

Active-Controlled Experience

- In Study 205MS301, the overall incidence of AEs was balanced across the 2 treatment groups (91% IFN β-1a, 91% Daclizumab). The incidence of AEs that were considered severe was 14% in the Daclizumab group and 12% in the IFN β-1a group. More subjects in the IFN β-1a group (65%) than in the daclizumab group (52%) had AEs that were considered by the Investigator to be related to study treatment. Excluding MS relapse, there was a higher incidence of SAEs and AEs leading to study treatment discontinuation in the daclizumab group compared with the IFN β-1a group (SAEs: 10% IFN β-1a, 15% daclizumab; AEs leading to discontinuation: 9% IFN β-1a, 14% daclizumab). The incidence of withdrawal from study due to AEs was similar for the 2 groups (7% in each group).

Total daclizumab Experience

- The overall incidence of AEs for all subjects who received daclizumab in the total daclizumab experience was 88%. In general, the incidence of subjects with AEs, moderate or severe AEs, AEs related to study treatment, and SAEs and AEs leading to study discontinuation in the total daclizumab experience was similar to the placebo- and active-controlled experiences.

Overall Incidence of Adverse Events

In the total daclizumab group, the most common AEs (≥ 20%) by SOC were infections and infestations (62%), nervous systems disorders (50%), skin and subcutaneous tissue disorders (35%), general disorders and administration site conditions (31%), gastrointestinal disorders (26%), musculoskeletal and connective tissue disorders (26%), and investigations (24%). The most common AEs (incidence ≥ 10%) in total daclizumab group are multiple sclerosis relapse, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection.

Table 30 Adverse Reactions Reported for daclizumab

System Organ Class	Adverse Reaction	Frequency
Infections and Infestations	Nasopharyngitis†	Very common
	Upper respiratory tract infection†	Very common
	Influenza†	Common
	Bronchitis	Common
	Pharyngitis	Common
	Respiratory tract infection	Common
	Tonsillitis†	Common
	Rhinitis*	Common
	Viral infection	Common
	Pneumonia	Common
	Laryngitis	Common
	Folliculitis	Common
Blood and lymphatic system disorders	Lymphadenopathy†	Common
	Anaemia*	Common
	Lymphadenitis	Common
Psychiatric disorders	Depression*	Common
Respiratory, thoracic and mediastinal disorders	Oropharyngeal pain†	Common
Gastrointestinal disorders	Diarrhea	Common
Skin and subcutaneous tissue disorders	Rash*†	Common
	Eczema†	Common
	Erythema	Common
	Pruritus	Common
	Acne†	Common
	Seborrhoeic dermatitis†	Common
	Dry skin	Common
	Dermatitis	Common
	Dermatitis allergic	Common
	Rash maculopapular	Common
	Psoriasis	Common
	Skin exfoliation	Common
	Exfoliative rash	Uncommon
	Eczema nummular	Uncommon
	Toxic skin eruption	Uncommon
General disorders and administration site conditions	Pyrexia*	Common
Investigations	ALT increased*	Common
	AST increased*	Common
	Liver function test abnormal	Common
	Hepatic enzyme increased	Common

*Observed with a ≥2% higher incidence than placebo.
†Observed with a ≥2% higher incidence than IFN β-1a IM.

Regarding suicidal behaviour in study 201: there were no serious events related to suicidal behaviour (completed suicide, attempted suicide, or suicidal ideation). However, there was an imbalance in adverse events related to depression and depressed mood in subjects treated with daclizumab in Study 201. All events were mild or moderate in intensity and no subject discontinued study drug for depressive adverse

events. In Study 201 and Study 205MS301, concomitant use of antidepressant / anxiolytic / antipsychotic medications was balanced across treatment arms. For these analyses, medications were identified using the ATC codes as designated in the WHO Drug Dictionary and included all drug codes that were assigned ATC code N06A ANTIDEPRESSANTS, NO5B ANXIOLYTICS and NO5A ANTIPSYCHOTICS for antidepressants, anxiolytics and antipsychotic medications, respectively, as well as the corresponding ATC codes that roll up to each of those classes.

Serious adverse events and deaths

Deaths

As of 31 October 2014, 10 deaths have been reported in the daclizumab clinical development program. Five deaths were reported among the 922 subjects who had received IFN β-1a, and 5 were reported among 2133 subjects who had received daclizumab. There were no deaths reported in the HV studies.

Seven subjects died while on study and are listed in Appendix Table 43. Two subjects (3011291 and 3010274) died after withdrawing from the study, and 1 subject (3010977) died after the data cut-off date. A summary of all deaths is provided in Table below. Of the 5 deaths that occurred during or after treatment with daclizumab, there were 2 cases in which a contributory role for daclizumab could not be excluded. In Study 205MS201, 1 subject who was treated with Daclizumab 150 mg and was recovering from a serious rash died due to ischemic colitis that occurred secondary to a psoas abscess. In Study 205MS202, 1 subject in the Daclizumab 300 mg/washout/ 300 mg reinitiation group died of liver failure due to autoimmune hepatitis. In the other 3 cases that occurred during or after treatment with daclizumab, death was not considered related to study treatment. In subjects treated with IFN β-1a in Study 205MS301, there were 4 deaths secondary to acute myocardial infarction, peritonitis, completed suicide, and metastatic cancer of the pancreas. After discontinuing from the study, 1 subject died from MS progression. None of the deaths were considered related to study treatment.

Table 31 Listing of Deaths

Treatment Group	Subject No.	Age, Sex, Country	Study Day of Death	Cause of Death	Relationship of Death to Study Treatment	Risk Factors or Relevant Medical History
Study 205MS201						
DAC HYP 150 mg	2010516	49-year-old, female, United Kingdom	402	Colitis ischemic and psoas abscess	Related	The subject had a complex clinical course beginning with hospitalization for a maculopapular rash.
Study 205MS202						
DAC HYP 300 mg/ washout/300mg	2010177	45-year-old, female, Ukraine	692 (Day 315 of Study 202)	Autoimmune hepatitis liver failure, multiple organ failure	Not related	None
Study 205MS301						
IFN β-1a	3010469	40-year-old, male, Russian Federation	145	Acute myocardial infarction	Not related	This subject had a medical history that included hypertensive disease, acute myocardial infarction, coronary disease, atherosclerosis of aorta, and coronary stenting.
	3011419	43-year-old, female, Russian Federation	148	Peritonitis	Not related	This subject developed peritonitis after an emergency laparotomy for abdominal pain.
	3011007	41-year-old, male, Ukraine	446	Suicide	Not related	None
	3010181	53-year-old, male, Czech Republic	924	Pancreatic cancer metastatic	Not related	This subject had neuropathic pain and was hospitalized. CT scan showed tumorous process in the left lung, tumorous enlargement of the pancreas, and metastatic process in the liver.
	3011291	28-year-old, male, India	284	Progressive relapsing MS	Not related	None
DAC HYP 150 mg	3010178	46-year-old, female, India	202	Multiple sclerosis, pneumonia aspiration, decubitus ulcer, sepsis, cardio-respiratory arrest	Not related	This subject developed acute exacerbation of MS that involved the brainstem and lost her ability to swallow.
	3010274	37-year-old, female, India	179	Acute respiratory distress syndrome, septic shock	Not related	This subject developed an acute exacerbation of MS that involved the brain stem.
Study 205MS303						
DAC HYP 150 mg	3010977	39-year-old, female, Russian Federation	193	Subdural haematoma, brain oedema, brain compression, traumatic intracranial haemorrhage	Not related	This subject fell in the bathroom and developed compression of ventricular system and large traumatic subarachnoid hemorrhage that led to brain edema and dislocation.

Sources: Individual Subject narratives in the respective CSRs and in Appendix Table 43 for 7 subjects who died on study. For 3 subjects (3011291 and 3010274, who died after leaving the study, and 3010977, who died after the data cut-off date), the Investigators reported the deaths to the Sponsor through the adverse event reporting system.

Other Serious Adverse Events

SAEs are described in this section for the placebo-controlled, active-controlled, and total daclizumab experiences.

Placebo-Controlled Experience

In Study 205MS201, the incidence of SAEs was 26%, 15%, and 17% in the placebo, Daclizumab 150 mg, and Daclizumab 300 mg groups, respectively. Excluding MS relapse, the incidence of SAEs was 6%, 7%, and 9% in the placebo, Daclizumab 150 mg, and Daclizumab 300 mg groups, respectively. The most common SAEs by SOC (≥ 1% in any treatment group) were nervous system disorders, infections and infestations, skin and subcutaneous disorders, and gastrointestinal events . The most common SAE by PT was MS relapse (22% placebo, 9% Daclizumab 150 mg, 9% Daclizumab 300 mg). All other SAEs by PT occurred in <1% of subjects each, and none occurred in more than 1 subject in any group. The

percentage of subjects reporting an SAE in each 3-month interval was consistent across the duration of the study, indicating no overall time-related pattern of reporting of SAEs.

Active-Controlled Experience

In Study 205MS301, the incidence of SAEs was higher in the daclizumab group than in the IFN β-1a group (24% vs. 21%, respectively). Excluding MS relapse, SAEs were reported in 10% of the IFN β-1a group and 15% of the daclizumab group. In the daclizumab group, SOCs with an incidence of SAEs ≥ 1% were nervous system disorders (12%); infections and infestations (4%); neoplasms, benign, malignant, and unspecified and skin and subcutaneous disorders (2% each); and blood and lymphatic system disorders and gastrointestinal disorders (1% each). SAEs reported in 3 or more daclizumab-treated subjects were MS relapse, urinary tract infection, pneumonia, lymphadenopathy, convulsion, fall, uterine leiomyoma, lymphadenitis, depression, dermatitis, and nephrolithiasis. With the exception of MS relapse, all of these SAEs were reported in <1% of subjects. In the IFN β-1a group, SOCs with an incidence of SAEs ≥ 1% were nervous system disorders (14%); infections and infestations (2%); and neoplasms, benign, malignant, and unspecified (1%). SAEs reported in 3 or more subjects in the IFN β-1a group were MS relapse, acute myocardial infarction, cholelithiasis, and ectopic pregnancy. With exception of MS relapse, all these SAEs were reported in <1% of subjects. In the active-controlled experience, to evaluate potential for atypical MS relapse, a search for SAEs of MS relapse considered related to study treatment and for verbatim terms of "atypical MS relapse" were performed. Based on this search and subsequent medical review, there were no confirmed events of atypical MS in the daclizumab group.

Total daclizumab Experience

In the total daclizumab experience, the overall incidence of SAEs was 25%; excluding MS relapse, the incidence of SAEs was 16%. The SOCs with the highest incidence of SAEs was nervous system disorders (13%). Excluding nervous system disorders, SOCs with the highest incidence (≥ 1%) of SAEs in the total daclizumab group were infections and infestations (4%); skin and subcutaneous tissue disorders (2%); gastrointestinal disorders (2%); neoplasms benign, malignant and unspecified: injury, poisoning, and procedural complications; and blood and lymphatic disorders (1% each). In the total daclizumab experience, other SAEs occurring in 3 or more subjects are described in Table 32. SAEs occurring in 5 or more subjects were MS relapse, pneumonia, urinary tract infection, lymphadenopathy, bronchitis, colitis ulcerative, hepatic enzyme increased, MS, and ovarian cyst. With the exception of MS relapse, all of these SAEs were reported in <1% of subjects.

Table 32 Serious Adverse Events Occurring in 3 or More Subjects

	DAC HYP 150 mg	DAC HYP 300 mg	Total DAC HYP
Number of subjects in the pooled safety population	1492 (100)	293 (100)	1785 (100)
Number of subjects with a serious event	345 (23)	102 (35)	447 (25)
MULTIPLE SCLEROSIS RELAPSE	155 (10)	54 (18)	209 (12)
PNEUMONIA	10 (<1)	2 (<1)	12 (<1)
URINARY TRACT INFECTION	11 (<1)	1 (<1)	12 (<1)
LYMPHADENOPATHY	5 (<1)	3 (1)	8 (<1)
BRONCHITIS	1 (<1)	4 (1)	5 (<1)
COLITIS ULCERATIVE	4 (<1)	1 (<1)	5 (<1)
HEPATIC ENZYME INCREASED	3 (<1)	2 (<1)	5 (<1)
MULTIPLE SCLEROSIS	4 (<1)	1 (<1)	5 (<1)
OVARIAN CYST	3 (<1)	2 (<1)	5 (<1)
APPENDICITIS	4 (<1)	0	4 (<1)
CONVULSION	4 (<1)	0	4 (<1)
FALL	4 (<1)	0	4 (<1)
HEPATITIS TOXIC	4 (<1)	0	4 (<1)
LYMPHADENITIS	4 (<1)	0	4 (<1)
NEPHROLITHIASIS	3 (<1)	1 (<1)	4 (<1)
ABORTION SPONTANEOUS	3 (<1)	0	3 (<1)
ADENOMYOSIS	2 (<1)	1 (<1)	3 (<1)
AUTOIMMUNE HEPATITIS	1 (<1)	2 (<1)	3 (<1)
CELLULITIS	3 (<1)	0	3 (<1)
DEPRESSION	3 (<1)	0	3 (<1)
DERMATITIS	3 (<1)	0	3 (<1)
DRUG HYPERSENSITIVITY	2 (<1)	1 (<1)	3 (<1)
ENDOMETRIOSIS	3 (<1)	0	3 (<1)
PULMONARY EMBOLISM	2 (<1)	1 (<1)	3 (<1)
URTICARIA	2 (<1)	1 (<1)	3 (<1)
UTERINE LEIOMYOMA	3 (<1)	0	3 (<1)
VIRAL INFECTION	3 (<1)	0	3 (<1)

NOTE 1: Numbers in parentheses are percentages.
2: A subject was counted only once within each preferred term.
3: Preferred terms are presented by decreasing incidence in the total column.

SOURCE: DACMS/BLA/BLA/T-AE-SER-PT-GE3SUBJ.SAS DATE: 29SEP2014

Upon request, the applicant performed a medical review of all available documentation which indicated that there were 11 subjects with severe depression, 9 of the 11 subjects had a history of depression prior to exposure to daclizumab. There were 7 suicide attempts in 6 subjects who were being treated with daclizumab and 2 of the subjects who attempted suicide had no prior history of depression.

In summary,

- Study 201 shows that daclizumab has an imbalance in depression events, favouring placebo. No events related to suicidality were reported in this study.
- Study 301 shows similar rates of depression events compared to IFN β-1a. The one completed suicide occurred in a subject treated with IFN β-1a. Suicidal ideation was balanced (2 daclizumab; 2 IFN β-1a), 2 subjects attempted suicide in IFN β-1a vs none in daclizumab, and there is one event of depression suicidal in daclizumab vs. none in IFN β-1a.
- On comprehensive review of all information available, across all studies, 6 subjects being treated with daclizumab attempted suicide. Two of these did not have a prior history of depression.

The applicant has acknowledged that Suicidal related behaviour is an important identified concern and that DAC may be related to an increase in the severity of this symptomatology, already frequent in MS. The applicant has upgraded depression in RMP to an important identified risk, and also proposes new wording to SmPC sections 4.4 as further measure for risk minimisation:

“Depression
Zinbryta should be administered with caution to patients with previous or current depressive disorders. Patients treated with Zinbryta should be advised to report any symptoms of new or worsening depression, and/or suicidal ideation to the prescribing physician. If a patient develops severe depression, and/or suicidal ideation, discontinuation of Zinbryta should be considered (see section 4.8).” These measures may be appropriate to minimise risk.

Laboratory findings

Hematology Results

Summary of hematology results:

- No clinically significant changes from baseline in aggregate haematological values were observed across treatment groups. However in the overall daclizumab group, the incidence of decreased post-baseline CD4+ (<400 cells/µL, <200 cells/µL) was 29% and 3%, respectively, and the incidence of decreased CD8+ counts (<200 cells/mm3, <100 cells/mm3) was 34% and 4%, respectively.

Blood Chemistry Results

Summary of blood chemistry results:

- With the exception of liver function tests, no treatment-related differences were noted in subjects treated with daclizumab compared to placebo or IFN β-1a.
- Laboratory results pertaining to liver function showed a higher incidence of elevations in transaminases in subjects treated with daclizumab than in subjects treated with placebo or IFN β-1a.

Liver Function Tests

In the total daclizumab population, the majority of subjects who experienced elevated transaminases (ALT or AST) had maximum post-baseline values <3×ULN. ALT or AST elevations >1×ULN at any time during the study occurred in 47% of daclizumab-treated subjects, elevations ≥ 3×ULN occurred in 11% of subjects, and elevations >5×ULN occurred in 6% of subjects. The incidence of ALT or AST elevations was consistent over time when measured by 6-month intervals.

Kidney Function

In the total daclizumab experience, shifts to high BUN or creatinine values occurred in ≤ 5% of subjects, and shifts to low were observed for creatinine in 1 subject and for BUN in 3 subjects. Mean values from baseline for BUN and creatinine remained stable throughout the study and showed no clinically relevant changes over time. Mean changes from baseline for BUN and creatinine were variable over time. The percentage increase from baseline after Week 48 for BUN and remained stable over time for creatinine. None of these changes were clinically relevant over time.

Urinalysis Results

In the total daclizumab experience, the incidences of shift to high/positive test results for all urinalysis parameters did not reveal any consistent pattern in the development of abnormalities.

Other Laboratory Test Results

In Study 205MS301, no clinically significant changes were observed for thyroid function across treatment groups. Shifts to high TSH and to low thyroxine were similar in the 2 treatment groups and occurred in ≤ 5% and ≤ 12% of subjects, respectively. Shifts to low TSH and to high thyroxine occurred in ≤ 8% and ≤

6% of subjects, respectively (CSR 205MS301, Table 55). Mean values and mean changes from baseline for TSH and total thyroxine remained stable throughout the study in both treatment groups and showed no clinically relevant changes over time; mean values were within the normal range at all timepoints during the study.

Vital Signs

Similar to the placebo- and active-controlled experiences, there were no clinically significant changes in vital signs from baseline to the end of treatment observed in the total daclizumab experience. Overall, the incidence of abnormal post-baseline vital signs and changes in vital signs from baseline using different criteria was comparable to the active-controlled experience, and no clinically relevant changes were noted.

Electrocardiogram

In the total daclizumab experience, ECG results were similar to the results from the placebo- and active-controlled experiences. The absolute values and changes in time from baseline by visit for ECG quantitative parameters (heart rate, PR interval, QRS interval, QT interval, QTcF interval, QTcB interval) showed no clinically significant changes.

Beck Depression Inventory, Second Edition

In the active-controlled experience (Study 205MS301), the results of the BDI-II showed no clinically meaningful differences between the 2 treatment groups, nor were there any clinically meaningful changes from baseline over time (CSR 205MS301, Table 335). Daclizumab-treated subjects had greater improvement on the MSIS-29 Psychological Impact score compared with the IFN β-1a group.

Immunogenicity Analyses

Subjects who were evaluated for immunogenicity were required to have at least 1 post-baseline immunogenicity test. Immunogenicity was determined by measuring anti-drug antibodies (ADAs) using validated assays. Samples that generated a positive response for ADA were further tested for the presence of neutralizing antibodies (NAbs).

Several analyses were performed to detect the impact of ADAs and NAbs on the safety profile of daclizumab for subjects who received Daclizumab 150 mg or 300 mg.

Results show that most ADA and NAb reactivity to daclizumab occurred early during treatment, and that this reactivity was transient. Also, the ADA titers observed were generally low. There was no discernible impact of immunogenicity status on the efficacy, PK, or PD profile of daclizumab. The immunogenicity data with 150 mg and 300 mg doses of daclizumab pooled from all clinical studies were used to summarize key safety parameters by antibody status to see whether there was any impact of ADAs and/or NAbs on the safety profile of daclizumab.

Safety in special populations

Adverse events were examined by the intrinsic factor subgroups of age, gender, race, and body weight, and the extrinsic factors of study region (based on geography and health care systems), prior MS treatment history, alcohol use, smoking status, and antibody status. Overall, although some differences in the incidence of AEs by age and race and by region were observed, there were no clinically relevant differences for these factors, and no impact on the use of daclizumab is expected. There were no significant clinically relevant differences in the safety profile of daclizumab in subjects with and without

prior DMTs (ABCR or immunomodulatory therapy). The available data were evaluated in the following special populations:

- Safety With Use of Systemic Steroids
- Effects on Influenza Vaccine Protection
- Pregnancy, Reproduction, and Lactation
- Pediatric and Elderly Populations
- Hepatic and Renal Impairment
- Overdose and drug abuse

No special safety concern was identified de novo, but it confirmed previous signals, such as hepatic failure risk.

Immunological events

Several analyses were performed to evaluate the impact of ADAs and NAbs on the safety profile of daclizumab for all evaluable subjects who received daclizumab (either 150 mg or 300 mg). There was no correlation with AEs or SAEs based on antibody-positive or -negative status for either ADAs or NAbs. Also, there was no pattern of association between antibody status and anaphylaxis/ hypersensitivity type events. These results suggest that ADAs or NAbs had no discernible effect on the safety profile of daclizumab.

- Anaphylaxis and hypersensitivity
- Autoimmune disorders

Safety related to drug-drug interactions and other interactions

A Therapeutic Protein-Drug Interaction (TP-DI) substudy showed that daclizumab did not affect the systemic exposure of concomitantly administered probe drugs for CYP isoenzymes. In addition, no safety signal of daclizumab related to concomitant IV treatment with corticosteroids was identified.

Interaction with antispastic agents or fampridine has not been discussed at MA submission. Upon request the applicant performed an analysis which did not find any relation suggesting a DDI. The applicant did not perform drug-drug specific trials. All data available for analysis came from efficacy trials. DAC is a monoclonal antibody which does not affect directly other frequently used concomitant treatments which include baclophen, diazepam / tetrazepam, tizanidine and tolperisone. As for fampridine, of all patients enrolled, only 15 were concomitantly treated with daclizumab and fampridine. Evaluation of the AE profile of each DAC-other agent combination did not reveal any discrepancy when compared to DAC alone + other agent alone. Considering that from a pharmacological point of view it is also not expected that interactions may occur on a clinically relevant level, the applicant explanation may be accepted.

Discontinuation due to AES

In the total daclizumab experience, the overall incidence of AEs that led to discontinuation of study treatment was 14%. SOCs with incidence ≥ 1% of AEs by SOC leading to study treatment discontinuation in the total daclizumab group were skin and subcutaneous tissue disorders (4%), investigations (4%) and nervous system disorders (1%). AEs by PT that led to treatment discontinuation in ≥ 1% of subjects in the

total daclizumab experience were ALT increased (2%), LFT abnormal (1%), and MS relapse (1%). The incidence of AEs that led to treatment discontinuation remained stable over time, ranging from 4% to 6% per year.

In the total daclizumab experience, the incidence of AEs that led to withdrawal from study was 9%. In general, the pattern of AEs leading to withdrawal from the study was similar to that observed for AEs leading to discontinuation of study treatment. The most common AEs by SOC leading to study withdrawal are investigations (3%) and skin and subcutaneous tissue disorders (2%). AEs by PT that led to withdrawal from study in ≥ 1% of subjects included ALT increased (1%).

2.6.1. Discussion on clinical safety

The safety of Daclizumab 150 mg has been characterized in clinical studies of 1785 MS subjects treated for up to 6 years, accounting for approximately 4100 subject-years of exposure. During the accumulation of this safety data, several important risks have emerged, including elevations of liver transaminases and hepatic injury, cutaneous events, infections, depression and colitis and strategies and approaches to monitor and mitigate these risks have been implemented and tested in the clinical studies.

daclizumab is associated with a risk of elevations of serum transaminases and cases of hepatic injury. Most often this risk manifests as a transient and asymptomatic increase in ALT/AST that resolves spontaneously or with discontinuation of dosing. In a small number of cases, serious events of hepatic injury, characterized by concomitant elevations of serum transaminases and bilirubin, were identified in which daclizumab may have played at least a significant contributory role based on independent adjudication of the events. With the exception of a fatal case of autoimmune hepatitis early in the clinical development program, prompt identification of these cases, discontinuation of daclizumab, and treatment of underlying or other contributory causes resulted in favourable outcomes. While a single dose of daclizumab given at the time of a transaminase abnormality generally did not appear to worsen or prolong events, the single case of fatal autoimmune hepatitis occurred in the setting of repeated administration of daclizumab during the elevation. Treatment discontinuation for patients meeting certain criteria (and possibly for others, based on physician judgment) is appropriate to limit the severity of the event and to reduce the risk of recurrence in susceptible individuals. The most common cutaneous events during daclizumab use were dermatitis, eczema, and rashes, which were manageable with treatment, including topical and/or systemic steroids, and treatment discontinuation. Some cases were serious and had features of a delayed-type hypersensitivity reaction. These cases typically presented with a more generalized, diffuse rash, and some cases required multiple courses of corticosteroids. While the most serious cases could be a source of significant discomfort to patients, the integrity of the skin was preserved and none of the events were directly life-threatening. Overall, the use of corticosteroids appeared to result in rapid improvement of many of the more serious cases. Over time, events generally resolved or substantially improved without permanent injury to the skin.

Infections were composed mainly of upper respiratory tract, urinary tract, and viral infections typical of those seen in a non-immunocompromised MS population. While the incidence of both minor and serious infections was increased during daclizumab use, the pattern and outcome of the events indicated that the ability of the subjects' immune system to effectively respond to the infection was preserved. Overall, the infections that have occurred during daclizumab use have been manageable with standard care, and the incidence of infections necessitating discontinuation of study treatment has been <1%.

Serious cases of colitis characterized by prolonged diarrhoea, fever, and abdominal pain have been reported in <1% of subjects treated with daclizumab. These events have had a late onset, occurring after 1 year of treatment. These cases had features different from Crohn's disease and did not progress to have

any of the serious sequelae of chronic inflammation, such as perforation, fistulas, or abscess formation. The events appeared to be limited and were managed by discontinuation of study treatment and by standard treatment with anti-inflammatory agents and steroids.

Overall, the safety profile of daclizumab includes several serious risks, including elevations of serum transaminases and hepatic injury, cutaneous events, infections, and colitis. Based on the known immunomodulatory effect of daclizumab and the pattern of AEs observed, including response to treatment, an immune-mediated mechanism was implicated in some of these events. During the development program, procedures were developed in conjunction with experts to enable early identification and management of these risks, and were tested during the clinical studies. These procedures can be translated into the clinical setting and used to provide guidance to prescribers. With appropriate physician and patient education and clinical vigilance, the risks associated with daclizumab can be managed by awareness and early recognition of developing risks, standard medical care, and treatment discontinuation.

There was one death following re-introduction of treatment with daclizumab in Study 205MS202. The Applicant proposed monthly monitoring of liver enzymes in patients treated with daclizumab. The Applicant has engaged a panel of independent expert hepatologists (the Hepatic Adjudication Committee; [HAC]) to adjudicate hepatic events. In the course of their duties, we have requested that the HAC review the proposed monitoring, treatment suspension, and discontinuation rules. The HAC endorsed the measures implemented in the protocols. The HAC was generally in agreement with the proposed recommendation in Section 4.4 of the Summary of Product Characteristics (SmPC) except that it felt that >3×ULN for transaminases was too low a threshold to hold dose, preferring 5× or 8×ULN (HAC 29/30 July 2014 minutes). Overall a conservative approach for treatment discontinuation (ALT or AST >5×ULN), treatment suspension (ALT or AST >3×ULN), and treatment resumption (ALT or AST <2×ULN) was adopted as described below, given its success in the clinical program. After D120 quest, the applicant revised the criteria, and maintains its position to consider that the original proposal that daclizumab dosing be held until the transaminases return to <2 x ULN is still appropriate. Considering that the risk of relapse if a patient stops skips one treatment or two at the most is at the verge of increasing the risk of relapse (which usually increases between the 4th and the 6th month, then reaching baseline levels), there is a time window where DAC may be stopped for safety reasons without jeopardising much efficacy.

2.6.2. Conclusions on the clinical safety

The safety database for daclizumab is sufficiently robust, with 2133 subjects with RMS who have received daclizumab. Of these, 348 subjects are not included in the safety population because they received their first dose of daclizumab in Study 205MS303, but had not yet had the first post-dosing safety visit at the time of database cut-off. The safety population includes 1785 subjects exposed to daclizumab for periods of up to 6 years, accounting for approximately 4100 subject-years. Of these, 1215 subjects were exposed for ≥ 2 years and 573 subjects for ≥ 3 years at or above the proposed commercial dose of 150 mg daclizumab. Thus, the safety database is sufficient for identifying uncommon risks and may also be able to detect risks associated with daclizumab with an incidence as low as 1 in 1000 subject-years.

The overall incidence of AEs was balanced in the placebo-controlled (79% placebo, 73% Daclizumab 150 mg) and active-controlled (91% IFN β-1a, 91% Daclizumab 150 mg) pivotal studies. The majority of subjects had events that were mild to moderate in severity. A higher incidence of severe events was seen in daclizumab treated subjects in the placebo-controlled (3% placebo, 4% Daclizumab 150 mg) and active-controlled (12% IFN β-1a, 14% daclizumab) studies.

There was an increased incidence of serious events excluding MS relapse in the daclizumab-treated subjects in the placebo-controlled (6% placebo, 7% daclizumab 150 mg) and active-controlled (10% IFN β-1a, 15% Daclizumab 150 mg) experience. In the placebo-controlled experience, the most common SAEs (≥ 1%) by SOC in the Daclizumab 150 mg group were nervous system disorders (10%), infections and infestations (3%), and gastrointestinal (GI) disorders (1%). In the active-controlled experience, the most common SAEs (≥ 1%) by SOC in the daclizumab group were nervous system disorders (12%); infections and infestations (4%); neoplasms, benign, malignant, and unspecified and skin and subcutaneous disorders (2% each); blood and lymphatic system disorders and GI disorders (1% each). Most of the increased incidence in serious events for daclizumab-treated subjects was attributable to a small incremental increase of 1% to 2% in serious infections and serious cutaneous events.

The most common (≥ 5%) adverse drug reactions (ADRs) reported at an increased incidence (≥ 2%) in subjects treated with daclizumab compared with placebo were upper respiratory tract infection, rash, depression, and ALT increased. The most common ADRs (≥ 5%) reported at an increased incidence (≥ 2%) in subjects treated with daclizumab compared with IFN β-1a were nasopharyngitis, upper respiratory tract infection, influenza, oropharyngeal pain, rash, and lymphadenopathy.

As of October 31 2014, 10 deaths were reported in the clinical development program, including 5 of 922 subjects who received IFN β-1a (acute myocardial infarction, peritonitis, suicide, metastatic pancreatic cancer, and progressive relapsing MS) and 5 of 2133 subjects who received daclizumab (ischemic colitis; autoimmune hepatitis; complications of brainstem lesions of MS in 2 subjects; trauma and acute subdural hematoma). In 2 cases (ischemic colitis, autoimmune hepatitis), a contributory role for daclizumab could not be excluded. None of the other deaths were considered related to study treatment, including one suicide event.

There was an increased incidence of hepatic events and transaminase elevations in subjects treated with daclizumab.

Compared with placebo and IFN β-1a, an increased incidence of infections (44% placebo vs. 50% Daclizumab 150 mg; 57% IFN β-1a vs. 65% Daclizumab 150 mg) and serious infections (0% placebo vs. 3% Daclizumab 150 mg; 2% IFN β-1a vs. 4% Daclizumab 150 mg) was observed in subjects who received daclizumab. The most common infections by high-level term (HLT) in daclizumab-treated subjects were upper respiratory tract infections, urinary tract infections, and viral infections. The time to onset, median duration, and percentage of infections that resolved were similar between the daclizumab and either placebo or IFN β-1a groups. The overall rate of infections and serious infections did not increase over time. The majority of subjects with infections continued on study treatment, and discontinuations due to infection were <1% for all daclizumab-treated subjects. The pattern and type of infections observed was consistent with those seen in the MS population and was not representative of the types of infections characteristically seen in immunocompromised or immunosuppressed populations.

Cutaneous events (13% placebo vs. 18% daclizumab 150 mg; 19% IFN β-1a vs. 37% Daclizumab 150 mg) and serious cutaneous events (0% placebo vs. <1% Daclizumab 150 mg; <1% IFN β-1a vs. 2% Daclizumab 150 mg) were increased in subjects who received daclizumab compared with those who received placebo or IFN β-1a. The most common cutaneous events in daclizumab-treated subjects were rash, dermatitis, and eczema. The majority of cutaneous events were mild or moderate in severity; 2% of subjects had severe events. Overall, 4% of subjects discontinued daclizumab due to cutaneous events. Most events resolved following treatment with topical or systemic corticosteroids.

Gastrointestinal (GI) events in the GI SOC were reported by more daclizumab-treated subjects in the placebo-controlled (11% placebo vs. 16% Daclizumab 150 mg) and active-controlled (24% IFN β-1a vs. 31% Daclizumab 150 mg) experiences. The majority of subjects with GI events had events that were mild

or moderate in severity. Diarrhea was the most commonly reported GI event. In general, events of diarrhea were similar in incidence, median duration, and percentage of events resolved across the IFN β-1a and daclizumab groups. There was an increased incidence of prolonged diarrhea (>3 weeks) in daclizumab-treated subjects compared with the IFN β-1a treated subjects.

In the total daclizumab experience, 1 out of 1785 subjects (0.06%) had an SAE of potential anaphylaxis (reported with a preferred term of circulatory collapse) that was characterized by dizziness, hypotension, and syncope after the first dose of daclizumab. The event was not life-threatening and the subject was treated with IV fluids and prednisone. In the active-controlled experience, 1 of 922 subjects (0.11%) in the IFN β-1a group and 0 subjects in the daclizumab group had an anaphylactic reaction. Analyses of AEs and SAEs within 24 hours of an injection, of SAEs during the first 6 injections, and of SAEs after discontinuation and reinitiation of treatment showed no other events of anaphylaxis.

In the daclizumab-treated subjects, there was a higher incidence of AEs in the hypersensitivity SMQ and allergic conditions HLGT than in placebo or IFN β-1a subjects. However, this difference was due primarily to an increase of events in the skin and subcutaneous tissue disorders SOC and was not consistent with anaphylaxis or immediated-type drug hypersensitivity events. In the opinion of the central dermatologist, the majority of cutaneous reactions appeared to be eczematous or psoriatic in nature or typical of normal conditions seen in a dermatology practice, with a small number of events characterized as delayed-type drug hypersensitivities.

The incidence of potential autoimmune disorders based on pre-specified terms was similar in the placebo-controlled (0% placebo vs. <1% Daclizumab 150 mg) and active-controlled (<1% IFN β-1a vs. 1% Daclizumab 150 mg) experiences. Events representing autoimmune thyroiditis were most common, and the incidence in daclizumab-treated subjects was similar to that observed in the MS population. The incidence of serious events was <1%, and there was no pattern to the events. Based on the limited number of events, there does not appear to be an association between daclizumab and potential autoimmune events.

There was an increased incidence of lymphadenopathy and lymphadenitis in subjects treated with daclizumab. The majority of subjects were asymptomatic. In cases in which biopsies were taken, the results were consistent with a reactive or inflammatory process, and there was no evidence of malignancy.

The incidence of depression was evaluated using the prespecified SMQ of depression and suicide/self-injury. In the placebo-controlled experience, events from the SMQ were reported at a higher incidence in daclizumab-treated subjects (3% placebo vs. 7% Daclizumab 150 mg), with no suicidal ideation, severe events, serious events, or events leading to treatment discontinuation reported in subjects who received daclizumab. In the active-controlled experience, the overall incidence of depression, self-injury, and suicidal ideation based on the SMQ was balanced across the 2 treatment groups (10% IFN β-1a vs. 11% daclizumab). There was 1 completed suicide in the IFN β-1a group and none in the daclizumab group. The Beck Depression Inventory, Second Edition (BDI-II) showed no clinically meaningful changes from baseline over time and the Multiple Sclerosis Impact Scale 29-item (MSIS-29) Psychological Impact score showed greater improvement in the daclizumab group. Also relevant, co-medication used by MS patients did not differ between treatment groups regarding antidepressant, antipsychotic or anxiolytic agents.

There were no clinically significant changes in aggregate hematological laboratory values (i.e., white blood cell [WBC], lymphocyte, and neutrophil counts) for subjects who received daclizumab in the placebo-controlled and active-controlled experiences. The incidence of hematological AEs based on the hematopoietic cytopenia SMQ was comparable in the placebo-controlled and active-controlled

experiences (0% placebo vs. 2% Daclizumab 150 mg; 7% IFN β-1a vs. 8% Daclizumab 150 mg). There were no clinically meaningful differences in the incidence or type of hematopoietic cytopenias observed in daclizumab-treated subjects compared with placebo- or IFN β-1a-treated subjects. In the 5 out of 1785 daclizumab-treated subjects who experienced SAEs of hematological disorders or cytopenias, all had confounding factors, such as concurrent infections, concomitant medications that cause cytopenias, and other complications; or the events occurred after discontinuation of study treatment, suggesting that an association with daclizumab in these cases was unlikely. Overall, based on medical review of the available data, the limited number of events, and the presence of other contributory factors in most of the cases, there does not appear to be an increased risk of hematological cytopenias during treatment with daclizumab. Although there was no significant change in aggregate haematological laboratory values, the incidence of decreased post-baseline CD4+ (<400 cells/µL, <200 cells/µL) was 29% and 3%, respectively, and the incidence of decreased CD8+ counts (<200 cells/mm3, <100 cells/mm3) was 34% and 4%, respectively in the overall daclizumab group. However because of the risk of leucopoenia monitoring of White blood cells is recommended every 3 months. Also it should be mentioned that no information is available regarding the risk of PML following treatment with Zinbryta.

The incidence of malignancies was 1% in daclizumab-treated subjects and was balanced across the treatment groups. The rate of malignancy in daclizumab-treated subjects was comparable to the background rate of malignancy in the general population of patients with MS.

Based on positive and negative status for anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs), there did not appear to be any correlations with AEs and SAEs, including AESIs such as hepatic, cutaneous, infectious, hypersensitivity, and other potential immune-mediated events. These results suggest that immunogenicity did not have a discernible effect on the safety profile of daclizumab. Overall, based on the totality of the clinical study data, daclizumab has a positive benefit/risk profile that supports its use in a broad population of adult patients with relapsing forms of MS. In the clinical studies, statistically significant and clinically relevant beneficial effects were seen consistently on clinical, radiographic, and patient-reported outcome measures in subjects with MS. The safety profile has been well characterized, and specific guidelines to monitor and manage the risks have been implemented and tested in the trials. The most important risk of hepatic events and elevations of serum transaminases can be effectively managed through raising Investigator awareness of the risk and monitoring of serum transaminases to allow for early recognition of events and for initiation of actions that can be taken. Other important risks involving the skin, infections, depression and colitis have been manageable with standard medical care, such as antibiotics, corticosteroids, treatment discontinuation, as appropriate for the event. Based on the profiles of these events, their response to treatment, and the mechanism of action of daclizumab, the immunomodulatory effects of daclizumab treatment are implicated as a possible underlying factor and were important in the development of management guidelines for these events in consultation with clinical experts.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The CHMP endorsed this advice without changes.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 4 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Transaminase elevations and serious hepatic injury Serious skin reactions Infections and serious infections Colitis Depression Serious lymphadenopathy
Important potential risks	Acute serious hypersensitivity reactions Opportunistic infections (including PML) Malignancies (particularly lymphoma) Sustained severe lymphopenia
Missing information	Use in patients under the age of 18 years Use in patients over the age of 55 years Use during pregnancy Exposure during lactation Use in patients with hepatic impairment Use in patients taking concomitant hepatotoxic medications

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Global paediatric study with 2 year treatment duration followed by 2-year extension (3)	To evaluate the activity, safety/tolerability, and PK of DAC HYP in patients from 10 to less than 18 years of age	Safety profile in patients under the age of 18 years	Planned	Submission date dependent on study dates. Study finish by August 2019 per the agreed PIP (EMEA-001349-PIP01-12-M01; Decision P/0147/2014)
Global Phase 4 pregnancy registry (109MS402) (3)	To prospectively evaluate pregnancy and infant outcomes in pregnant women with MS who were exposed to DAC HYP since the first day of their last menstrual period (LMP) prior to conception or at any time during pregnancy	Use during pregnancy	Planned	Planned final report: 2029
Epidemiological database study (3)	To assess the effectiveness of risk minimisation measures	Transaminase elevations/serious hepatic injury	Planned	Planned final report: Dependent on dates study is conducted
Central tracking of distribution of physician guide to HCPs in EEA (3)	To evaluate process indicators of effectiveness of the distribution of physician education materials	Transaminase elevations/serious hepatic injury	Planned	With PSURs
Feasibility study of MS registries (3)	To assess the feasibility of conducting PASS using MS registries	To assess whether important potential risks could be studied using MS registries	Planned	Report of feasibility assessment within 6 to 12 months of marketing in the EU

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Transaminase elevations and serious hepatic injury	Text in SmPC (4.4; 4.8) and Package Leaflet	Hepatic Risk Management Guide Patient Card
Serious skin reactions	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Infections and serious infections	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Colitis	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Depression	Text in SmPC (4.4; 4.8) and Package Leaflet	None
Serious lymphadenopathy	Text in SmPC (4.8) and Package Leaflet	None
Acute serious hypersensitivity reactions	None [1]	None
Opportunistic infections (including PML)	Text in SmPC (4.4) and Package Leaflet [2]	None
Malignancy (particularly lymphoma)	None	None
Sustained severe lymphopenia	Text in SmPC (4.4) and Package Leaflet	None
Use in patients under the age of 18 years	Text in SmPC (4.2) and Package Leaflet	None
Use in patients over the age of 55 years	Text in SmPC (4.2) and Package Leaflet	None
Use during pregnancy	Text in SmPC (4.6) and Package Leaflet	None
Exposure during lactation	Text in SmPC (4.6) and Package Leaflet	None
Use in patients with hepatic impairment	Text in SmPC (4.2; 4.4) and Package Leaflet	None
Use in patients taking concomitant hepatotoxic medications	Text in SmPC (4.4) and Package Leaflet	None

[1] Acute serious hypersensitivity reactions have not been observed with DAC HYP but were observed with another form of the daclizumab antibody (Zenapax). Therefore, the prescriber and patient information include a contraindication for DAC HYP in patients with a history of severe hypersensitivity (e.g., anaphylaxis or anaphylactoid reactions) to daclizumab or to any of the excipients.

[2] An increased risk of opportunistic infection has not been observed with DAC HYP. SmPC and Package Leaflet provide information on infections and serious infections and a recommendation for tuberculosis screening and monitoring during treatment in patients who have had tuberculosis or who live in endemic areas of the disease.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zinbryta (daclizumab) is included in the additional monitoring list as a biological product that is not a new active substance but is authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

2.10. New active substance claim

2.10.1. Applicant's position

The applicant presented the following arguments to defend the claim of a new active substance:

Quality aspects:

The applicant claimed that daclizumab which is the active substance in Zinbryta, should be considered a new active substance as it significantly differs from the daclizumab in Zenapax with respect to the three key pillars for a biological active substance:

a. the host/vector (as the source material) used for expressing the recombinant glycoprotein, is different for Zinbryta;

b. the manufacturing processes, including the cell cultivation conditions and purification processes, are significantly different for Zinbryta; and

c. the resulting molecular structure is significantly and meaningfully different in terms of the glycosylation composition and structure of Zinbryta.

The main differences claimed relate to the use of a different expression system to generate a new recombinant cell line for Zinbryta, which was cultured under different conditions and without the use of animal-derived materials to produce a recombinant protein with a distinctly different glycosylation profile to Zenapax. A different sequence and set of purification steps was also used for Zinbryta, yielding a

product of high purity and demonstrating greater structural homogeneity than Zenapax. In particular, Zinbryta has lower levels of high mannose and other non-fucosylated glycans than Zenapax, and also lacks glycan structures of murine origin.

Non Clinical and Clinical aspects

The applicant claimed that structural glycosylation is a critical determinant of the therapeutic function of an antibody. In the case of Zinbryta, the differences in glycosylation (resulting from the modifications to the expression system and the cell cultivation conditions) manifest in significant differences in pharmacokinetic and pharmacodynamics properties which could change the safety and/or efficacy profile of the product and, therefore, differentiate daclizumab in Zinbryta from the daclizumab in Zenapax. These pharmacological effects seen with Zinbryta are related to:

a. differences in biological activity as measured by antibody-dependent cell-mediated cytotoxicity (ADCC)

b. in vivo clearance, and hence the extent of systemic exposure to the circulating therapeutic protein;

c. immunogenicity; and

d. binding to the biologically relevant receptors which are linked mechanistically to the homeostasis of T regulatory cells.

Differences in In Vitro ADCC Activity

Antibody-dependent cell-mediated cytotoxicity (ADCC) measures the killing of antibody-coated target cells by cytotoxic effector cells. This biological effect is triggered through interaction of target-bound antibodies with Fc gamma receptors (FcγRs) present on the surface of effector cells. IgG Fc glycans are required for optimal binding of the antibody to FcγRs and for the effector functions that control the clinical properties of some therapeutic antibodies [Arnold 2007; Shi and Goudar 2014]. Natural killer (NK) cells mediate ADCC. NK cells are activated to lyse target cells when Fc receptors expressed on the surface of NK cells binds the Fc portion of antibodies bound to target cells. CD16 (FcγRIII) is the predominant Fcγ receptor expressed on NK cells.

Consistent with the differences in glycan profile, Zinbryta had a significantly lower binding potency for CD16 than Zenapax as measured in an AlphaScreen competitive binding assay. The relative binding of Zenapax to CD16 is 156% compared to Zinbryta. As a result, Zinbryta induces less down-modulation of CD16 on NK cells than Zenapax under in vitro conditions designed to replicate those of the in vitro ADCC assay.

Consistent with the differences in CD16 binding and CD16 down-modulation on NK cells, Zinbryta has a significant reduction in ADCC activity in vitro when compared to Zenapax. The maximal ADCC activity achieved with Zinbryta tested at graded concentrations was approximately 30-40% lower than the activity elicited by the same concentration of Zenapax.

Zinbryta has significantly ($p<0.05$) reduced levels of in vitro cytotoxicity in comparison to levels observed for Zenapax when effects of increasing concentrations of antibody were evaluated against fixed Effector to Target (E:T) ratios. Antibody-dependent cytotoxicity was measured by 51Cr release from IL-2 receptor-expressing KIT-225 K6 target cells in the presence of human peripheral blood mononucleated (PBMC) effector cells. The level of cytotoxicity was calculated as a percentage of maximum cell lysis. Mean and Standard Error results were obtained from six independent experiments using peripheral blood mononuclear cells obtained from healthy donors.

Zinbryta has significantly ($p<0.05$) reduced levels of ADCC in comparison to levels observed for Zenapax when effects of a single antibody concentration was evaluated against changes in Effector to Target (E:T) ratios in vitro.

The differences in ADCC activity can be linked to the differences in glycan profile between Zinbryta and Zenapax. In particular, Zinbryta has lower levels of high mannose and other non-fucosylated glycans than Zenapax. High mannose (non-fucosylated) glycans are well described to enhance ADCC activity in vitro and target cell depletion in vivo [Shi and Goudar 2014]. This general effect of increased high-mannose glycans causing increased ADCC was specifically demonstrated for daclizumabFigure 13. A high-mannose daclizumab was generated and mixed with Zinbryta at varying percentages of antibodies with high mannose glycans to reflect varying glycan profiles. Reflecting the comparison between Zinbryta and Zenapax, as the percentage of high mannose species increases, ADCC activity increases. Thus, the glycan structural differences between Zinbryta and Zenapax are manifested as a change in biological activity, specifically as reduced in vitro ADCC activity for Zinbryta, which is relevant to an assessment of the safety profile.

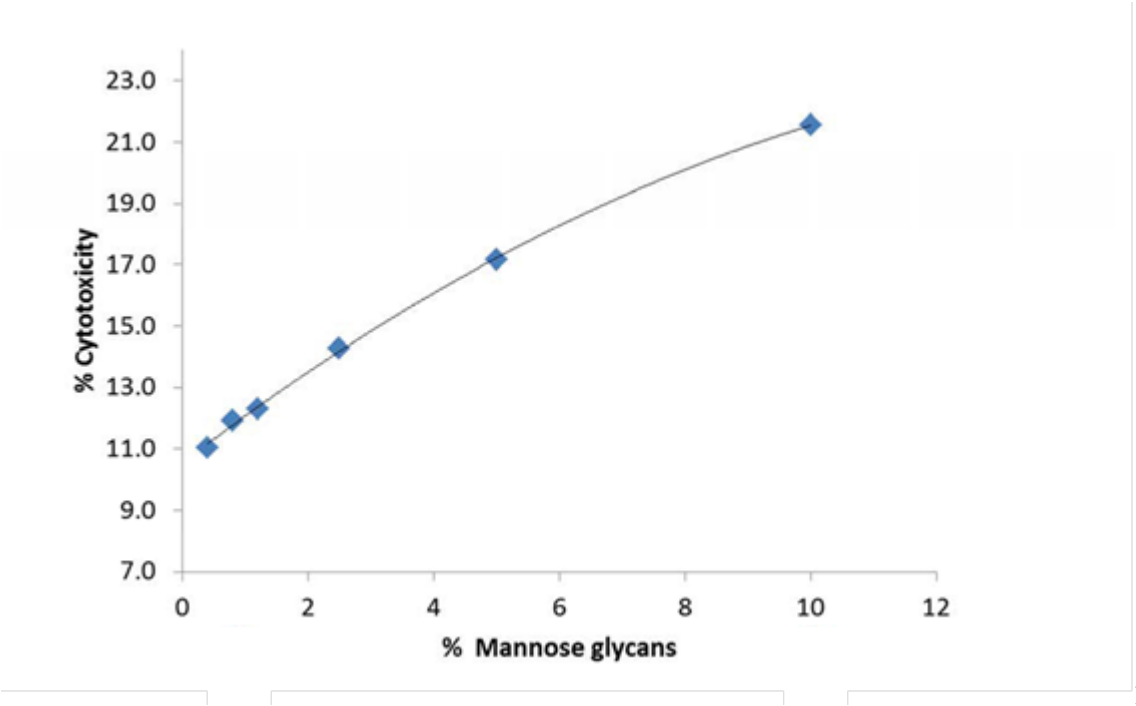


Figure 11: Correlation of High-Mannose Glycans with Daclizumab Cytotoxicity

Correlation has been demonstrated between the levels of mannose glycans in the sample and the percent in vitro cytotoxicity. High mannose afucosylated DAC (positive control with mannosylation of about 100%) was spiked into Zinbryta Drug Substance with initial 0.4% of mannose to produce samples with the following levels of mannosylation: 0.8, 1.2, 2.5, 5.0, and 10 %. In this study each sample was tested in duplicate at 3 different effector:target cell ratios with PBMCs from 3 different donors. Final % cytotoxicity represent averages for each sample across all replicates, effector: target cell ratios, and donors.

Differences in Clinical Immunogenicity as a Safety Measure

Glycan modifications of therapeutic antibodies directly impact functional properties and immunogenicity. Altered glycosylation patterns may decrease or increase the immunogenic properties of mAbs, e.g. alpha Gal. Non-typical glycosylation patterns, e.g. as encountered when adopting entirely novel expression systems, may introduce a higher immunogenicity risk as compared with more commonly used expression systems (Guideline on immunogenicity assessment of mAb intended for in vivo clinical use -

EMA/CHMP/BMWP/86289/2010). In this regard, the documented differences in glycosylation profile between Zinbryta and Zenapax are relevant.

Clinical data suggests a reduction in Zinbryta immunogenicity when compared to Zenapax. In the 205MS301 study, a large, Phase 3 trial of Zinbryta in MS patients, the persistent anti-drug antibody (ADA) and neutralizing antibody (NAb) responses were 7% and 2%, respectively. In comparison, the reported anti-idiotype immunogenicity of Zenapax is 14% (Zenapax US Prescribing Information, revised 2005)). Possible clinical consequences of higher immunogenicity include anaphylaxis, reduced drug half-life and neutralization of the therapeutic protein [van Beers and Bardor 2012]. Even though a direct comparison of the immunogenicity rates of the two products is not feasible, the observation of reduced Zinbryta immunogenicity is notable given that one would expect that Zinbryta would have higher immunogenicity than Zenapax, because the 205MS301 study was performed in immunocompetent MS patients, while the Zenapax trials were conducted in significantly immunosuppressed transplant patients. Furthermore, Zinbryta is administered by subcutaneous injection, which is considered a more immunogenic route of administration when compared to the intravenous route of administration used for Zenapax. In particular, it is well established that glycosylation can have an impact on antigenicity and immunogenicity [van Beers and Bardor 2012]. The structural differences in glycosylation between Zinbryta and Zenapax could account for the observed difference in immunogenicity profiles of the two products that could have a direct impact on safety and potency.

Differences in Clinical Pharmacokinetics

In addition to effects on ADCC, glycans can directly affect the pharmacokinetics of antibody therapeutics. In vivo studies in both humans and mice have shown that high mannose mAbs are cleared from serum more rapidly than mAbs of any other glycoform type [Goetze 2011; Kanda 2007; Shi and Goudar 2014]. Zinbryta, which contains a lower percentage of high mannose glycans as compared to Zenapax, has been reported to have an approximately 30% reduced systemic clearance as compared to Zenapax [Othman 2014]. This observation is consistent with a glycan-mediated clearance. [Alessandri, L et al 2012: Goetze, A.M., et al 2011].

Therefore, the structural differences between Zinbryta and Zenapax are also implicated in a change in human pharmacokinetics and hence systemic exposure to the therapeutic protein which is relevant to an assessment of the safety and efficacy profile of the product

Impact on Mechanism of Action

As regards the mechanism of action of Zinbryta in MS, the significant differences in ADCC between Zinbryta and Zenapax are directly linked mechanistically to the pharmacodynamic effects on regulatory T cells (Tregs) and to the assessment of the safety profile in MS patients.

Treg cells play a critical role in limiting immune activation and preventing autoimmune pathology [Sakaguchi 2008; Brusko 2008; Josefowicz 2012]. In preclinical and clinical studies, reductions in Treg numbers or reduction in Treg function are linked to the development of autoimmune pathology. Furthermore, there is increasing recognition of the importance of Tregs in limiting MS disease. Depletion of Tregs exacerbates animal models of MS and defects in Treg function have been reported in MS patients [Viglietta 2004; Kleinewietfeld and Hafler 2014; Costantino 2008]. Thus in the context of a therapy for MS, reductions in Tregs may increase incidence of autoimmune adverse events and potentially limit efficacy.

In vitro ADCC activity is taken as a relative indication of cell-killing capability in vivo. Tregs express very high levels of CD25, rendering them particularly susceptible to the cell killing by an ADCC promoting anti-CD25 specific antibody. The higher ADCC of Zenapax is considered an undesirable attribute as it

would potentially result in increased Treg depletion and increased incidence of autoimmune pathologies associated with therapy. In an animal model comparing two forms of an anti-CD25 antibody that differ only in Fc- mediated ADCC activity in vivo, the antibody with higher ADCC showed greater depletion of Treg cells (~50% vs. ~25% reduction in Tregs). Treatment with the highly-depleting antibody but not the antibody lacking ADCC activity, resulted in immune dysregulation and the emergence of a large proportion of pro-inflammatory lymphocytes.

Zinbryta therapy results in an approximately 50% reduction in circulating Tregs in MS patients [Huss 2014]. As best evidenced by the clinical benefit seen in MS, the aggregate impact of Zinbryta is a reduction in CNS autoimmune pathology [Gold 2013; Giovannoni 2014], but treatment with Zinbryta is also associated with risks of adverse immune-mediated events. A relationship between reductions in Tregs and the safety profile of Zinbryta is supported by the adverse event profile observed in Zinbryta treated MS patients which is consistent with a reduction in Treg mediated immune homeostasis. In both mice and humans genetic deficiencies in Tregs are characterized by inflammatory pathologies of the skin and intestinal tract, immune-mediated hepatitis, elevated IgE, lymphoproliferation, lymphoid hyperplasia and lymphadenopathy [Bezrodnik 2014; Goudy 2013; Caudy 2007; Sharfe 1997; Wildin 2002; Willerford 1995; Fontenot 2003]. An overlapping set of sequelae are observed in Zinbryta treated MS patients. Therefore, it can reasonably be hypothesized that further reductions in Tregs, driven by higher ADCC, may increase the incidence and/or severity of such events. In this context, the lower ADCC activity of Zinbryta compared to Zenapax is believed to be beneficial for safety by limiting the depletion of CD25-expressing Treg cells.

Based on these cumulative data, the applicant concluded that the change in glycan structure and corresponding reduction in ADCC assay observed in Zinbryta results in an antibody with a change in pharmacodynamic properties that may be relevant to an assessment of the safety profile.

2.10.2. Additional Applicant's justification provided in response to the request from the Committee

Further to the CHMP request for additional substantiation on the claim of new active substance for daclizumab in Zinbryta, the Applicant provided four specific areas of scientific justification, assumed to be relevant to differentiating the efficacy and safety profile of Zinbryta from Zenapax:

I. How post-translational modifications (and in particular differences in glycosylation) have likely affected immunogenicity and in vivo clearance of Zinbryta when compared to Zenapax.

II. Through PK-PD modelling, how the differences in clearance rates impact systemic drug exposure and dosing of the two products.

III. How the structural differences can impact ADCC and T regulatory (Treg) cell levels.

IV. How the depletion of Tregs can impact the safety profile. Data to show differences in cutaneous adverse events is provided in this regard.

I. Post-translational modifications and impact to clearance

Post-translational modifications (and in particular glycosylation) of a protein can affect its in vivo clearance. The Zinbryta N-linked glycosylation profile differs from that of Zenapax, and the distinct glycosylation profiles of these two products can be linked to the observed differences in clearance. Although the levels and types of glycans on the Fc domain do not impact binding to the FcRn receptor (Simmons et al., 2002; Ha et al., 2011), which gives antibodies their relatively long half-life compared to other therapeutic proteins, exposed glycans near the exterior of the antibody protein may impact clearance through other receptors. High mannose glycans in particular can directly affect the

pharmacokinetics of antibody therapeutics, whereas other glycan structures known to affect clearance of a range of glycoproteins (Solá and Griebenow, 2010) may have limited effect on antibody clearance.

Glycans can also affect immunogenicity. Differences in immune response can also impact the clearance and pharmacokinetics of the molecule. Clinical data suggests a reduction in the immunogenicity of Zinbryta when compared to Zenapax. In a large Phase 3 trial of Zinbryta in MS patients (Study 205MS301), the persistent anti-drug antibody (ADA) and neutralizing antibody (NAb) responses were 7% and 2%, respectively. In comparison, the reported anti-idiotype immunogenicity of Zenapax is 14% (Zenapax US Prescribing Information, revised 2005). Even though a direct comparison of the immunogenicity rates of the two products is not feasible, the observation of reduced Zinbryta immunogenicity is notable given that one would expect that Zinbryta would have higher immunogenicity than Zenapax, because the 205MS301 study was performed in immunocompetent MS patients, while the Zenapax trials were conducted in significantly immunosuppressed transplant patients. Furthermore, Zinbryta is administered by subcutaneous injection, which is considered a more immunogenic route of administration when compared to the intravenous route of administration used for Zenapax.

Possible clinical consequences of higher immunogenicity include anaphylaxis, reduced drug half-life and neutralization of the therapeutic protein (van Beers and Bardor, 2012). Population PK analyses showed that time-dependent NAb-positive status increased Zinbryta clearance by an average of 19%. Therefore, the structural differences between Zinbryta and Zenapax that are implicated in differences in immunogenicity can also lead to a change in PK and hence systemic exposure to the therapeutic protein. Differences in clearance between Zinbryta and Zenapax/DAC Penzberg have been observed in the clinic, based on Phase 3 data for Zinbryta as well as the DAC-1012 CHOICE study of DAC Penzberg. The totality of these clinical data further demonstrate non-similarity between Zenapax and Zinbryta and are supportive of the impact of glycosylation on both receptor-mediated clearance and immune antibody-mediated clearance, a finding that is consistent with what is available in the published literature for glycoproteins.

II. PK and dose-response analysis of Zinbryta vs. Zenapax/DAC Penzberg

In order to assess the impact that the above-noted changes in immunogenicity and PK have on clinical efficacy, the applicant has constructed population PK and dose-response models for Zinbryta and Zenapax using Gd-enhancing lesions on cranial MRI as the response variable. The use of this measure as a reflection of clinical outcome under treatment is appropriate as these lesions are believed to mediate clinical MS relapses and are empirically closely correlated with the relapse rate in this disease. The results of the PK and dose-response models demonstrate that MS patients treated with a monthly dose of Zenapax equal to the proposed clinical dose of Zinbryta would have meaningfully higher levels of brain inflammation as measured by Gd+ lesions on MRI. As such, these differences are reasonably predicted to translate directly into higher clinical MS relapse rates during Zenapax treatment as compared to Zinbryta treatment.

The most relevant data to perform this comparison of response come from the SELECT study (205MS201) with Zinbryta and the CHOICE study (DAC-1012) with DAC Penzberg, a form of daclizumab that is structurally identical to Zenapax. Both studies were conducted in populations of MS patients with similar demographics and baseline characteristics (Table 33). In both studies the mean EDSS, age and baseline Gd lesions were similar. There was a slightly higher proportion of subjects who were female in CHOICE (74.3% versus 65% in SELECT). The history of relapse at baseline was similar after accounting for the difference in the time interval history. As outlined above the data from these studies were used to establish the dose-response relationship and model the efficacy impact of the lower exposures expected with equimolar doses of Zenapax/DAC Penzberg vs. Zinbryta.

Table 33: Summary of demographics and baseline disease characteristics

	SELECT (205MS201)			CHOICE (DAC-1012)		
	Placebo (n=204)	DAC HYP 150 mg (n=208)	DAC HYP 300 mg (n=209)	Placebo (n=77)	1 mg/kg (n=78)	2 mg/kg (n=75)
Age (years)	36.6 (9.0)	35.3 (8.9)	35.2 (8.7)	40.8 (9.0)	38.2 (9.3)	40.4(8.5)
Female: n %	128 (63)	140 (67)	134 (64)	55 (71.4)	58 (74.4)	58 (77.3)
Weight (kg)	70.0 (14.4)	68.3 (15.9)	68.2 (15.2)	77.5 (18.0)	73.6 (16.8)	80.7 (19.9)
Number of Gd lesions	2.0 (4.5)	2.1 (3.5)	1.4 (3.3)	1.1(2.7)	2.7 (7.0)	0.8 (1.7)
Relapses past year	1.3 (0.6)	1.4 (0.7)	1.3 (0.7)	na	na	na
Relapses past two year	na	na	na	2.6 (1.7)	2.6 (1.6)	2.4 (1.2)
Baseline EDSS	2.7 (1.2)	2.8 (1.2)	2.7 (1.2)	3.0 (1.2)	3.0 (1.2)	3.0 (1.3)

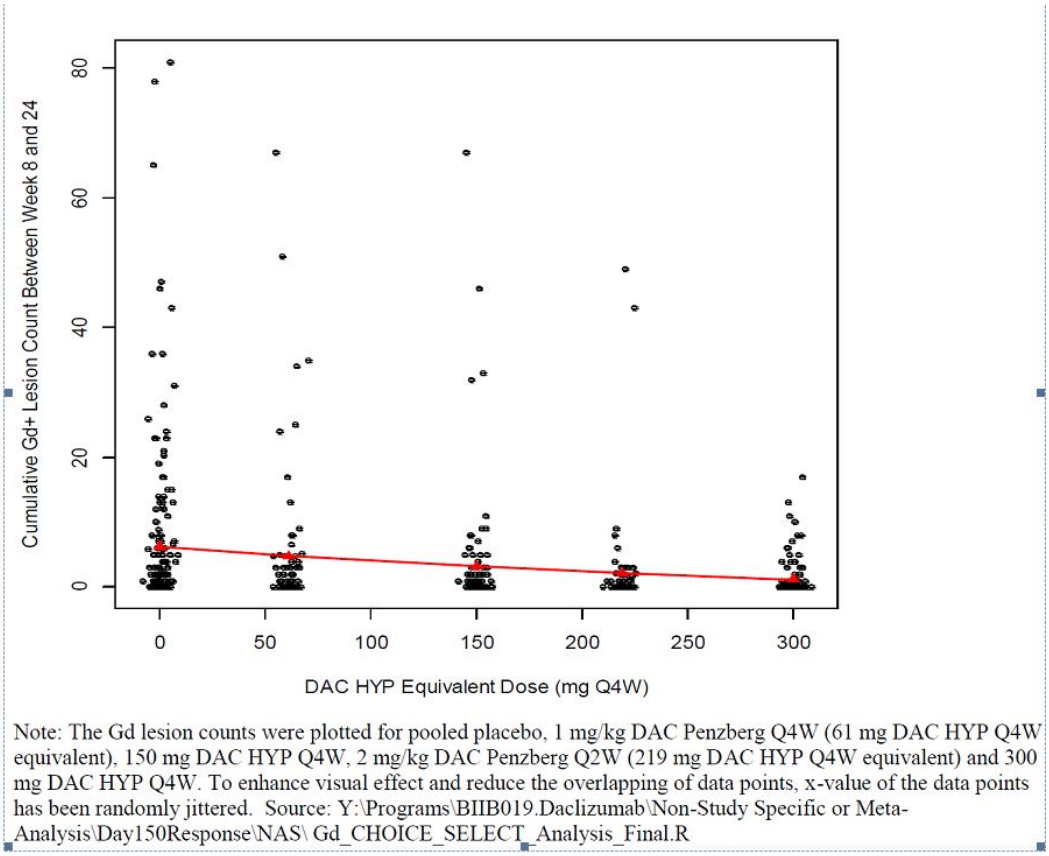
Note: Numbers presented are mean and standard deviation unless otherwise noted. na = Not available

In summary, the combined PK and dose-response models estimate a 27% increase in the mean number of new Gd+ lesions between Week 8 and Week 24 using 150 mg Q4 Weeks of DAC Penzberg as compared to 150 mg Q4 weeks of Zinbryta. There is strong association between the effect of treatment on MRI lesions and the effect on relapses, and, based on prior quantitative analyses of the relationship between these two variables for MS immunomodulatory therapies, this increase in Gd lesions is expected to result in approximately a 13% increase in relapse rate in 150 mg Q4W of DAC Penzberg compared to 150 mg Q4W of Zinbryta (Sormani and Bruzzi, 2013).

Applicant's conclusions from population PK and dose-response modelling

The simulated PK (steady-state AUC) of the two products derived using Population PK models of clearance for each product resulted in a finding that 150 mg of DAC Penzberg is estimated to be approximately equivalent to 110 mg Zinbryta with regard to resulting systemic exposure. Based on the simulated steady-state AUC differences, the body weight-based dose regimens evaluated in the CHOICE study using DAC Penzberg were converted into equivalent Zinbryta Q4W dose levels, and a dose-response model was fitted to the cumulative new or enlarging Gd lesion count between Week 8 and Week 24 in CHOICE and SELECT. The analysis suggested a significant dose-response relationship for the cumulative Gd lesions described using a negative binomial model (Figure 14). The point estimate (95% CI) for the dose effect is -0.0059 (-0.0073, -0.0045), with a corresponding p-value <0.0001.

From the estimated dose-response relationship, the mean Gd lesion count was estimated for doses of 150 mg Zinbryta Q4W and 110 mg Zinbryta Q4W (determined to be equivalent to 150 mg Q4W of DAC Penzberg, as described above). Assuming a population with an average baseline Gd lesion count of 1.77, it is estimated that the mean (95% CI) new Gd lesion count between Week 8 and Week 24 would be 2.16 (1.82, 2.51) for 150 mg Zinbryta Q4W and 2.74 (2.31, 3.19) for the 150 mg DAC Penzberg Q4W dosing. This equals a 27% approximate increase in the mean number of new Gd+ lesions between Week 8 and Week 24 of therapy for 150 mg DAC Penzberg Q4W compared to 150 mg Zinbryta Q4W, and a 13% increase in the annual relapse rate (ARR). Since a key goal of using daclizumab in MS patients is to reduce brain inflammation and clinical relapses, this distinct difference in the expected relapse rate and number of new Gd+ lesions during treatment with DAC Penzberg vs. Zinbryta should be clinically meaningful.



Note: The Gd lesion counts were plotted for pooled placebo, 1 mg/kg DAC Penzberg Q4W (61 mg DAC HYP Q4W equivalent), 150 mg DAC HYP Q4W, 2 mg/kg DAC Penzberg Q2W (219 mg DAC HYP Q4W equivalent) and 300 mg DAC HYP Q4W. To enhance visual effect and reduce the overlapping of data points, x-value of the data points has been randomly jittered. Source: Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\NAS\ Gd_CHOICE_SELECT_Analysis_Final.R

Figure 12: Observed cumulative new or enlarging Gd lesion count between Week 8 and Week 24 vs. Zinbryta equivalent dose every 4 weeks.

Table 34: Percentiles of stimulated steady state AUC for 150 mg Q4W based on Population PK model

Dose (mg Q4W)	Steady State AUC (ug/mL*hr)	DAC HYP	Penzberg	Ratio (DAC HYP/Penzberg)
150	5%	8486	6276	
	25%	12204	8995	
	50%	15445	11311	1.37
	75%	19299	14548	
	95%	25520	20400	

Source: Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\PKSim\SimData_Gen.R; Y:\Programs\BIIB019.Daclizumab\Non-Study Specific or Meta-Analysis\Day150Response\PKSim\SimData_Analysis.R

III. Impact of Structural Differences on Biological Function and T Regulatory Cells

Glycosylation of therapeutic antibodies can affect their functional properties, with an impact on Antibody-dependent Cell-Mediated Cytotoxicity (ADCC) being widely reported (Thomann et al, 2015). The Zinbryta N-linked glycosylation profile is distinct to that of Zenapax, and these differences have been linked to differences in ADCC between the two products that are linked mechanistically to pharmacodynamic effects on regulatory T cells (Tregs). In vitro ADCC activity is taken as a relative indication of cell-killing capability in vivo. Tregs express very high levels of CD25, rendering them particularly susceptible to the cell killing by an ADCC-promoting anti-CD25 specific antibody. The higher ADCC of Zenapax is considered an undesirable attribute as it increases the risk of Treg depletion and an increased incidence of autoimmune pathologies associated with therapy.

IV. Relevance of Treg cell suppression for safety and cutaneous adverse events

Clinical relevance of Treg suppression

A key clinical consequence of Treg suppression during daclizumab use in MS is believed to be a higher incidence of cutaneous adverse events, as a similar pattern of cutaneous adverse events is observed in conditions of known Treg cell deficiency. During clinical use of daclizumab, the risks of Treg suppression are partly balanced by the effects of CD25 antagonism on the effector T-cell response as well as the expansion of immunoregulatory CD56bright NK cells. When daclizumab treatment is stopped, the process of antibody elimination and reversal of the immunoregulatory effects that are caused by anti-CD25 treatment create a dynamic period in which the risks associated with Treg antagonism could theoretically be increased in some patients, particularly if Treg suppression is substantial and has not recovered by the time the other immunoregulatory effects of daclizumab have reversed.

Evidence for the involvement of Tregs

- In the CHOICE study with DAC Penzberg, there was evidence of an increased incidence of cutaneous adverse events during the washout period as compared to the on-treatment period. For example, during the 6-month washout period with DAC Penzberg, the incidence of the most common cutaneous AE “rash” was 8.1 % compared to an incidence of 3.3% during the 6-month on-treatment period (Study DAC1012 CSR).
- In contrast the increased risk of a cutaneous adverse event during the washout period was not observed with Zinbryta use when assessed using a randomized withdrawal design in study 205MS202. During Zinbryta washout, the incidence of “rash” during the 6-month washout period was 2% (Study 202) as compared to 2% during the initial 6-month on-treatment period.

Therefore, given the higher level of ADCC and greater antagonism of Tregs expected with Zenapax treatment, as well as the clinical data indicating differences in the safety profile, MS patients treated with

Zenapax may be at increased risk of cutaneous adverse events during the treatment washout period as compared to treatment with Zinbryta.

OVERALL CONCLUDING ARGUMENTS BY THE APPLICANT:

Overall, the Applicant was of the view that the findings presented support that there is a clinically significant impact of the structural differences in the glycan profile and resulting changes in PK, immunogenicity, and ADCC between DAC Penzberg/Zenapax vs. Zinbryta.

1. First, these differences result in a lower exposure with use of Zenapax/DAC Penzberg as compared to Zinbryta that would expose MS patients to meaningfully higher risks of brain inflammation and clinical relapses (estimated 27% increase in new Gd+ lesions over 16 weeks of treatment and an anticipated 13% increase in ARR in subjects treated with Zenapax vs. Zinbryta). Since a key goal of using daclizumab in MS patients is to reduce brain inflammation and clinical relapses, this distinct difference in the expected relapse rate and number of new Gd+ lesions during treatment with DAC Penzberg vs. Zinbryta should be clinically meaningful.
2. Second, while the effects of Treg antagonism may be partially balanced by other immunomodulatory effects of CD25 blockade during the on-treatment period, patients with greater Treg suppression may be at higher risk during the washout period. The clinical data obtained during washout with DAC Penzberg vs. Zinbryta support that the known structural differences between DAC Penzberg /Zenapax vs. Zinbryta translate into significant differences in the clinical safety profile of daclizumab in the target MS population.

The totality of the data available indicate that the structural distinctions in glycosylation between Zenapax and Zinbryta result in differences in PK and immunogenicity which directly impact the risk-benefit of daclizumab use in MS, and support the designation of Zinbryta as a new active substance. The magnitude and significance of these differences would preclude an assumption of biosimilarity, should these be presented in the context of a biosimilar application. As the two products could not be considered comparable from a therapeutic perspective, a full clinical development program was necessary to confirm the safety and efficacy of Zinbryta in MS, and accordingly an application for marketing authorisation was submitted under Article 8.3 of the Directive.

2.10.3. CHMP Scientific evaluation of the Applicant's position

Assessment of the Applicant's arguments on the quality aspects

The applicant claims that Zinbryta was developed starting from a distinct proprietary expression vector, NS0 sub-strain host cell line, and a new manufacturing process, that results in a new active substance different from the one previously authorised in the EU (i.e. daclizumab contained in Zenapax).

a) the host/vector (as the source material) used for expressing the recombinant glycoprotein, is different for Zinbryta

The Applicant indicates that a different expression vector was used in a different recombinant cell line. The MCB for Zinbryta is said to be generated using a different recombinant cell line to Zenapax, although it was derived from a substrain of the old recombinant NS0 cells by a series of subcloning, expanded and frozen as seed bank. The present MCB was generated from this seed bank expanded in serum-free medium. The gene expression generates the same amino acid sequence of Zinbryta and Zenapax albeit with minor differences in the Heavy Chain N-terminus, either from unprocessed signal sequence or with changes frequent in this type of products. Differences solely in the regulatory components of the

expression system of the same genetic sequence leading to the same amino acid sequence are not considered valid for the establishment of NAS.

b) the manufacturing processes, including the cell cultivation conditions and purification processes, are significantly different for Zinbryta; and

Again, the present considerations on differences in manufacturing process cannot be considered sufficient *per se* to qualify the active substance as NAS. It is recognised that different culture conditions might impact on molecular features of the molecule that might be of relevance for the pharmacological action or pharmacodynamics. Nevertheless, from a quality point of view, changes in the process such as growth medium, additional polishing step as well as a different manufacturing facility or different manufacturer cannot be the basis to confer the NAS status as they in itself do not lead to significant quality changes that could translate in significant differences in S/E.

c) the resulting molecular structure is significantly and meaningfully different in terms of the glycosylation composition and structure of daclizumab in Zinbryta.

The Applicant reiterates that Zinbryta glycosylation profile differs from Zenapax both in terms of glycan distribution and the types of oligosaccharides formed. The majority of the N-linked glycans on Zinbryta display very little heterogeneity, while the glycan profile for Zenapax is much more heterogeneous. The predominant glycan species are asialylated core-fucosylated bi-antennary structures. There is a lower abundance of high mannose forms and other non-fucosylated forms compared to Zenapax.

It is agreed that core fucosylation is important in modulating the affinity of the Mab to the Fc gamma receptor binding present in effector cells with implication in ADCC. Nevertheless, from the data provided, it is questionable to consider as major the differences in the relative percentages of the total amount when all fucosylated forms are added.

The other difference claimed is on the different proportion of uncapped mannose forms. The Applicant presented data on ADCC increase according to the relative content of mannose. Again, the significance of such differences are difficult to establish solely in terms of *in vitro* studies as various factors contribute both synergistically as well as antagonistically to the affinity to the Fc gamma receptor and ADCC and the behaviour *in vivo*. Also *in vivo* clearance of the exposed mannose forms through the Man-6-P receptor in lysosomes should be considered.

Structural glycans may have an impact in the various studies *in vitro* based upon antibody Fc domain interactions with Fc receptors (FcRs) expressed on lymphocytes. Nevertheless, ADCC was not considered to be the primary mode of action for this product targeted to compete with the IL-2 receptor present in activated lymphocytes. This CD25 binding was the mechanism of action considered for potency determination measuring proliferation inhibition of T-cell expressing CD25 when exposed to IL-2. CD25 binding is not affected by variations in the content of these various glycan variants.

CHMP Conclusions on the quality aspects:

From a quality point of view, the differences identified cannot be considered significant. In particular:

a) the differences in the expression system do not result in differences in the amino acid sequence,

b) the differences in the manufacturing process such as different growth medium and an additional polishing step do not lead to differences in the amino acid sequence.

c) Structural differences observed were related to differences in glycan profile that are known to impact Fc mediated ADCC and reflect a more homogeneous preparation. Variability of glycosylation is a known condition and co-existence of variants with differences in glycosylation does not imply to have a major

impact in vivo. Glycosylation is generally not considered a distinctive attribute unless the primary mode of action is associated to a specific structure and a given function related to the indication.

ADCC was not considered to be the primary mode of action for this product targeted to compete with the IL-2 receptor present in activated lymphocytes. This CD25 binding was the mechanism of action considered for potency determination measuring proliferation inhibition of T-cell expressing CD25 when exposed to IL-2. CD25 binding is not affected by variations in the content of these various glycan variants.

In order to further substantiate the NAS claim, it is required to establish whether the differences in glycosylation profile translate in significant differences in terms of safety and/or efficacy. This can only be addressed more appropriately at the non-clinical and clinical level.

CHMP assessment of the Applicant's arguments on the non-clinical aspects:

The applicant has presented in vitro data showing that the material differences in glycosylation (resulting from the modifications to the expression system and the cell cultivation conditions) manifest in significant differences in:

- differences in biological activity as measured by antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro;

- in vivo clearance, and hence the extent of systemic exposure to the circulating therapeutic protein;

- immunogenicity ;

- binding to the biologically relevant receptors which are linked mechanistically to the homeostasis of T regulatory cells.

Although a direct clinical comparison of the immunogenicity and pharmacokinetic rates of the two products was not feasible, non-clinical data were provided by the applicant to demonstrate differences in ADCC activity, immunogenicity, pharmacokinetics and pharmacodynamics.

CHMP Conclusions on non-clinical aspects:

From a non-clinical perspective data were provided to reveal differences in ADCC activity, immunogenicity, pharmacokinetics and pharmacodynamics that may be relevant to assume a different safety and efficacy profile of Zinbryta, but these needed to be further confirmed by clinical data.

Taking into account the clinical assessment and the clarifications provided by the company during the assessment, it became clear that the assumptions arising from the non-clinical data did not translate into a clinically relevant safety and efficacy different profile for Zinbryta when compared to Zenapax, as further elaborated below.

CHMP assessment of the Applicant's arguments on the clinical aspects:

Differences in glycan profile and ADCC activity have been elaborated further during the procedure. The argument centres on the differences in ADCC observed and the mechanistic link to the pharmacodynamic effects on regulatory T cells (Tregs) and to the assessment of the safety profile in MS patients. The role of Treg cells in limiting immune activation and autoimmune pathology is discussed in the context of the pathophysiology of MS. Reduction in Treg cells are hypothesised to increase incidence of autoimmune events and potentially limit efficacy. The Applicant provided details supporting this hypothesis. The higher degree of ADCC in Zenapax is considered by the applicant to potentially increase Treg depletion relative to Zinbryta with the associated consequences concerning safety and efficacy from increased autoimmune pathologies. This leads the Company to conclude that the lower ADCC activity of Zinbryta compared to Zenapax is potentially beneficial for safety by limiting the depletion of CD25-expressing Treg cells.

From the data available on MS patients treated with daclizumab manufactured at Penzberg (DAC Penzberg), the safety data – namely regarding Nabs against daclizumab, favours Zinbryta over DAC Penzberg with 7.9% NAbs in MS patients treated with doses up to 200 mg in study DAC 1012) against the frequency of 2% of Nabs with Zinbryta. The NAbs of Zenapax in a different population is less prone to an adequate comparison. The Applicant claims that this is indicative of Zenapax being potentially more immunogenic than Zinbryta in the absence of direct comparison of immunogenicity via a head to head clinical study. This information is unexpected given the relative immunogenicity of the different routes of injection (intravenous for Zenapax and subcutaneous for Zinbryta).

Glycan mediated clearance has been discussed and reference made to published data which reports Zinbryta has a 30% reduced clearance rate compared to Zenapax.

There are no clinical data adequately comparing efficacy of Zenapax and Zinbryta in MS patients.

The applicant argued that, based on the immunological responses observed for DAC Penzberg, Zenapax and Zinbryta, which may correlate to the differences in the glycan profile, there should be a significant difference in clinical properties. A significant part of the claim of the clinical significance of the differences in the quality profiles between Zenapax and Zinbryta was hypothesised by extrapolation of available clinical information and based on biological and clinical plausibility. The CHMP considered though that the applicant's argumentation and data provided were insufficient to substantiate that the differences observed with Zinbryta translate into significant differences in term of safety and efficacy.

The Applicant followed to present in further detail the differences in molecular structure and how this would impact upon clinical response, namely: a) PK modelling comparing clearance and extrapolating the impact on efficacy; b) how these differences could be clinically meaningful; c) how Zinbryta lower Treg depletion could translate into potential beneficial safety outcomes; and d) describe the observed differences in immunogenicity.

Regarding the PK/PD impact of glycosylation and the potential meaning of these differences, the presented model exhibited several problems:

- the applicant used a 90% confidence interval instead of the usual 95% to show non-equivalence;
- the applicant assumed that patients weighed a mean of 75 kg (DAC-1012 dosing being 1mg/kg Q4W – max dosing 100 mg or 2 mg/kg Q2W – max dosing 200 mg per visit 6 doses max) while in trial 205MS201 dosing was 150 or 300 mg Q4W 6 month treatment.
- Moreover, all DAC1012 patients were on beta interferon (IfN) treatment while all 205MS201 were not.

Considering all these aspects, the clinical data provided could not be considered comparable, as the population was substantially different, and the administered treatment was also not identical. Likewise, the prediction of 14% lower exposure of DAC Penzberg as compared to Zinbryta could not be directly linked to an improved efficacy profile, as the DAC Penzberg was tested in patients receiving beta IfN treatment.

The applicant tried to highlight that patients on DAC Penzberg had 12.6% more cutaneous AEs as compared to placebo whilst patients on Zinbryta had only 7% more cutaneous AEs as compared to placebo. Again, the CHMP considered that in this case the population was different: in the placebo arm, 26% of DAC 1012 patients exhibited cutaneous events while in the 205MS201 placebo arm only 13% had cutaneous AEs. Moreover, cutaneous AEs were more frequent in the DAC 1012 trial than in the 205MS201.This fact (which reduces the clinical relevance of these AEs for effectiveness and safety), and more importantly the fact that the DAC 1012 population was concomitantly treated with beta IfN further

supports the conclusion that the data provided cannot be considered sufficient to demonstrate a clinically significant benefit in either efficacy or safety.

CHMP conclusions on clinical aspects

The Applicant provided arguments to justify that daclizumab from Zenapax and daclizumab from Zinbryta should be considered different active substances. The Committee's conclusions, addressing in detail the different sections of the argumentation are as follows:

I. Post translational differences have been noted, however the amino acid sequence of daclizumab in Zinbryta is unchanged from the daclizumab in Zenapax. The pharmacodynamic properties of Zenapax are not seen to be very different from those of Zinbryta as demonstrated by a similar text in section 5.1 of the SmPC for Zenapax (now withdrawn), compared to that proposed for Zinbryta.

II. Differences in clearance were noted but the use of different PK models for Zinbryta and DAC Penzberg was not considered acceptable. The Applicant subsequently presented a new PK model, where all data were included and the effect of the different agents on clearance was evaluated. The relevance of this effect was noted by presenting a 90% CI based on 1000 bootstraps with values of 1.13 (1.02 – 1.26) for the ratio between DAC Penzberg and Zinbryta typical clearance. The Applicant claimed that this showed lack of bioequivalence between the two active substances. However, the bootstrap procedure is used to evaluate the relevance of the estimation of a particulate parameter, and in this case, typically a 95% CI would be calculated. Although this 95% CI was not presented, it is possible that the lower bound will be below 1 and the difference in clearance would not be statistically significant. As a consequence, the data from the new model cannot support the Applicant's claim that Zinbryta has lower in vivo clearance than DAC Penzberg.

III and IV. The structural differences are noted and could result in different ADCC activity, however the clinical impact of this cannot be measured but only hypothesised.

The applicant notes that in the CHOICE study (DAC 1012) with DAC Penzberg, there was an increased incidence of cutaneous adverse events during the washout period as compared to the on-treatment period, with an incidence of the most common cutaneous AE "rash" was 8.1 % in the wash-out period compared to an incidence of 3.3% during the 6-month on-treatment period. This actually relates to 5/123 patients during treatment and in 12/153 in the washout period. There is no discussion in terms of severity of the rash or whether this resulted in a discontinuation of treatment in the treatment period.

In study 205MS201/2 the incidence of "rash" during the 6-month washout period was 2% as compared to 2% during the initial 6-month on-treatment period; however the incidence of "rash" in the placebo group on treatment is very different to that seen in study DAC 1012 (1% 205MS201 vs. 5.2% DAC1012) making it difficult to conclude on the differences in safety profile.

It has been previously advocated that higher rate of immunogenicity was seen with Zenapax/DAC Penzberg (~8% NAbs vs. 2% with Zinbryta) and that NAbs cause an additional increase in antibody clearance. However this cannot be considered on its own to be significant and sufficient difference in safety or efficacy to justify a NAS status.

Of note, study DAC 1012 differed from study 205MS201/2 in several aspects:

a) study population: in DAC 1012 all patients were treated withIFN-beta and DAC Penzberg or placebo, whilst in 205M201/2 DAC was given as monotherapy;

b) dosing: for DAC1012 max dose was 100 mg per dosing visit in the 1mg/kg Q4w arm, and 200 mg per dosing visit in the 2mg/kg Q2w (IV over 15 minutes) vs 150 mg or 300 mg per dosing (subcutaneous), Q4w;

c) development phase: in the earlier phases, investigators and patients are more attentive to adverse events, and may report better and more adverse events; and

d) treatment duration.

Both clinical observation data – primary and secondary endpoints - and MRI lesion data are insufficient to allow for a decision on whether there is a difference between products based on clinical grounds.

As a conclusion, the discussion of the available data does not provide sufficient evidence of a difference in terms of clinical response (efficacy or safety) to support the relevance of the claimed structural differences between Zinbryta and Zenapax and, consequently, to support the NAS claim through demonstration of significant differences in terms of safety and/or efficacy.

CHMP OVERALL CONCLUSIONS ON THE NEW ACTIVE SUBSTANCE CLAIM:

Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP decided that there are insufficient data to demonstrate that the observed differences for Zinbryta would translate into significant differences in terms of safety / efficacy compared to the previously authorized product that could support the NAS claim. Based on the overall assessment it is concluded that Daclizumab in Zinbryta cannot be qualified as a new active substance.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of daclizumab has been tested in 2 randomized, double-blind, controlled, pivotal studies. In 1 study (Study 201), the efficacy of daclizumab was compared to placebo, and in the other study (Study 301), the efficacy of daclizumab was compared to a current standard of MS treatment, IFN β-1a. Both of these studies demonstrated consistent treatment effects of daclizumab across validated clinical, radiographic, and patient-reported MS outcome measures. The effects of DAC HYP were apparent after the first dose as defined radiographically and within 3 months as defined by clinical endpoints. The benefits of daclizumab were then sustained over up to 3 years during continuous treatment.

Both clinical studies enrolled a broad population of RRMS patients who had had relapses. The mean age of subjects was approximately 36 years, and the percentage of subjects with highly active MS (≥ 2 relapses in the prior year and ≥ 1 Gd+ lesion on baseline MRI) at study entry was 16% - 21%. In both studies, a minority of enrolled subjects had received prior DMT, but the proportion was higher in Study 301 (41%) compared to Study 201 (20%).

The primary endpoint of both Studies 201 and 301 was the annualized relapse rate. Both studies demonstrated a robust effect of daclizumab on the reduction in clinical MS relapses: a 54% reduction versus placebo in Study 201 and a 45% reduction versus IFN β-1a in Study 301. Relapse rate in the daclizumab-treated subjects was 0.211 over 1 year in Study 201 and 0.249 over 1 year in Study 301. The annualized relapse rate for severe or serious relapses in the daclizumab arm at 1 year was 0.096 in Study 201 and 0.094 in Study 301.

Daclizumab treatment resulted in a 70% reduction in new or newly enlarging T2 lesions compared to placebo at 1 year in Study 201 and a 54% reduction compared to IFN β-1a at 2 years in Study 301 ($p < 0.0001$ for both comparisons). Gd enhancement, T2 lesion volume and the number and volume of T1

hypointense black holes also have shown a consistent and robust effect of daclizumab by Week 24 and sustained for the duration of daclizumab treatment.

In both pivotal studies, there was some evidence that daclizumab reduced the risk of confirmed disability progression. In Study 201, daclizumab reduced the risk of 12-week confirmed disability progression by 57% relative to placebo (p = 0.0211) and the risk of 24-week confirmed disability progression by 76% (p = 0.0037). In Study 301, daclizumab reduced the risk of 12-week confirmed disability progression by 16% (p = 0.1575) [not statistically significant] and the risk of 24-week confirmed disability progression by 27% (p = 0.0332). The differences in the daclizumab efficacy estimates for disability progression between Studies 201 and 301 are consistent with the established effect of IFN β-1a on confirmed disability progression compared to placebo (37% vs. placebo in registrational studies). Overall, the magnitude of the treatment effect on confirmed disability progression against IFN β-1a in Study 301 (16% to 27% reduction) is confirmatory of the 57% to 76% reduction in confirmed disability progression against placebo in Study 201, recognizing the effect of IFN β-1a on this endpoint.

In Study 301, confirmed disability progression was common after a tentative disability progression among subjects with at least one tentative disability progression in the trial: 35% for 12-week confirmed progression and 24% for the 24-week confirmed progression. Censoring after a tentative disability progression was nearly twice as common in the IFN β-1a group compared to the daclizumab group (43 vs. 24 for the 12-week confirmed progression), reflecting a proportionally higher number of tentative disability progressions in the IFN β-1a arm of the trial. While the number of subjects censored after a tentative disability progression (n = 67) was small relative to the total number of subjects with a tentative disability progression in the trial (n = 736), assumptions made about disability progression in these censored subjects impacted whether the test of statistical significance for disability progression was above or below the 0.05 significance threshold in Study 301. Prespecified analyses of disability progression in Study 301 supported a significant treatment effect of daclizumab over IFN β-1a on both 12- and 24-week confirmed disability progression analyses, except when analysed under the assumption that disability progression did not occur in any patient who was censored after a tentative disability progression.

Additionally, a positive effect on disability progression in all forms of RMS, including the relapsing forms of Secondary Progressive Multiple Sclerosis was demonstrated. In the clinical development of daclizumab in MS, the 2 pivotal trials were of sufficient duration and size that certain subjects included in these trials could during the trials be identified as having SPMS with superimposed relapses based on the observation of sustained disability progression that occurred independently of, or in the absence of, clinical relapses. Furthermore, analysis of these subjects provided evidence that daclizumab was more effective than IFN β-1a at preventing the progression of sustained disability progression that occurred independently of clinical relapses. This finding, in conjunction with the analyses provided, demonstrating efficacy of daclizumab in subjects with both highly active (approximately 40% of subjects) and less active (approximately 60% of subjects) forms of MS, demonstrated that daclizumab has efficacy across a broad spectrum of MS subjects which was considered essential in an indication for “relapsing forms of MS.”

Uncertainty in the knowledge about the beneficial effects.

The extrapolation of annualised relapse rate to more than the study period adds significant uncertainty: it is not known for the individual patient, when they are going to progress to SPMS, particularly when limited number of patients with high disease activity were included in the clinical studies. The assumption of whether daclizumab has any efficacy over non-RMS (efficacy on secondary progressive MS) was discussed, but there is still uncertainty on the magnitude and duration of such an effect.

The number of new lesions per time unit is a known relevant endpoint, but in the individual patient, the locations of the new lesions are very important, depending whether they occur in more loquacious or silent areas of white matter.

Disability was measured by the use of EDSS and it has to be taken into account that EDSS is not a disability tool, as interpreted like the disruption of the patient in his role within society, but is more an impairment tool. Nevertheless, there seems to be a reasonable correlation between impairment as measured by EDSS and disability.

Risks

Unfavourable effects

The safety of Daclizumab 150 mg has been well characterized in clinical studies of 1785 MS subjects treated for up to 6 years, accounting for approximately 4100 subject-years of exposure. During the accumulation of these safety data, several important risks have emerged, including elevations of liver transaminases and hepatic injury, cutaneous events, infections, and depression and strategies and approaches to monitor and mitigate these risks have been implemented and tested in the clinical studies.

Daclizumab is associated with a risk of elevations of serum transaminases and cases of hepatic injury. Most often this risk manifests as a transient and asymptomatic increase in ALT/AST that resolves spontaneously or with discontinuation of dosing. In a small number of cases, serious events of hepatic injury, characterized by concomitant elevations of serum transaminases and bilirubin, were identified in which daclizumab may have played at least a significant contributory role based on independent adjudication of the events. With the exception of a fatal case of autoimmune hepatitis early in the clinical development program, prompt identification of these cases, discontinuation of daclizumab, and treatment of underlying or other contributory causes resulted in favourable outcomes. While a single dose of daclizumab given at the time of a transaminase abnormality generally did not appear to worsen or prolong events, the single case of fatal autoimmune hepatitis occurred in the setting of repeated administration of daclizumab during the elevation. Treatment discontinuation for patients meeting certain criteria (and possibly for others, based on physician judgment) is appropriate to limit the severity of the event and to reduce the risk of recurrence in susceptible individuals.

The most common cutaneous events during daclizumab use were dermatitis, eczema, and rashes, which were manageable with treatment, including topical and/or systemic steroids, and treatment discontinuation. Some cases were serious and had features of a delayed-type hypersensitivity reaction. These cases typically presented with a more generalized, diffuse rash, and some cases required multiple courses of corticosteroids. While the most serious cases could be a source of significant discomfort to patients, the integrity of the skin was preserved and none of the events were directly life-threatening. Overall, the use of corticosteroids appeared to result in rapid improvement of many of the more serious cases. Over time, events generally resolved or substantially improved without permanent injury to the skin.

Infections were composed mainly of upper respiratory tract, urinary tract, and viral infections typical of those seen in a non-immunocompromised MS population. While the incidence of both minor and serious infections was increased during daclizumab use, the pattern and outcome of the events indicated that the ability of the subjects' immune system to effectively respond to the infection was preserved. Overall, the infections that have occurred during daclizumab use have been manageable with standard care, and the incidence of infections necessitating discontinuation of study treatment has been <1%.

Upon comprehensive review of all information available, across all studies, 6 subjects being treated with daclizumab attempted suicide. Two of these did not have a prior history of depression. Three serious

adverse events of depression were noted following treatment with daclizumab and depression was found as a safety concern and reflected in the risk minimization activities.

Overall, the safety profile of daclizumab includes several serious risks, including elevations of serum transaminases and hepatic injury, cutaneous events, infections, and depression. Based on the known immunomodulatory effect of daclizumab and the pattern of AEs observed, including response to treatment, an immune-mediated mechanism was implicated in some of these events. During the development program, procedures were developed in conjunction with experts to enable early identification and management of these risks, and were tested during the clinical studies. These procedures can be translated into the clinical setting and used to provide guidance to prescribers. With appropriate physician and patient education and clinical vigilance, the risks associated with daclizumab can be managed by awareness and early recognition of developing risks, standard medical care, and treatment discontinuation.

Uncertainty in the knowledge about the unfavourable effects

The hepatic failure risk, although more frequent at starting of treatment, is not eliminated when the patient is in maintenance phase. The relevance of cutaneous disorders may have different value from patient to patient. Serious cutaneous adverse reactions are frequent and may require repeated corticosteroid use, which may result in skin atrophy or long-term adverse events.

Daclizumab has an impact over the immune system and the body response to external biological agents. Increased infections are very relevant, even as compared to IFN. Usually the risk of having a severe or disabling infection is time dependent. Therefore, this risk will increase as treatment duration progresses. Although no PML case has been reported with daclizumab, severe lymphopenia which is a known risk factor for the emergence of PML, has occurred in some patients.

Effects table

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
Favourable Effects							
ARR	Relapses per year	Rate	0.211 (0.15, 0.29)	0.458 (0.37,0.57)	-	The effect is robust, supported by sensitivity and subgroup analyses	1
		Rate	0.212 (0.19, 0.24)		0.393 (0.35, 0.44)		2
12-week SDP	Estimated proportion with 12-week sustained increase in EDSS (W52)	%	0.059	0.133	-	Hazard ratio=0.43 (0.21, 0.88) Effect is statistically and clinically significant	1

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
	Estimated proportion with 12-week sustained increase in EDSS (W96)	%	0.120	-	0.143	Hazard ratio=0.84 (0.66, 1.07) Trend was positive but not statistically significant with the prespecified analysis	2
24-week SDP	Estimated proportion with 24-week sustained increase in EDSS (W52)	%	0.026	0.111	-	Hazard ratio=0.24 (0.09, 0.63) Effect is statistically and clinically significant	1
	Estimated proportion with 24-week sustained increase in EDSS (W96)	%	0.092	-	0.121	Hazard ratio=0.73 (0.55, 0.98) p=0.0332 Effect is statistically and clinically significant	2
T2 hyperintense lesions	New or newly enlarging T2 hyperintense (W52)	Adjusted mean	2.42 (1.96, 2.99)	8.13 (6.65, 9.94)	-	Percent reduction=70.2% p<0.0001	1
	New or newly enlarging T2 hyperintense (W96)	Adjusted mean	4.31 (3.85, 4.81)	-	9.44 (8.46, 10.54)	Percent reduction=54.4% p<0.0001	2
Gd-enhancing lesions	Adjusted mean number of new Gd lesions (week 8 to 24)	Adjusted mean	1.46 (1.05, 2.03)	4.79 (3.56, 6.43)	-	Percent reduction=69.5% p<0.0001	1
	Adjusted mean number of new Gd lesions (W96)	Mean	0.4	-	1.0	Odds ratio=0.25 (0.20, 0.23) p<0.0001	2

Effect	Short Description	Unit	Treatment daclizumab 150 mg	Control Placebo	Control IFN β-1a 30 µg	Uncertainties/ Strength of evidence	Refs
MSIS-29 physical score	Percentage of subjects with a significant worsening at Week 52	%	20.4	31.6	-	Odds ratio=0.56 (0.35, 0.88) P= 0.0125	1
	Percentage of subjects with a significant worsening at Week 48	%	17		20	Odds ratio=0.83 (0.65, 1.06) P= 0.1329	2

Unfavourable Effects							
Hepatic events	Incidence of hepatobiliary events	%	3%	2%		SOC	1
		%	16%	-	14%	SMQ	2
Elevated liver enzymes	Elevation > 5 ULN	%	4%	<1%	-	Increased risk over comparator. Monthly monitoring required up to 4 months after treatment is stopped	1
		%	6%	-	3%		2
CD4 count	Number of subjects with post-baseline value <400 cells/mm^3	N (%)	186 (22)		141 (17)	The decrease in CD4 is more pronounced with daclizumab than with IFN β-1a	2
	Number of subjects with post-baseline value <200 cells/mm^3	N (%)	20 (2)		10 (1)		2
Infections	Incidence of infections	%	50%	44%	-	Increased incidence over IFN β-1a	1
		%	65%	-	57%		2
Cutaneous reactions	Incidence of cutaneous reactions	%	18%	13%	-	Increased over placebo	1
		%	37%	-	19%	Increased over IFN β-1a	2
Depression	Incidence of depression	%	7%	3%	-	SMQ Increased over placebo	1
		%	11%	-	10%	SMQ	2

Abbreviations: ARR: Annualized Relapse Rate; SDP: sustained disability progression; MSIS (29): Multiple sclerosis impact scale physical score; Refs: References; W: week; ULN: upper limit of normal.

Notes: 1: study 205MS201; 2: study 205MS301

Benefit-risk balance

Importance of favourable and unfavourable effects

There are several factors that may distinguish daclizumab from current therapies and that enable it to address current gaps in therapeutic options for RMS patients.

- Daclizumab is the first MS therapy whose primary mechanism of action is related to the modulation of IL-2 signaling, and its immunologic effects are reversible in a time frame consistent with its serum half-life.
- Daclizumab provides superior efficacy to IM IFN β-1a, currently one of the most widely used treatments for RMS, and the efficacy of daclizumab was evident across the spectrum of the RMS study populations with respect to key factors such as prior treatment history, level of MS inflammatory activity, and EDSS range at baseline. Daclizumab was significantly effective versus placebo and versus IM IFN β-1a in subjects with highly active and less active subgroups .
- Daclizumab will be the first approved MS therapy that has a monthly SC dosing regimen.

RMS patients with highly active MS are at elevated risk for long-term disability progression, and achieving early and complete control of MS activity with DMTs is currently recommended to provide a patient with the best opportunity to preserve function. High-efficacy DMTs are the mainstay of treatment for these patients, but their response to any individual treatment is variable, and therefore it is beneficial for physicians to have several treatments with differentiated mechanisms of action from which to select and tailor therapy.

For patients with active MS and who need a high-efficacy MS therapeutic but have known risk factors for the serious adverse effects of other MS therapies that have shown superior efficacy to IFN β-1a (e.g., patients who are JCV positive [in the case of natalizumab] or patients with cardiac disease [in the case of fingolimod]), or for those patients who are concerned about long-term immunosuppression and do not want to use a potentially irreversible therapy (such as alemtuzumab), daclizumab provides atreatment alternative although it should be noted that no information is available as for the risk of PML following treatment with Zinbryta.

RMS patients with less active forms of MS may also benefit from high-efficacy MS therapies considering the present therapeutic goal of eliminating MS activity as completely as possible to preserve function over the long term.

Benefit-risk balance

Discussion on the benefit-risk balance

The CHMP considers that daclizumab has shown statistically and clinically robust data in patients suffering from Relapsing Multiple Sclerosis. The clinical and MRI effect seen with the treatment was reproduced in several studies over up to 3 years and it was established that maintenance of treatment beyond one year was beneficial. The most significant adverse events relate to hepatic injury and elevated hepatic enzymes, infections, cutaneous reactions and depression.

The risk of hepatic injury and elevated liver enzymes is clear and monthly monitoring of liver enzymes is required during treatment and amendments have been made in the Product Information documents to guide monitoring of hepatic function. Monitoring of white blood cells and a warning regarding cases of tuberculosis in patients treated with daclizumab has also been implemented, and the present risk minimisation strategies are considered sufficient.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zinbryta in the treatment of adult patients with relapsing forms of Multiple sclerosis is favourable, and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Hepatic Risk Management Guide, Patient Card

Prior to launch of Zinbryta in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

Objective and rationale:

To educate patients and physicians about the risk of severe hepatic injury and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity.

Proposed action:

The Hepatic Risk Management Guide will contain information for the physician on the risk of elevations in liver enzyme levels and severe liver injury in patients treated with Zinbryta, as well guide the physician/patient discussion around hepatic risk and the measures to manage this risk. The physician should discuss the risk of hepatic injury with the patient and provide them with a Patient Card.

The Patient Card informs patients of the risk of severe hepatic injury, and the possible symptoms, so that they are aware of situations in which they should contact a physician in a timely manner. In addition, the Patient Card explains the need for monitoring of liver function and educates the patient on the importance of adherence to their monthly blood tests

The Patient Card is designed to enable the physician to present patient-friendly information about Zinbryta to a patient at the time Zinbryta is prescribed. It will focus on the potential for severe hepatic injury with Zinbryta, and will also include information about symptoms of liver injury and instructions about monthly liver function monitoring.

- **Obligation to complete post-authorisation measures**

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers by consensus that daclizumab is not qualified as a new active substance as significant differences in properties with regard to safety and/or efficacy from the previously authorised substance due to differences in molecular structure, nature of source materials or manufacturing process were not warranted.

Monoclonal Antibodies

In October 2008, the International Nonproprietary Name (INN) Working Group Meeting on Nomenclature for Monoclonal Antibodies (mAb) met to review and streamline the monoclonal antibody nomenclature scheme. Based on the group's recommendations and further discussions, the INN Experts published changes to the monoclonal antibody nomenclature scheme.

In 2011, the INN Experts published an updated "International Nonproprietary Names (INN) for Biological and Biotechnological Substances—A Review" (PDF) with revisions to the monoclonal antibody nomenclature scheme language.

The USAN Council has modified its own scheme to facilitate international harmonization. This page outlines the updated scheme and supersedes previous schemes. It also explains policies regarding post-translational modifications and the use of 2-word names.

The council has no plans to retroactively change names already coined. They believe that changing names of monoclonal antibodies would confuse physicians, other health care professionals and patients.

Manufacturers should be aware that nomenclature practices are continually evolving. Consequently, further updates may occur any time the council believes changes are necessary. Changes to the monoclonal antibody nomenclature scheme, however, should be carefully considered and implemented only when necessary.

Elements of a Name

The suffix "-mab" is used for monoclonal antibodies, antibody fragments and radiolabeled antibodies. For polyclonal mixtures of antibodies, "-pab" is used. The

-pab suffix applies to polyclonal pools of recombinant monoclonal antibodies, as opposed to polyclonal antibody preparations isolated from blood. It differentiates polyclonal antibodies from individual monoclonal antibodies named with -mab.

Sequence of Stems and Infixes

The order for combining the key elements of a monoclonal antibody name is as follows:

1. Prefix
2. Infix representing the target or disease
3. Infix indicating the source
4. Stem used as a suffix

Prefix

To create a unique name, a distinct, compatible syllable or syllables should be selected as the starting prefix.

Suggested prefixes should comply with the USAN Program's **rules for coining names**. In addition, we ask that manufacturers watch for potential conflicts with names of other monoclonal antibodies, because approximately 200 monoclonal antibodies have already been named. Although it is desirable that names be as short as possible, a prefix that is 2 or more syllables long may be necessary to distinguish the name from those previously assigned.

Target/Disease Class Infix

The general disease state subclass must be incorporated into the name. This is accomplished with the target/disease class infix. The USAN Council has approved specific syllables to denote diseases or targets. Additional subclasses may be added as necessary.

The choice of infix is determined by the available information regarding initial clinical indications and antibody action. The council may request more details and evidence regarding antibody action and indications if necessary.

The target/disease infix has been truncated to a single letter when the source infix begins with a vowel. Using a single letter can create problems with pronunciation, such as with humanized and chimeric antibodies. Therefore a second letter—a

vowel—is added. The infixes that refer to the disease or target class are shown in the table.

Target/Disease Class Infixes for Monoclonal Antibodies (Infix, Definition and Example Suffixes as Used):

Infix: -tu-/-t-
Definition: tumors
Example: -tuzumab/-tumab/-tomab

Infix: -li-/-l-
Definition: immunomodulator
Example: -liximab/-lumab/-lixizumab

Infix: -ba-/-b-
Definition: bacterial
Example: -bixumab/-bumab

Infix: -ci-/-c-
Definition: cardiovascular
Example: -cixumab/-cumab

Infix: -fu-/-f-
Definition: antifungal
example: -fuzumab/-fumab

infix: -gr(o)-
Definition: skeletal muscle mass related growth factors and receptors as target
Example: -grumab

Infix: -ki-/-k-
Definition: interleukins
Example: -kiximab/-kumab

Infix: -ne-/-n-
Definition: neurons as targets
Example: -nezumab/-numab

Infix: -so-/-s-
Definition: bone
Example: -somab/-sumab

Infix: -vi-/-v-
Definition: viruses, antiviral indications
Example: -vizumab/-vumab

The tumor-specific infixes have been discontinued because most monoclonal antibodies with oncology indications are investigated for more than 1 type of tumor. Thus, the following infixes are no longer used: -col- (colon cancer), -mel- (melanoma), -got- (testes), -gov- (ovarian), and -po- (prostate).

Source Infix

Identification of the "source" of the antibody is an important safety consideration, as some products may cause source-specific antibodies to develop in patients. Because an antibody may be based on the sequence of one species but manufactured in cell lines derived from another, "source" is defined as referring to the species on which the immunoglobulin sequence of the mAb is based. This definition harmonizes with that used by the INN Program.

A series of infixes which immediately precede -mab or -pab indicate the source. A limited subset of infixes used most often accounts for nearly all the monoclonal antibody names.

The distinction between chimeric and humanized antibodies is as follows:

Chimeric: A chimeric antibody is one for which both chain types are chimeric as a result of antibody engineering. A chimeric chain is a chain that contains a foreign variable domain (originating from 1 species other than human, or synthetic or engineered from any species including human) linked to a constant region of human origin. The variable domain of a chimeric chain has a V region amino acid sequence which, when analyzed as a whole, is closer to nonhuman species than to human.

Humanized: A humanized antibody is one for which both chain types are humanized as a result of antibody engineering. A humanized chain is typically a chain in which the complementarity determining regions (CDR) of the variable domains are foreign (originating from 1 species other than human, or synthetic) whereas the remainder of the chain is of human origin. Humanization assessment is based on the resulting amino acid sequence, and not on the methodology itself, which allows protocols other than grafting to be used. The variable domain of a humanized chain has a V region amino acid sequence which, when analyzed as a whole, is closer to human than to other species.

New Monoclonal Antibody Rules (PDF)

Source Infixes Used Frequently

Infix: -zu-
Definition: humanized

Infix: -o-
Definition: mouse

Infix: -u-
Definition: fully human

Infix: -xi-
Definition: chimeric

Infix: -xizu-
Definition: combination of humanized and chimeric chains

Source Infixes Used Seldom

Infix: -axo-
Definition: rat/mouse chimer

Infix: -e-
Definition: hamster

Infix: -a-
Definition: rat

Infix: -i-
Definition: primate

USAN Modified Designations for Monoclonal Antibodies

In several instances, the name of a monoclonal antibody incorporates additional clarifying words.

If the antibody is conjugated to a payload—such as radiolabel or toxin, this conjugate is identified by using a separate, second word or other acceptable chemical designation. For monoclonals conjugated to a toxin, the "-tox" stem must be included as part of the name selected for the toxin (e.g., zolimomab aritox, in

which aritox identifies ricin A-chain). In other cases (e.g., brentuximab vedotin) the payload may receive a name based on a stem or a chemical name.

For radiolabeled products, the word order is

1. Name of the isotope
2. Element symbol
3. Isotope number
4. Name of the monoclonal antibody, as follows:

-technetium Tc 99m biciromab
-indium In 111 altumomab pentetate

The peg- prefix may be used for pegylated mAbs, but it should be avoided if it leads to an overly long name. Usually a 2-word name is preferable with the first word referring to the monoclonal antibody and "pegol" as the second word.

When firms apply to name an antibody conjugated to a payload, they should file separate USAN applications for the antibody and the payload, as well as the application for the conjugate. This allows the USAN Council to assign separate USAN designations to each component. The **USAN Modified Application** may be used for the additional names.

USAN Requirements for Monoclonal Antibodies

When naming Monoclonal Antibodies the following items are required to be submitted with your application materials:

- Complete mature amino acid sequence in a **Microsoft Word document**
- Single-letter codes for each amino acid, displayed in groups of 10 characters with 5 groups per line and a number indicating the position of the last amino acid at the end of each line
- Glycosylation patterns, including site and type of sugar, etc.
- Precursor nucleotide sequence with spaces between codons and translation, with numbered lines
- CDR-IMGT and sequence analysis of the variable regions showing percentage of human content (if –ximab, -zumab, or -umab is requested; 85%+ -zumab or -umab, <85% -ximab)

- IG class and subclass, IG format
- Species or taxonomy related structure (chimeric, humanized, etc.)
- Name and/or structure of targeted antigen
- List of all disulfide bridges and their locations
- Expression system
- Clone name(s) and laboratory code name(s)
- If appropriate, the closest human V, J, and C genes and alleles (results obtained with IMGT/DomainGapAlign tool)

Nonproprietary Naming of Biological Products

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2017
Labeling

OMB control number XXXX-XXXX
Expiration Date: xx/xx/xxxx

The information collection provisions in this guidance regarding submission of proposed suffixes are under OMB review and are not for current implementation.
See additional PRA statement in section VII of this guidance.

Nonproprietary Naming of Biological Products

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

and/or

Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2017
Labeling

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Contains Nonbinding Recommendations

Nonproprietary Naming of Biological Products

Guidance for Industry[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance describes FDA's current thinking on the need for biological products licensed under the Public Health Service Act (PHS Act) to bear a *nonproprietary name*[2] that includes an FDA-designated suffix. Under this naming convention, the nonproprietary name designated for each *originator biological product*, *related biological product*, and *biosimilar product* will be a proper name that is a combination of the *core name* and a distinguishing suffix that is devoid of meaning and composed of four lowercase letters.[3] The suffix format described in this guidance is applicable to originator biological products, related biological products, and biosimilar products previously licensed and newly licensed under section 351(a) or 351(k) of the PHS Act. FDA is continuing to consider the appropriate suffix format for *interchangeable products.*

This naming convention will facilitate pharmacovigilance for originator biological products, related biological products, and biosimilar products containing related drug substances when other means to track a specific dispensed product are not readily accessible or available, as described in section IV.A of this guidance. Distinguishable nonproprietary names will also facilitate accurate identification of these biological products by health care practitioners and patients. Further, distinguishing suffixes should help minimize inadvertent substitution of any such products that have not been determined to be interchangeable. Application of the naming convention to biological products licensed under the PHS Act should (1) encourage routine use of designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices and (2) avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway, as described in detail in this guidance.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

[2] See the Glossary for definitions and usage of specific terms used throughout this guidance.

[3] The nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act is its proper name (section 351(a)(1)(B)(i) of the PHS Act (42 U.S.C. 262(a)(1)(B)(i)) and § 600.3(k) (21 CFR 600.3(k)).

This guidance provides information to industry, the health care community, other regulatory agencies, and the public on FDA's rationale for this naming convention. It is also intended to assist applicants and license holders in proposing the suffix to be incorporated in the nonproprietary name (referred to throughout this guidance as the *proper name*) for an originator biological product, a related biological product, or a biosimilar product.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. SCOPE

This guidance describes FDA's approach to designating the proper name for originator and related biological products licensed under section 351(a) of the PHS Act and for biosimilar products licensed under section 351(k) of the PHS Act. FDA intends to apply a naming convention to interchangeable products that will feature a core name and a suffix included in the proper name; however, FDA is continuing to consider the appropriate format of the suffix for these products. FDA intends to apply the naming convention discussed in this guidance to both newly licensed and previously licensed biological products. As discussed further in section V of this guidance, the revised proper name of biological products previously licensed under the PHS Act generally would include the product's original proper name serving as the core name plus the distinguishing suffix attached with a hyphen. FDA is continuing to consider the process for implementation of this naming convention for previously licensed products but, in the near term, intends to assign distinguishing suffixes to a limited group of these products[4] and also will accept submissions of prior approval labeling supplements that include proposed suffixes.

This guidance also will apply to those biological products that are approved under the Federal Food, Drug, and Cosmetic Act (FD&C Act) on or before March 23, 2020, when such products are deemed to be licensed under section 351 of the PHS Act on March 23, 2020 (section 7002(e)(2) through (e)(4) of the Biologics Price Competition and Innovation Act of 2009 (BPCI Act)). [5] FDA intends to provide additional guidance regarding administrative issues associated with the transition (including the process for implementing the naming convention described in this guidance).

[4] The Agency published a proposed rule in the *Federal Register* of August 28, 2015 (80 FR 52224) ("Designation of Official Names and Proper Names for Certain Biological Products").

[5] See the draft guidance for industry *Implementation of the 'Deemed to be a License' Provision of the Biologics Price Competition and Innovation Act of 2009.* When final, this guidance will represent FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For the purposes of this document, unless otherwise specified, references to biological products include biological products licensed under the PHS Act, such as therapeutic protein products, vaccines, allergenic products, and blood derivatives, and do not include certain biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)), such as in vitro reagents (e.g., antibody to hepatitis B surface antigen, blood grouping reagents, hepatitis C virus encoded antigen) and blood donor screening tests (e.g., HIV and hepatitis C). Also, for the purposes of this document, unless otherwise specified, references to biological products do not include products for which a proper name is provided in the regulations (e.g., 21 CFR part 640) or to certain categories of biological products for which there are well-established, robust identification and tracking systems to ensure safe dispensing practices and optimal pharmacovigilance (e.g., ISBT 128 for cord blood products and blood components).

III. BACKGROUND

A. The Biologics Price Competition and Innovation Act of 2009

With the passage of the BPCI Act,[6] which established an abbreviated licensure pathway for products demonstrated to be biosimilar to or interchangeable with an FDA-licensed *reference product*, a growing number of biological products will be entering the marketplace.

Section 351(k) of the PHS Act (42 U.S.C. 262(k)), added by the BPCI Act, sets forth the requirements for an application for a proposed biosimilar product and an application or a supplement for a proposed interchangeable product. Section 351(i) defines biosimilarity to mean "that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components" and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (see section 351(i)(2) of the PHS Act). To meet the additional standard of interchangeability, an applicant must provide sufficient information to demonstrate biosimilarity and also to demonstrate that the biological product can be expected to produce the same clinical result as the reference product in any given patient and, if the biological product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch (see section 351(k)(4) of the PHS Act). Interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider (see section 351(i)(3) of the PHS Act).

B. Evaluation of the Appropriate Naming Convention

The proper name of a biological product reflects certain scientific characteristics of the product, such as chemical structure and pharmacological properties. This name is different from a

[6] Sections 7001 through 7003 of the Patient Protection and Affordable Care Act (Public Law 111-148).

proprietary name, which generally is trademarked and registered for private use. For biological products licensed under the PHS Act, FDA designates the proper name in the license for use upon each package of the biological product (see section 351(a)(1)(B)(i) of the PHS Act and 21 CFR 600.3(k)). Among other things, the proper name of a biological product helps health care providers identify the product's drug substance and distinguish biological products from one another.

As part of FDA's implementation of the BPCI Act, the Agency requested public comment on its development of a framework for safe use and optimal pharmacovigilance for biosimilar products and interchangeable products that is informed by current experience and industry best practices, including the role of a product's proper name.

FDA has evaluated comments received on the approaches to naming biosimilar products and interchangeable products.[7] In light of the issues considered for biosimilar products and interchangeable products, FDA also evaluated its approach to designating proper names for biological products licensed under section 351(a) of the PHS Act.

In implementing the BPCI Act, FDA has carefully considered the appropriate naming convention to maximize the success of biosimilar products and interchangeable products and to help ensure the safety of patients receiving biological products licensed under the PHS Act.

IV. CONSIDERATIONS FOR NONPROPRIETARY NAMING OF ORIGINATOR BIOLOGICAL PRODUCTS, RELATED BIOLOGICAL PRODUCTS, AND BIOSIMILAR PRODUCTS

This section discusses the main considerations that led FDA to adopt the naming convention described in section V of this guidance.

A. Enhancing Biological Product Pharmacovigilance

The Agency considers appropriate pharmacovigilance fundamentally important for biological products. Although safety of biological products is rigorously assessed before approval, safety issues that are specific to a manufacturer may arise after approval with any marketed product. To help ensure patient safety and allow the Agency and the manufacturer to swiftly identify and address a problem, FDA aims to track adverse events to a specific manufacturer (and as appropriate, to a lot or manufacturing site for a particular biological product) and allow surveillance systems to detect safety signals throughout the life cycle of a product. Identifying a biological product's manufacturer can help target remedial action (including recall) to avoid implicating a broader set of products for which no such problem exists.

[7] See, for example, notices that published in the *Federal Register*, "Approval Pathway for Biosimilar and Interchangeable Biological Products; Public Hearing; Request for Comments" (75 FR 61497, October 5, 2010); "Draft Guidances Relating to the Development of Biosimilar Products; Public Hearing; Request for Comments" (77 FR 12853, March 2, 2012); "Nonproprietary Naming of Biological Products; Draft Guidance for Industry; Availability" (80 FR 52296, August 28, 2015); and other public dockets established by FDA.

Pharmacovigilance systems, both active and passive, vary in their use of identifiers to differentiate among biological products. These identifiers may include the proprietary name, proper name, manufacturer, national drug code (NDC) number, lot number, and billing codes. However, many active pharmacovigilance systems, which generally identify adverse events by querying privately held electronic health care data such as administrative and billing data, have limited ability to track to its manufacturer a biological product that shares the same proper name with other biological products. Other product identifiers, such as NDC numbers, are not routinely recorded in billing and patient records in many clinical settings in which biological products are dispensed and administered, and therefore the utility of these alternative identifiers in active pharmacovigilance is limited. Similarly, proprietary names and NDC numbers are often not included in adverse event reports. As a result, the use of alternative identifiers, including distinct proprietary names or NDC numbers, is insufficient to address concerns regarding pharmacovigilance.

Nonproprietary names that include distinguishing suffixes can serve as a key element to identify specific products in spontaneous adverse event reporting and to reinforce accurate product identification in billing and claims records used for active pharmacovigilance. Other product-specific identifiers, such as proprietary names or NDCs, may not be available or could change over time. A distinguishing suffix will also support the tracking of product-specific events over time, thereby enhancing the accurate attribution of product-specific adverse event reports.[8]

The Agency's approach to nonproprietary naming of biological products will provide another critical tool for accurately identifying and facilitating pharmacovigilance for originator biological products, related biological products, and biosimilar products.

B. Ensuring Safe Use for Biological Products

Biological products generally consist of large, complex molecules and raise unique safety concerns related to immunogenicity. FDA believes the nonproprietary naming convention for originator biological products, related biological products, or biosimilar products should help prevent inadvertent substitution. Inadvertent substitution may lead to unintended alternating or switching of biological products that are not determined by FDA to be interchangeable with each other. This naming convention should facilitate safe use and help to protect the safety of patients.

Related biological products may be licensed for different indications. Biosimilar products may be licensed for fewer than all indications for which the reference product is licensed. Likewise, related biological products and biosimilar products may be licensed for fewer than all routes of administration and may be packaged in different delivery systems than those approved for the

[8]See the draft guidance for industry *Postmarketing Safety Reporting for Human Drugs and Biological Products Including Vaccines*. When final, this guidance will represent FDA's current thinking on this topic.

originator biological product. If originator biological products, related biological products, and biosimilar products all share the same proper name, inadvertent substitution may lead to medication errors. For example, a patient could inadvertently receive a product with a different delivery system or route of administration than was prescribed, which may lead to confusion among patients and result in dosing errors.

Confusion may also arise among health care providers who, based on their experience with small-molecule drugs and generic versions of those drugs, may incorrectly assume that FDA has determined biological products with the same proper name to be interchangeable. Information on alternating or switching between a proposed product and its reference product is required to support a demonstration of interchangeability, but is not required to support a demonstration of biosimilarity (see section 351(k)(4) of the PHS Act). Applications for related biological products are not required to include any comparative data to any other biological product in support of licensure (see section 351(a) of the PHS Act). Although many biological products may have proprietary names, many health care systems mainly use proper names instead of proprietary names for ordering, prescribing, and dispensing products.

The naming convention discussed in this guidance will also facilitate use of the Purple Book[9] for biological products. The Purple Book enables a user to readily see all licensed biological products and identify whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference product (a previously licensed biological product). Biosimilar products and interchangeable products licensed under section 351(k) of the PHS Act will be listed under the reference product to which biosimilarity or interchangeability was demonstrated.

C. Advancing Appropriate Practices and Perceptions Regarding Biological Products

With the introduction of more biological products, FDA believes it is important to encourage routine use of designated suffixes in ordering, prescribing, dispensing, recordkeeping, and pharmacovigilance practices for biological products, irrespective of their licensure pathway and date of licensure. The designated suffix will provide a consistent, readily available and recognizable mechanism for patients and health care professionals, including providers and pharmacists, to correctly identify these products. FDA believes it is likely that FDA-designated suffixes will be used routinely when identifying, describing, and recording use of biological products if such suffixes are present in the proper names of all biological products licensed under the PHS Act.

[9] FDA published the *Purple Book*: *Lists of Licensed Biological Products With Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations* in September 2014, which is publicly available at http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm411418.htm. The Purple Book is updated periodically to reflect FDA licensure of a biological product under section 351(a) or section 351(k) of the PHS Act and/or to reflect a determination regarding date of first licensure for a biological product licensed under section 351(a) of the PHS Act.

The inclusion of an FDA-designated suffix in the nonproprietary name of biological products licensed under section 351(a) or 351(k) of the PHS Act should have the added benefit of helping to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway. The safety and effectiveness of biological products is rigorously assessed before approval. Through FDA's implementation of the BPCI Act's standards for biosimilarity and interchangeability, FDA can ensure that the products it determines to be biosimilar to or interchangeable with a reference product can be relied upon by providers and patients to be safe and effective. Applying this naming convention only for products licensed under section 351(k) of the PHS Act—but not for the reference product licensed under 351(a) of the PHS Act—could adversely affect health care provider and patient perceptions of these new products. Specifically, such an approach could be misinterpreted as indicating that biosimilar products differ from their reference products in a clinically meaningful way or are inferior to their reference products for their approved conditions of use.

D. Prospective and Retrospective Application of Naming Convention

FDA's current thinking is that a proper name that includes a distinguishing suffix is warranted for both newly licensed and previously licensed originator biological products, related biological products, and biosimilar products. As with prospective application of the naming convention, retrospective application will help (1) prevent a patient from receiving a product different from what was intended to be prescribed; (2) facilitate manufacturer-specific pharmacovigilance by providing a means of determining which biological product is dispensed to patients; (3) encourage routine use of FDA-designated suffixes in ordering, prescribing, dispensing, and recordkeeping practices for these products; and (4) advance accurate perceptions of these biological products.

V. FRAMEWORK FOR DESIGNATING THE PROPER NAME OF A BIOLOGICAL PRODUCT

FDA's naming convention for biological products licensed under the PHS Act will be a proper name consisting of a core name[10] and an FDA-designated suffix. Proper names designated by FDA for originator biological products, related biological products, and biosimilar products will include a combination of a core name and a distinguishing suffix.

For originator biological products, FDA intends to use a core name that is the adopted name designated by the USAN Council[11] for the relevant biological substance when available. If the biological product is a related biological product, a biosimilar product, or an interchangeable

[10] Two examples of a *core name* are filgrastim and epoetin alfa. The *proper name* for all biological products will include a distinguishing suffix composed of four lowercase letters attached to the core name with a hyphen.

[11] The United States Pharmacopeial Convention, 2016, Guiding Principles for Coining United States Adopted Names for Drugs (2016 USP Dictionary of USAN and International Drug Names at http://www.uspusan.com/usan/pub/index1.html).

product, the core name will be the same as the core name identified in the proper name of the relevant previously licensed product.[12] A distinguishing suffix that is devoid of meaning and composed of four lowercase letters will be attached with a hyphen to the core name of each originator biological product, related biological product, or biosimilar product.[13] Use of a shared core name will indicate a relationship among products. The placement of the identifier as a suffix, rather than a prefix, should result in biological products with the same core name being grouped together in electronic databases to help health care providers locate and identify these products.[14]

To illustrate, the proper names for products sharing the core name replicamab may be displayed as follows:

replicamab-cznm
replicamab-hjxf

To illustrate, the proper names for products sharing the core name putonastim alfa may be displayed as follows:

putonastim alfa-jnzt
putonastim alfa-kngx

In designating proper names for related biological products, the Agency has in some instances designated a proper name that includes an identifier attached as a prefix to distinguish the products from previously licensed biological products; for example, ado-trastuzumab emtansine. In this case, designation of a proper name that includes a unique prefix was necessary to minimize certain medication errors and to facilitate pharmacovigilance. FDA determined that a unique proper name including a prefix was necessary for ado-trastuzumab emtansine to distinguish the product from trastuzumab, a previously licensed biological product submitted in a different BLA.[15] FDA may continue such practices on a limited basis, where appropriate, when the Agency determines that the designation of a prefix, in addition to a suffix as contemplated by this guidance, is necessary to ensure patient safety.

[12] FDA will work with stakeholders that play a role in national drug naming and listing to help ensure that the suffixes added to the core name of biological products are recorded appropriately in drug listing systems.

[13] FDA determined that a hyphen should separate the shared core name from the suffix. A hyphen is a common punctuation mark used in writing and electronic systems; it is a readily recognized mark. Another punctuation mark, such as an underscore, may not be normally used in handwriting and may not be readily seen in handwriting, electronic systems, or both.

[14] The license holder and all distributors of a biological product should use the proper name designated by FDA in the license for that product.

[15] As described in the BLA submission for ado-trastuzumab emtansine, medication errors involving administration of the wrong drug (trastuzumab emtansine versus trastuzumab) during clinical trials resulted in serious adverse events.

A. Prospective Naming of Biological Products Submitted Under Section 351(a) of the PHS Act

An applicant should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase[16] or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference. We recommend including any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in this guidance.

B. Retrospective Naming of Biological Products Licensed Under Section 351(a) of the PHS Act

A BLA holder may propose a suffix, as described in this guidance, for use in the proper name of currently licensed biological products held by the company by submitting a prior-approval labeling supplement to its BLA (see section VI of this guidance). As part of that labeling supplement, a BLA holder should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference. We recommend including any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in this guidance.

C. Naming of Biosimilar Products Submitted Under Section 351(k) of the PHS Act

An applicant for a proposed biosimilar product submitted under section 351(k) of the PHS Act should propose a suffix composed of four lowercase letters for use as the distinguishing identifier included in the proper name designated by FDA at the time of licensure (see section VI of this guidance). Such submissions can be made during the investigational new drug application (IND) phase[17] or at the time of BLA submission. An applicant should submit up to 10 proposed suffixes, as described in this section, in the order of the applicant's preference. We recommend including any supporting analyses of the proposed suffixes for FDA's consideration based on the factors described in this guidance.

[16] A request for FDA review of a proposed suffix submitted during the investigational new drug application (IND) phase should be submitted no earlier than at the request for a pre-biologics license application (pre-BLA) meeting for biological products to be submitted under section 351(a) of the PHS Act.

[17] A request for FDA review of a proposed suffix submitted during the investigational new drug application (IND) phase should be submitted no earlier than at the request for a biosimilar biological product development (BPD) type 4 meeting for biological products to be submitted under section 351(k) of the PHS Act.

VI. PROPOSING A SUFFIX FOR THE PROPER NAME OF AN ORIGINATOR BIOLOGICAL PRODUCT, A RELATED BIOLOGICAL PRODUCT, OR A BIOSIMILAR PRODUCT

The proposed suffix ***should***:

- Be unique
- Be devoid of meaning
- Be four lowercase letters of which at least three are distinct
- Be nonproprietary
- Be attached to the core name with a hyphen
- Be free of legal barriers that would restrict its usage

The proposed suffix ***should not:***

- Be false or misleading, such as by making misrepresentations with respect to safety or efficacy
- Include numerals and other symbols aside from the hyphen attaching the suffix to the core name
- Include abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as another element on the prescription or order
- Contain or suggest any drug substance name or core name
- Look similar to or be capable of being mistaken for the name of a currently marketed product (e.g., should not increase the risk of confusion or medical errors with the product and/or other products in the clinical setting)
- Look similar to or otherwise connote the name of the license holder
- Be too similar to any other FDA-designated nonproprietary name suffix

FDA encourages applicants to conduct due diligence on their proposed suffixes to ensure that no other restrictions apply to use of the proposed suffix in this context. Any supporting information can be provided to FDA with the submission of the proposed suffix(es).

The final determination on the acceptability of a proposed suffix is based on FDA's review of all information and analyses described in this guidance, along with any information submitted by the sponsor.

FDA will evaluate proposed suffixes against the factors described in this section and may consider other factors if they impact the utility of the suffix in meeting the goals of the naming convention articulated in this guidance. Upon completion of the Agency's evaluation, FDA will notify applicants if a proposed suffix is acceptable or if all of the proposed suffixes are determined to be unacceptable. If all of the proposed suffixes are determined to be unacceptable, applicants may submit additional proposed suffixes for FDA's consideration. If an applicant does not submit a suffix that FDA finds acceptable or does not propose suffix candidates within an appropriate time frame to allow sufficient time for FDA review, FDA may elect to assign a four-letter suffix for inclusion in the proper name designated in the license at the time FDA approves the application.

VII. PAPERWORK REDUCTION ACT OF 1995

This guidance contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). Specifically, the guidance recommends that applicants and application holders submit up to 10 proposed suffixes, in the order of the applicant's preference. FDA also recommends including any supporting analyses for FDA's consideration, demonstrating that the proposed suffixes meet the factors described in the final guidance.

FDA estimates that the time required to complete this information collection will average 420 hours per response, including the time to review instructions, search existing data sources, gather the data needed, and complete and review the information collection. Send comments regarding this burden estimate or suggestions for reducing this burden to:

> Office of Medical Policy, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Avenue, Bldg. 51, rm. 6337, Silver Spring, MD 20993-0002

This guidance also refers to previously approved collections of information found in FDA regulations. The collections of information related to the submission of a BLA under section 351(k) of the PHS Act have been approved under OMB control number 0910-0719, and the collections of information in 21 CFR part 601 have been approved under OMB control number 0910-0338.

An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. The information collection provisions in this guidance, including resulting proposed modifications to the information collections approved under OMB control number 0910-0338, have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995 **and are not for current implementation**. Before implementing the information collection provisions contained in this guidance, we will publish a notice in the *Federal Register* announcing OMB's decision to approve, modify, or disapprove those information collection provisions.

GLOSSARY

Biosimilar Product means a biological product submitted in a 351(k) application that has been shown to be highly similar to the reference product notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product (see section 351(i)(2) of the PHS Act).

Core Name means the component shared among an originator biological product and any related biological product, biosimilar product, or interchangeable product as part of the proper names of those products. Two examples of a *core name* are filgrastim and epoetin alfa.

Interchangeable Product means a biological product that has been shown to meet the standards described in section 351(k)(4) of the PHS Act and may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product (see section 351(i)(3) of the PHS Act).

Nonproprietary Name means a name unprotected by trademark rights that is in the public domain. It may be used by the public at large, both lay and professional.

Originator Biological Product means a biological product submitted in a BLA under section 351(a) of the PHS Act (i.e., a stand-alone BLA) that is not a related biological product.

Proper Name means the nonproprietary name designated by FDA in the license for a biological product licensed under the PHS Act.[18]

Proprietary Name means the trademark or brand name.

Reference Product means the single biological product licensed under section 351(a) of the PHS Act against which a biological product is evaluated in a 351(k) application (section 351(i)(4) of the PHS Act).

Related Biological Product means a biological product submitted in a BLA under section 351(a) of the PHS Act (i.e., a stand-alone BLA) for which there is a previously licensed biological product submitted in a different section 351(a) BLA that contains a drug substance for which certain nomenclature conventions (e.g., United States Adopted Names (USAN) Guiding Principles[19]) would be expected to provide for use of the same drug substance name.[20]

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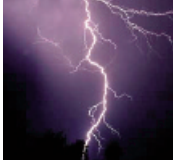
[18] Section 351(a)(1)(B)(i) of the PHS Act (42 U.S.C. 262(a)(1)(B)(i) and § 600.3(k)(21 CFR 600.3(k)).

[19] The United States Pharmacopeial Convention, 2016, Guiding Principles for Coining United States Adopted Names for Drugs (*2016 USP Dictionary of USAN and International Drug Names at* http://www.uspusan.com/usan/pub/index1.html).

[20] FDA's description of a biological product as a *related biological product* in this guidance is separate from any determination FDA may make about whether a related biological product is eligible for a period of exclusivity under section 351(k)(7) of the PHS Act.



This alert is based on information from the National Medication Errors Reporting Program operated by the Institute for Safe Medication Practices.

April 17, 2013

Confusion regarding the generic name of the HER2-targeted drug KADCYLA (ado-trastuzumab emtansine)

On February 22, 2013, the US Food and Drug Administration (FDA) approved **KADCYLA** with the generic name of **ado-trastuzumab emtansine**. Unfortunately, some confusion surrounding the drug's generic name exists.

The original generic name for Kadcyla, as established by the US Adopted Name (USAN) Council in 2009, was trastuzumab emtansine. Given its similarity to the generic name for **HERCEPTIN** (trastuzumab) and the potential for confusion between the two medications, the FDA approved the addition of the contrived prefix "ado" to the generic name for Kadcyla. Thus the official FDA-approved generic name for Kadcyla is now ado-trastuzumab emtansine.

In the *ISMP Medication Safety Alert!* published on March 7, 2013, the Institute for Safe Medication Practices (ISMP) described the potential confusion between the two drugs due to the similarity in generic names, even with the prefix "ado." Specifically, the official generic name, ado-trastuzumab emtansine, may not be fully communicated when the drug is prescribed, fully displayed in automated systems, or may be read incompletely, thus creating a significant risk of being confused with trastuzumab.

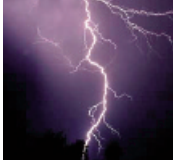
Given that the dosing and treatment schedules for these drugs are quite different, confusion could lead to dosing errors and potential harm to the patient. For example, the recommended dose of ado-trastuzumab emtansine (Kadcyla) is 3.6 mg/kg given as an IV infusion every 3 weeks (21-day cycle) as a **SINGLE AGENT** until disease progression or unacceptable toxicity. Doses higher than that should not be given. However, trastuzumab (Herceptin) is prescribed in doses up to 8 mg/kg per loading dose, followed by a maintenance dose of 6 mg/kg every 3 weeks—about twice the maximum dose of Kadcyla.

Further, it has come to our attention that certain drug information content publishers have utilized the initial generic name of Kadcyla without the "ado" prefix. As such, certain drug information publications, compendia references, and health information systems (e.g., wholesaler ordering, pharmacy ordering, and electronic health record systems) may display the generic name as "trastuzumab emtansine." Users searching with the prefix "ado" may not find "ado-trastuzumab emtansine" in these publications or systems. As a result, healthcare providers may not be able to place orders for Kadcyla, prescribe the drug, or find drug information for Kadcyla, and patients may not receive proper therapy. Furthermore, even if the generic name is manually corrected in your information systems, routine automated updates from drug information content publishers that do not list the prefix "ado" may override and reverse the manual correction.

Thus, we advise healthcare practitioners to take these steps to avoid harmful errors:

- **Use the correct generic name.** Whether you are a healthcare practitioner, an author, editor, indexer, medical records librarian, or other health-related professional, use only the correct generic name listed with

continued on page 2—Kadcyla ▸



This alert is based on information from the National Medication Errors Reporting Program operated by the Institute for Safe Medication Practices.

April 17, 2013

Kadcyla

continued from page 1

the prefix "ado" for Kadcyla, as used for all Kadcyla product labeling and packaging from the manufacturer, Genentech. (We understand that Genentech has alerted the FDA of the problem with the generic name, and a resolution is still pending.)

- **List by generic name.** List Kadcyla alphabetically by its generic name, using a dash between ado and trastuzumab (ado-trastuzumab emtansine).

- **Include brand and generic name.** Ideally, prescribers and other healthcare professionals should use the brand name and include the generic name of Kadcyla when communicating orders on preprinted order sets or in computerized order entry systems (prescriber and pharmacy). Such a redundancy can be helpful in reducing the risk of an error.

- **Differentiate generic names.** Proactively employ strategies to differentiate Kadcyla and Herceptin generic names, and warn against confusion in medication-related computer systems and guidelines.

- **Increase awareness.** Be aware of the potential for the generic name of Kadcyla to be listed both with or without the prefix "ado" in third-party publications and information systems, and on the Internet; amend search criteria accordingly.

ISMP has contacted major drug information vendors, including Medi-Span, Facts & Comparisons, Lexicomp, Multum, Gold Standard, UpToDate, Micromedex (Truven Health Analytics), and First Databank. At the time of publication of the Alert, only Micromedex was still using trastuzumab emtansine without the "ado" prefix and had not confirmed its response to our request to add the prefix. Still, the generic name may continue to be seen without the prefix in some drug information resources and on the Internet. ISMP is also contacting major drug wholesalers to confirm the use of proper nomenclature.

Kadcyla, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination. Patients should have received prior therapy for metastatic disease or developed disease recurrence during or within 6 months of completing adjuvant therapy. Kadcyla is associated with a Boxed Warning regarding the potential for hepatotoxicity, cardiac toxicity, and embryo-fetal toxicity. Additionally, the label warns that Kadcyla should not be substituted for or with trastuzumab.

The National Alert Network **(NAN)** is a coalition of members of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP). The network, in cooperation with the Institute for Safe Medication Practices (ISMP) and the American Society of Health-System Pharmacists (ASHP), distributes NAN Alerts to warn healthcare providers of the risk for medication errors that have caused or may cause serious harm or death. NCC MERP, ISMP, and ASHP encourage the sharing and reporting of medication errors both nationally and locally, so that lessons learned can be used to increase the safety of the medication use system.

INN Working Doc. 14.342
Rev. Final October 2015
Distr.:* *UNRESTRICTED
ENGLISH ONLY

Biological Qualifier
An INN Proposal

Programme on International Nonproprietary Names (INN)

Technologies Standards and Norms (TSN)
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)
World Health Organization, Geneva

Proposal for Assignment of Biological Qualifiers (BQ)

Executive summary

A scheme is proposed in which a unique identification code named a Biological Qualifier (BQ) is assigned to all biological substances having (or eligible to have) INNs. The BQ is an additional and independent element used in conjunction with the INN to uniquely identify a biological substance to aid in the prescription and dispensing of medicines, pharmacovigilance and the global transfer of prescriptions. The BQ is a code formed of four random consonants in two 2-letter blocks separated by a 2-digit checksum. The BQ scheme is designed to provide a uniform global means of identification to avoid the proliferation of differing national schemes.

The scheme will be administered by the WHO INN Secretariat who will set up and maintain a secure database of the BQ, INN, the BQ Applicant and relevant manufacturing and regulatory data. The BQs will be immediately assigned to BQ Applicants by an automated online system for use by relevant Marketing Authorisation Holders (MAHs) and National Regulatory Authorities (NRAs). The BQ Applicant will provide the required data to the WHO INN and will update the data when changes occur. An initial fee will be charged to register a BQ which will also cover any updates required so that the scheme is self-funding. Only security-approved WHO Secretariat staff will be able to enter and edit information on the database. All information that is already in the public domain will be available to all on the WHO website. Access to confidential information on the database will be restricted to read-only for NRAs and to their own applications for BQ Applicants.

Introduction and Background Information

Biological medicinal products are an increasingly important sector of therapeutic and prophylactic medicines. Biological active substances now comprise more than 40% of applications to the INN Programme and the percentage is increasing. By their nature biotechnological products are not composed of a single, pure substance, but are invariably complex, microheterogeneous mixtures of isoforms of the desired substance.

An INN is specific to a given defined substance regardless of the manufacturer and manufacturing site even though the profile of impurities may not be qualitatively or quantitatively the same. Biological substances are assigned an INN by the general principles applicable to all INN and by a specific framework developed especially for them (*see INN for Biological and Biotechnological Substances (a review)-2013- INN Working Document 05.179*).

While a single INN has been adequate to identify simple, well-characterised chemical substances, the complex, microheterogeneous nature of biological medicines does lead to differing efficacy and safety profiles of these substances. For this reason differing glycoforms of the same protein were distinguished by adding a Greek letter to the INN. Several national regulatory authorities proposed naming policy or have actually named biological medicines using a prefix, suffix or separate identifier to distinguish conjugates, glycoforms or biosimilars (e.g. Japan, Australia and USA). To avoid proliferation of separate and distinct national qualifier systems, some drug regulatory authorities have requested the INN Programme to develop and administer a voluntary and global complementary nomenclature scheme. This was begun in 2012 and has involved several rounds of feedback from stakeholders in general and NRAs in particular, during which it was clearly indicated

by all sectors that the WHO should devise and operate the BQ scheme, applicable prospectively and, where possible, retrospectively to all biological substances assigned INNs, that could be adopted on a voluntary basis by any regulatory authority and would be recognised globally. The proposed scheme has evolved from a three letter random code to a four letter random code incorporating a digital checksum.

It is acknowledged that the BQ will only be as useful as the breadth with which it is taken up globally, how widely it is recognised and its purpose understood by prescribers, dispensers, patients and those involved in pharmacovigilance. It is therefore necessary that as well as voluntary acceptance of the scheme, regulatory authorities and BQ Applicants should take appropriate steps to bring attention to and explain the existence and purpose of the BQ to these groups of people.

The Biological Qualifier (BQ) scheme

Purpose
The scheme is intended to provide a unique identification code (Biological Qualifier or BQ), distinct from the INN, for all biological substances that are assigned INNs. The BQ is an additional and independent element used in conjunction with the INN for a biological substance to uniquely identify the active substance in a biological product distributed by a MAH. It is envisaged that the BQ will assist in the identification of biological substances for:

- prescription and dispensing of medicines (in those jurisdictions requiring it);
- pharmacovigilance (in those jurisdictions requiring it); and
- aid transfer of prescriptions globally.

The BQ scheme is designed to provide a uniform global means of identification for biological substances and so avoid the proliferation of separate and distinct schemes developed by individual regulatory authorities.

Usage of the BQ
Adoption of the BQ scheme is a voluntary decision of the individual regulatory authority. The scheme is overseen by the WHO INN Expert Group and administered and operated by the WHO INN Secretariat. The scheme is intended to apply to as many biological medicines as possible, so while it will apply prospectively, mechanisms to allow retrospective application are being investigated. The use of the BQ offers a means (a) which uniquely identifies the drug substance even if used alone and/or (b) of crosschecking other information supplied in a prescription/dispensing or pharmacovigilance setting.

The BQ code
The code will consist of four random consonants and an optional two digits as a checksum. The WHO INN will issue the BQ letters with a checksum, but it is at the discretion of the individual regulatory authority whether the checksum is used as part of the BQ. The form of the BQ may take:

- four letters;
- four letters followed by the checksum; or
- two letters, two digits and two letters, thus mimicking car registration plates to be more memorable.

For instance:

TRADENAME	INN	BQ

GROKINO	anonutropin alfa	bxsh
GROKINO	anonutropin alfa	bxsh08
GROKINO	anonutropin alfa	bx08sh

Each code issued will be assigned to applicants at random by an automated online system. The choice of letters used will be made to facilitate transliteration into various languages and to avoid meaningful, trademarked or inappropriate words or acronyms being used. The use of four letters offers 160 000 codes (20^4) (vowels being excluded) and is expected to provide sufficient capacity and flexibility for the foreseeable future.

The checksum is calculated from the four randomly assigned consonants and their position and gives the ability to detect errors in transcription, both the use of an erroneous letter and the transposition of the correct letters.

Who should apply for a Biological Qualifier

The applicant for a BQ (termed the BQ Applicant) is foreseen to be a corporate body that makes or manages the making of a single substance by a single process controlled by the same quality system globally. This body applies for a BQ for global use and allows its use for substance made in all manufacturing sites demonstrated to be of a similar standard of quality and by all marketing authorisation holders (MAH) distributing products which contain the substance. Should a regulatory authority find that a manufacturing site does **not** produce a comparable product, they may require application for a different BQ for that manufacturing site, but the two BQ's would be hyperlinked in the INN BQ database.

Application for a Biological Qualifier code

The application for a Biological Qualifier code is made to the WHO INN Secretariat by the BQ Applicant at the time of submission of a marketing authorisation application to a regulatory authority. The assigned BQ code is immediately provided by the WHO to the BQ Applicant through an automated online system. The BQ Applicant can either:

- supply the BQ directly to regulatory authority/ authorities when the BQ Applicant is also the Marketing Authorisation Holder (MAH); or
- provide the BQ to the MAH making the authorisation application.

A fee for each application is payable so that the scheme is self-funding. No further fee is levied for processing updates to the information submitted for the BQ code. Consequently, the initial fee will be set taking this into consideration.

For situations wherein a previously licensed biological drug substance is to be assigned a BQ at the requirement of a regulatory authority, the same application procedure occurs with the immediate provision of a BQ through the automated online application system. The initial fee would also apply in this situation.

Information to be submitted in an application

Application will be made online in an automated system administered by the WHO INN Secretariat. The application and data submitted in it will be held on a secure database at WHO that is operated only by WHO personnel. All information submitted will be treated as confidential and not disclosed outside the WHO Secretariat except under the conditions described under 'The database of Biological Qualifiers and Access to Stakeholders', below.

The information to be submitted with the application includes:

- Name and address of BQ Applicant.
- The INN.

- Intended trade name(s) of product(s) in all relevant jurisdictions.
- Name(s) and address(es) of Marketing Authorisation Holder(s) (MAH) for which the code is requested and the jurisdictions for which they are responsible.
- Name and address of relevant manufacturing site(s) if different to above.
- Regulatory information: relevant regulatory authority, nature of the marketing authorisation (e.g., biosimilar within a named jurisdiction, stand-alone within another named jurisdiction), INN, where and when the substance has been authorised, tradename(s).

It is envisaged that information that is publically available would be made available to all who access the database. Examples of what information might be displayed are given in tables in the FAQ document.

Updating information

To be of value the data held should be kept up to date. The WHO INN should be informed and the database updated following:

- Changes to information published in the database at the time that a code is issued, for example addition, deletion or changing of manufacturing sites and of trade names.
- Authorisation issued or cancelled by a regulatory authority.
- Changes in regulatory status, for example when approval is obtained from additional regulatory authorities.
- Withdrawal of active substance and/or product or tradename.

The database will carry the date of the most recent change. Updates are the joint responsibility of the BQ Applicant, the relevant marketing authorisation holder and the relevant regulatory authority and are sent to the WHO INN Secretariat as soon as a change has been approved.

Access of the BQ Database to Stakeholders

A secure database will be held by the WHO Secretariat holding details of applications, codes issued, and updated as changes are submitted. The following access to the database would be granted:

- Only security-approved WHO Secretariat staff will be able to enter and edit information on the database.
- All regulatory authorities will have full read-only access to the database.
- BQ Applicants will be able to make applications for a code or update online, will be able to track the progress of the processing of their own applications and to see all details pertaining to their own previous applications.
- All information that is already in the public domain will be made available on the WHO INN website except for details about manufacturing site(s) and any other commercially sensitive information.

Lifecycle of the BQ

It is intended that a drug substance would have the same BQ as long as it has the same basic structure (amino acid sequence in the case of proteins) and is marketed with the same INN. A new BQ may be issued by WHO INN if a national regulatory authority determines changes to the substance render it different to the original substance, however the new BQ would be hyperlinked to the original on the BQ database.

International Nonproprietary Names for Pharmaceutical Substances (INN)

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, the names given in the list on the following pages are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1–113) and Recommended (1–74) International Nonproprietary Names can be found in *Cumulative List No. 16, 2015* (available in CD-ROM only). The statements indicating action and use are based largely on information supplied by the manufacturer. **This information is merely meant to provide an indication of the potential use of new substances at the time they are accorded Proposed International Nonproprietary Names**. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature, these descriptors will neither be revised **nor included in the Cumulative Lists of INNs**.

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Il est notifié que, conformément aux dispositions de l'article 3 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques les dénominations ci-dessous sont mises à l'étude par l'Organisation mondiale de la Santé en tant que dénominations communes internationales proposées. L'inclusion d'une dénomination dans les listes de DCI proposées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

On trouvera d'autres listes de Dénominations communes internationales proposées (1–113) et recommandées (1–74) dans la *Liste récapitulative No. 16, 2015* (disponible sur CD-ROM seulement). Les mentions indiquant les propriétés et les indications des substances sont fondées sur les renseignements communiqués par le fabricant. **Elles ne visent qu'à donner une idée de l'utilisation potentielle des nouvelles substances au moment où elles sont l'objet de propositions de DCI**. L'OMS n'est pas en mesure de confirmer ces déclarations ni de faire de commentaires sur l'efficacité du mode d'action ainsi décrit. En raison de leur caractère provisoire, ces informations **ne figureront pas dans les listes récapitulatives de DCI.**

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

De conformidad con lo que dispone el párrafo 3 del "Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas", se comunica por el presente anuncio que las denominaciones detalladas en las páginas siguientes están sometidas a estudio por la Organización Mundial de La Salud como Denominaciones Comunes Internacionales Propuestas. La inclusión de una denominación en las listas de las DCI Propuestas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1–113) y Recomendadas (1–74) se encuentran reunidas en *Cumulative List No. 16, 2015* (disponible sólo en CD-ROM). Las indicaciones sobre acción y uso que aparecen se basan principalmente en la información facilitada por los fabricantes. **Esta información tiene por objeto dar una idea únicamente de las posibilidades de aplicación de las nuevas sustancias a las que se asigna una DCI Propuesta**. La OMS no está facultada para respaldar esas indicaciones ni para formular comentarios sobre la eficacia de la acción que se atribuye al producto. Debido a su carácter provisional, esos datos descriptivos **no deben incluirse en las listas recapitulativas de DCI.**

Proposed International Nonproprietary Names: List 116

Comments on, or formal objections to, the proposed names may be forwarded by any person to the INN Programme of the World Health Organization within four months of the date of their publication in *WHO Drug Information*, i.e., for **List 116 Proposed INN not later than 02 May 2017.**
Publication date: 03/01/2017

Dénominations communes internationales proposées: Liste 116

Des observations ou des objections formelles à l'égard des dénominations proposées peuvent être adressées par toute personne au Programme des Dénominations communes internationales de l'Organisation mondiale de la Santé dans un délai de quatre mois à compter de la date de leur publication dans *WHO Drug Information*, c'est à dire pour la **Liste 116 de DCI Proposées le 02 mai 2017 au plus tard.**
Date de publication: 03/01/2017

Denominaciones Comunes Internacionales Propuestas: Lista 116

Cualquier persona puede dirigir observaciones u objeciones respecto de las denominaciones propuestas, al Programa de Denominaciones Comunes Internacionales de la Organización Mundial de la Salud, en un plazo de cuatro meses, contados desde la fecha de su publicación en *WHO Drug Information*, es decir, para **la Lista 116 de DCI Propuestas el 02 de mayo de 2017 a más tardar.**
Fecha de publicación: 03/01/2017

Proposed INN (Latin, English, French, Spanish)	*Chemical name or description: Action and use: Molecular formula Chemical Abstracts Service (CAS) registry number: Graphic formula*
DCI Proposée	*Nom chimique ou description: Propriétés et indications: Formule brute Numéro dans le registre du CAS: Formule développée*
DCI Propuesta	*Nombre químico o descripción: Acción y uso: Fórmula molecular Número de registro del CAS: Fórmula desarrollada*

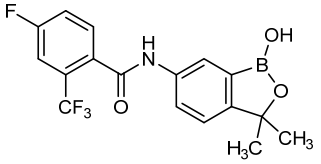
acoziborolum

acoziborole — 4-fluoro-*N*-(1-hydroxy-3,3-dimethyl-1,3-dihydro-2,1-benzoxaborol-6-yl)-2-(trifluoromethyl)benzamide
antiparasitic

acoziborole — 4-fluoro-*N*-(1-hydroxy-3,3-diméthyl-1,3-dihydro-2,1-benzoxaborol-6-yl)-2-(trifluorométhyl)benzamide
antiparasitaire

acoziborol — 4-fluoro-*N*-(1-hidroxi-3,3-dimetil-1,3-dihidro-2,1-benzoxaborol-6-il)-2-(trifluorometil)benzamida
antiparasitario

$C_{17}H_{14}BF_4NO_3$ 1266084-51-8



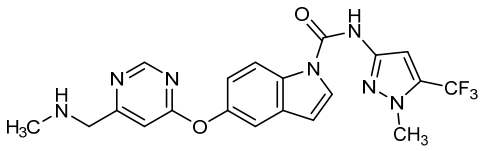
acrizanibum

acrizanib — 5-({6-[(methylamino)methyl]pyrimidin-4-yl}oxy)-*N*-[1-methyl-5-(trifluoromethyl)-1*H*-pyrazol-3-yl]-1*H*-indole-1-carboxamide
angiogenesis inhibitor

acrizanib — 5-({6-[(méthylamino)méthyl]pyrimidin-4-yl}oxy)-*N*-[1-méthyl-5-(trifluorométhyl)-1*H*-pyrazol-3-yl]-1*H*-indole-1-carboxamide
inhibiteur de l'angiogénèse

acrizanib — 5-({6-[(metilamino)metil]pirimidin-4-il}oxi)-*N*-[1-metil-5-(trifluorometil)-1*H*-pirazol-3-il]-1*H*-indol-1-carboxamida
inhibidor de la angiogénesis

$C_{20}H_{18}F_3N_7O_2$ 1229453-99-9



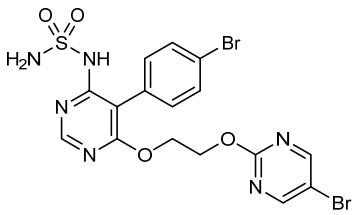
aprocitentanum

aprocitentan — *N*-[5-(4-bromophenyl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]ethoxy}pyrimidin-4-yl]sulfuric diamide
endothelin receptor antagonist

aprocitentan — diamide *N*-[5-(4-bromophényl)-6-{2-[(5-bromopyrimidin-2-yl)oxy]éthoxy}pyrimidin-4-yl]sulfurique
antagoniste du récepteur de l'endothéline

aprocitentán — diamida *N*-[5-(4-bromofenil)-6-{2-[(5-bromopirimidin-2-il)oxi]etoxi}pirimidin-4-il]sulfúrico
antagonista del receptor de la endotelina

$C_{16}H_{14}Br_2N_6O_4S$ 1103522-45-7



atelocantelum

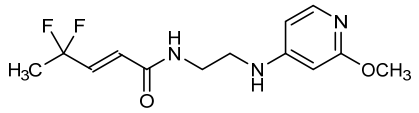
atelocantel — (2*E*)-4,4-difluoro-*N*-{2-[(2-methoxypyridin-4-yl)amino]ethyl}pent-2-enamide
anthelmintic (veterinary drug)

atélocantel — (2*E*)-4,4-difluoro-*N*-{2-[(2-méthoxypyridin-4-yl)amino]éthyl}pent-2-enamide
antihelmintique (usage vétérinaire)

atelocantel

(2*E*)-4,4-difluoro-*N*-{2-[(2-metoxipiridin-4-il)amino]etil}pent-2-enamida
antihelmíntico (uso veterinario)

$C_{13}H_{17}F_2N_3O_2$ 1370540-16-1



atesidorsenum
atesidorsen

all-P-ambo-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-P-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidine
growth hormone receptor (GHR) expression inhibitor

atésidorsen

tout-P-ambo-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-désoxy-*P*-thioguanylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-désoxy-P-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthylcytidine
inhibiteur de l'expression du récepteur de l'hormone de croissance

atesidorsén

todo-P-ambo-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioguanilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-2'-desoxi-P-tioadenilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-(2-metoxietil)-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metilcitidina
inhibidor de la expresión del receptor de la hormona del crecimiento

$C_{230}H_{321}N_{64}O_{124}P_{19}S_{19}$ 872063-57-5

(3'-5')(*P*-thio)(m^{5}Umoe-m^{5}Cmoe-Amoe-Gmoe-Gmoe-dG-m^{5}dC-dA-dT-dT-m^{5}dC-dT-dT-dT-m^{5}dC-m^{5}Cmoe-Amoe-m^{5}Umoe-m^{5}Umoe-mCmoe)
Legend: d (as prefix) = 2'-deoxy
m^5 (as prefix) = 5-methyl
moe (as suffix) = 2'-*O*-(2-methoxyethyl)

atogepantum

atogepant

(3'*S*)-*N*-[(3*S*,5*S*,6*R*)-6-methyl-2-oxo-1-(2,2,2-trifluoroethyl)-5-(2,3,6-trifluorophenyl)piperidin-3-yl]-2'-oxo-1',2',5,7-tetrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide
calcitonin gene-related peptide receptor antagonist

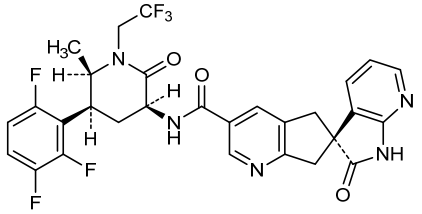
atogépant

(3'*S*)-*N*-[(3*S*,5*S*,6*R*)-6-méthyl-2-oxo-1-(2,2,2-trifluoroéthyl)-5-(2,3,6-trifluorophényl)pipéridin-3-yl]-2'-oxo-1',2',5,7-tétrahydrospiro[cyclopenta[*b*]pyridine-6,3'-pyrrolo[2,3-*b*]pyridine]-3-carboxamide
antagoniste du récepteur du peptide lié au gène de la calcitonine (CGRP)

atogepant

(3'*S*)-*N*-[(3*S*,5*S*,6*R*)-6-metil-2-oxo-1-(2,2,2-trifluoroetil)-5-(2,3,6-trifluorofenil)piperidin-3-il]-2'-oxo-1',2',5,7-tetrahidrospiro[ciclopenta[*b*]piridina-6,3'-pirrolo[2,3-*b*]piridina]-3-carboxamida
antagonista del receptor del péptido relacionado con el gen de la calcitonina (CGRP)

$C_{29}H_{23}F_6N_5O_3$ 1374248-81-3



azeloprazolum

azeloprazole

2-[(*R*)-{4-[(2,2-dimethyl-1,3-dioxan-5-yl)methoxy]-3,5-dimethylpyridin-2-yl}methanesulfinyl]-1*H*-benzimidazole
proton pump inhibitor

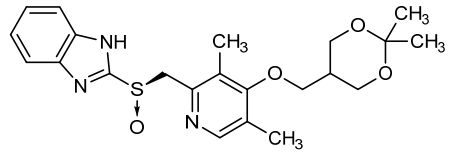
azéloprazole

2-[(*R*)-{4-[(2,2-diméthyl-1,3-dioxan-5-yl)méthoxy]-3,5-diméthylpyridin-2-yl}méthanesulfinyl]-1*H*-benzimidazole
inhibiteur de la pompe à protons

azeloprazol

2-[(*R*)-{4-[(2,2-dimetil-1,3-dioxan-5-il)metoxi]-3,5-dimetilpiridin-2-il}metanosulfinil]-1*H*-benzoimidazol
inhibidor de la bomba de protones

$C_{22}H_{27}N_3O_4S$ 955095-45-1



azintuxizumabum #

azintuxizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* SLAMF7 (SLAM family member 7, CD2 subset 1, CS1, CD2-like receptor-activating cytotoxic cells, CRACC, 19A24, CD319)], humanized and chimeric monoclonal antibody; gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-7*01 (91.80%) -(IGHD) -IGHJ4*01 L123>T (112) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), hinge (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-disulfide with kappa light chain chimeric (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dimer (226-226'':229-229'')-bisdisulfide
immunomodulator, antineoplastic

azintuxizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* SLAMF7 (membre 7 de la famille SLAM, CD2 subset 1, CS1, récepteur de type CD2 activant les cellules cytotoxiques, CRACC, 19A24, CD319)], anticorps monoclonal humanisé et chimérique;
chaîne lourde gamma1 chain (1-447) [VH humanisé (*Homo sapiens* IGHV3-7*01 (91.80%) -(IGHD) -IGHJ4*01 L123>T (112)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), charnière (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-disulfure avec la chaîne légère kappa chimérique (1'-220') [V-KAPPA *Mus musculus* (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dimère (226-226'':229-229'')-bisdisulfure
immunomodulateur, antinéoplasique

azintuxizumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* SLAMF7 (miembro 7 de la familia SLAM, CD2 subset 1, CS1, receptor de tipo CD2 que activa las células citotóxicas, CRACC, 19A24, CD319)], anticuerpo monoclonal humanizado y quimérico;
cadena pesada gamma1 cadena (1-447) [VH humanizado (*Homo sapiens* IGHV3-7*01 (91.80%) -(IGHD) -IGHJ4*01 L123>T (112)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), bisagra (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-disulfuro con la cadena ligera kappa quimérica (1'-220') [V-KAPPA *Mus musculus* (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dímero (226-226'':229-229'')-bisdisulfuro
inmunomodulador, antineoplásico

1826819-57-1

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS DYYMAWVRQA PGKGLEWVAS  50
INYDGSSTYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARDR 100
GYYFDYWGQG TTVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK    447
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Light chain / Chaîne légère / Cadena ligera

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DVVMTQTPLS LSVTPGQPAS ISCRSSQSLV HSNGNTYLHW YLQKPGQSPQ  50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YFCSQSTHVP 100
PFTFGGGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA 150
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC 200
EVTHQGLSSP VTKSFNRGEC                                   220
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22''-96'' 144''-200'' 261''-321'' 367''-425''
Intra-L (C23-C104) 23'-93' 140'-200'
23'''-93''' 140'''-200'''
Inter-H-L (h 5-CL 126) 220-220' 220''-220'''
Inter-H-H (h 11, h 14) 226-226'' 229-229''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297''
Fucosylated complex bi-antennary CHO-type glycans (G0F, G1F) / glycanes de type CHO bi-antennaires complexes fucosylés (G0F, G1F) / glicanos de tipo CHO biantenarios complejos fucosilados (G0F, G1F)

azintuxizumabum vedotinum #
azintuxizumab vedotin

immunoglobulin G1-kappa, anti-[*Homo sapiens* SLAMF7 (SLAM family member 7, CD2 subset 1, CS1, CD2-like receptor-activating cytotoxic cells, CRACC, 19A24, CD319)], humanized and chimeric monoclonal antibody antibody conjugated to auristatin E;
gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-7*01(91.80%) -(IGHD) -IGHJ4*01 L123>T (112)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), hinge (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-

	disulfide with kappa light chain chimeric (1'-220') [*Mus musculus* V-KAPPA (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dimer (226-226'':229-229'')-bisdisulfide; conjugated, on an average of 3 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker For the *vedotin* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.* *immunomodulator, antineoplastic*
azintuxizumab védotine	immunoglobuline G1-kappa, anti-[*Homo sapiens* SLAMF7 (membre 7 de la famille SLAM, CD2 subset 1, CS1, récepteur de type CD2 activant les cellules cytotoxiques, CRACC, 19A24, CD319)], anticorps monoclonal humanisé et chimérique conjugué à l'auristatine E; chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV3-7*01(91.80%) -(IGHD) -IGHJ4*01 L123>T (112)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), charnière (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-disulfure avec la chaîne légère kappa chimérique (1'-220') [V-KAPPA *Mus musculus* (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dimère (226-226'':229-229'')-bisdisulfure; conjugué, sur 3 cystéinyl en moyenne, au monométhylauristatine E (MMAE), via un linker clivable de type maléimidocaproyl-valyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) Pour la partie *védotine*, veuillez-vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.* *immunomodulateur, antinéoplasique*
azintuxizumab vedotina	inmunoglobulina G1-kappa, anti-[*Homo sapiens* SLAMF7 (miembro 7 de la familia SLAM, CD2 subset 1, CS1, receptor de tipo CD2 que activa las células citotóxicas, CRACC, 19A24, CD319)], anticuerpo monoclonal humanizado y quimérico conjugado con la auristatina E; cadena pesada gamma1 (1-447) [VH humanizado (*Homo sapiens* IGHV3-7*01(91.80%) -(IGHD) -IGHJ4*01 L123>T (112)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (214) (118-215), bisagra (216-230), CH2 (231-340), CH3 E12(366), M14 (368) (341-445), CHS (446-447) (118-447)], (220-220')-disulfuro con la cadena ligera kappa quimérica (1'-220') [V-KAPPA *Mus musculus* (IGKV1-110*01 (93.00%) -IGKJ4*01) [11.3.10] (1'-113') -*Homo sapiens* IGKC*01, Km3 A45.1 (159), V101 (197) (114'-220')]; dímero (226-226'':229-229'')-bisdisulfuro; conjugado, en 3 residuos cisteinil por término medio, con monometilauristatina E (MMAE), con un conector de type maleimidocaproil-valil-citrulinil-*p*-aminobenziloxicarbonil (mc-val-cit-PABC) escindible Para la fracción *védotine*, se pueden referir al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*.* *inmunomodulador, antineoplásico*

1826819-58-2

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS DYYMAWVRQA PGKGLEWVAS  50
INYDGSSTYY VDSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARDR 100
GYYFDYWGQG TTVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK    447
```

Light chain / Chaîne légère / Cadena ligera

```
DVVMTQTPLS LSVTPGQPAS ISCRSSQSLV HSNGNTYLHW YLQKPGQSPQ  50
LLIYKVSNRF SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YFCSQSTHVP 100
PFTFGGGTKV EIKRTVAAPS VFIFPPSDEQ LKSGTASVVC LLNNFYPREA 150
KVQWKVDNAL QSGNSQESVT EQDSKDSTYS LSSTLTLSKA DYEKHKVYAC 200
EVTHQGLSSP VTKSFNRGEC                                   220
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261"-321" 367"-425"
Intra-L (C23-C104) 23'-93' 140'-200'
23'"-93'" 140'"-200'"
Inter-H-L (h 5-CL 126)* 220-220' 220"-220'"
Inter-H-H (h 11, h 14)* 226-226" 229-229"
*Two or three of the inter-chain disulfide bridges are not present, an average of 3 cysteinyl being conjugated each via a thioether bond to a drug linker. *Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 3 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif. *Faltan dos o tres puentes disulfuro inter-catenarios, una media de 3 cisteinil está conjugada a conectores de principio activo.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans (G0F, G1F) / glycanes de type CHO bi-antennaires complexes fucosylés (G0F, G1F) / glicanos de tipo CHO biantenarios complejos fucosilados (G0F, G1F)

baliforsenum

baliforsen

all-P-ambo-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-ethane-1,1-diyl]-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-ethane-1,1-diyl]-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-ethane-1,1-diyl]-*P*-thioguanylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-ethane-1,1-diyl]-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)adenosine
dystrophia myotonica-protein kinase (DMPK) synthesis inhibitor

baliforsen

tout-P-ambo-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-éthane-1,1-diyl]-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-éthane-1,1-diyl]-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-désoxy-*P*-thioguanylyl-(3'→5')-2'-désoxy-*P*-thioadénylyl-(3'→5')-2'-désoxy-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-*P*-thioguanylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-éthane-1,1-diyl]-*P*-thioguanylyl-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-éthane-1,1-diyl]-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)adénosine
inhibiteur de la synthèse de la protéine-kinase de la dystrophie myotonique (DMPK)

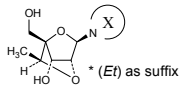
baliforsén

todo-P-ambo-2'-*O*-(2-metoxietil)-5-metil-*P*-tiouridilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-etano-1,1-diil]-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-etano-1,1-diil]-5-metil-*P*-tiocitidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-2'-desoxi-*P*-tioadenilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-*P*-tioguanilil-(3'→5')-*P*-tiotimidilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-2'-desoxi-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-etano-1,1-diil]-*P*-tioguanilil-(3'→5')-2'-*O*,4'-*C*-[(1*S*)-etano-1,1-diil]-*P*-tioadenilil-(3'→5')-2'-*O*-(2-metoxietil)-5-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-(2-metoxietil)adenosina
inhibidor de la síntesis de la proteína-kinasa de la distrofia miotónica (DMPK)

$C_{180}H_{240}N_{59}O_{90}P_{15}S_{15}$ 1698048-23-5

(3'-5')-(P-thio)(m5Umoe-m5Cmoe-m5C(Et)-m5C(Et)-dG-dA-dA-dT-dG-dT-m5dC-m5dC-G(Et)-A(Et)-m5Cmoe-Amoe)

Legend:
d as prefix = 2'-deoxy
(Et) as suffix = 2'-*O*,4'-*C*-[(1*S*)-ethane-1,1-diyl]*
m5 as prefix = 5-methyl
moe as suffix = 2'-*O*-(2-methoxyethyl)



* (*Et*) as suffix

balipodectum

balipodect

1-[2-fluoro-4-(1*H*-pyrazol-1-yl)phenyl]-5-methoxy-3-(1-phenyl-1*H*-pyrazol-5-yl)pyridazin-4(1*H*)-one
antipsychotic

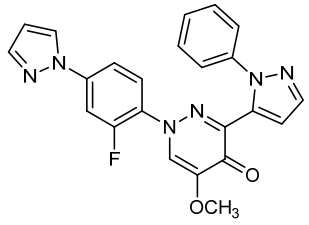
balipodect

1-[2-fluoro-4-(1*H*-pyrazol-1-yl)phényl]-5-méthoxy-3-(1-phényl-1*H*-pyrazol-5-yl)pyridazin-4(1*H*)-one
antipsychotique

balipodect

1-[2-fluoro-4-(1*H*-pirazol-1-il)fenil]-5-metoxi-3-(1-fenil-1*H*-pirazol-5-il)piridazin-4(1*H*)-ona
antipsicótico

$C_{23}H_{17}FN_6O_2$ 1238697-26-1



balovaptanum

balovaptan

8-chloro-5-methyl-1-{*trans*-4-[(pyridin-2-yl)oxy]cyclohexyl}-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepine
vasopressin receptor antagonist

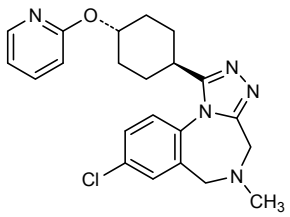
balovaptan

8-chloro-5-méthyl-1-{*trans*-4-[(pyridin-2-yl)oxy]cyclohexyl}-5,6-dihydro-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazépine
antagoniste du récepteur de la vasopressine

balovaptán

8-cloro-5-metil-1-{*trans*-4-[(piridin-2-il)oxi]ciclohexil}-5,6-dihidro-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepina
antagonista del receptor de la vasopresina

$C_{22}H_{24}ClN_5O$ 1228088-30-9



baloxavirum marboxilum
baloxavir marboxil

({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihydrodibenzo[*b*,*e*]thiepin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1*H*-[1,4]oxazino[3,4-*c*]pyrido[2,1-*f*][1,2,4]triazin-7-yl}oxy)methyl methyl carbonate
antiviral

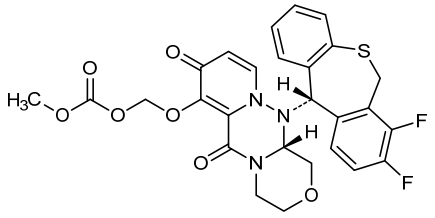
baloxavir marboxil

carbonate de({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihydrodibenzo[*b*,*e*]thiépin-11-yl]-6,8-dioxo-3,4,6,8,12,12a-hexahydro-1*H*-[1,4]oxazino[3,4-*c*]pyrido[2,1-*f*][1,2,4]triazin-7-yl}oxy)méthyle et de méthyle
antiviral

baloxavir marboxil

carbonato de({(12a*R*)-12-[(11*S*)-7,8-difluoro-6,11-dihidrodibenzo[*b*,*e*]tiepin-11-il]-6,8-dioxo-3,4,6,8,12,12a-hexahidro-1*H*-[1,4]oxazino[3,4-*c*]pirido[2,1-*f*][1,2,4]triazin-7-il}oxi)metilo y de metilo
antiviral

$C_{27}H_{23}F_2N_3O_7S$ 1985606-14-1



baltaleucelum
baltaleucel

Autologous Epstein-Barr virus (EBV)-specific T cells derived from peripheral blood mononuclear cells (PBMCs) stimulated and expanded for enrichment of CD4+ and CD8+ memory and effector T cells with specificity for a range of epitopes across four EBV antigens (latent membrane protein 1 (LMP1), latent membrane protein 2 (LMP2), EBV nuclear antigen 1 (EBNA1), and BamHI-A rightward frame 1 (BARF1)).
Contains $CD3^+$ T cells, $CD3^-$ $CD16^+$ $CD56^+$natural killer (NK) cells and $CD3^+$ $CD56^+$ natural killer T (NKT) cells in proportions varying per individual patient.
cell therapy (antineoplastic)

baltaleucel

Lymphocytes T autologues spécifiques du virus d'Epstein-Barr (EBV) dérivés de cellules mononucléaires du sang périphérique (PMBCs), stimulés et expansés pour enrichissement des lymphocytes T mémoire CD4+ et CD8+ ayant une spécificité vis-à-vis d'un éventail d'épitopes de quatre antigènes d'EBV (protéine latente de membrane 1 (LMP1), protéine latente de membrane 2 (LMP2), antigène nucléaire de EBV 1 (EBNA1), et BARF1 (BamHI-A rightward frame 1)).
contient des lymphocytes T CD3+, cellules tueuses naturelles (NK) CD3- CD16+ CD56+ et des lymphocytes T NK CD3+ CD56+ en proportions variables pour chaque patient
thérapie cellulaire (antinéoplasique)

baltaleucel

Linfocitos T autólogos específicos frente al virus de Epstein-Barr (EBV) derivados de células mononucleares de sangre periférica (PBMCs), estimulados y expandidos para enriquecimiento de los linfocitos T CD4+ y CD8+ efectores y de memoria con especificidad para un rango de epítopos presentes a lo largo de cuatro antígenos de EBV (proteína latente de membrana 1 (LMP1), proteína latente de membrana 2 (LMP2), antígeno nuclear de EBV 1 (EBNA1), y BARF1).
Contiene linfocitos T CD3+, células NK CD3- CD16+ CD56+ y linfocitos T NK CD3+ CD56+ en proporciones variables para cada paciente individual.
terapia celular (antineoplásico)

benzodrocortisonum
benzodrocortisone

11β,21-dihydroxy-3,20-dioxopregn-4-en-17-yl benzoate
corticosteroid

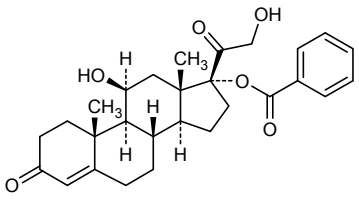
benzodrocortisone

benzoate de 11β,21-dihydroxy-3,20-dioxoprégn-4-én-17-yle
corticostéroïde

benzodrocortisona

benzoato de 11β,21-dihidroxi-3,20-dioxopregn-4-en-17-ilo
corticosteroide

$C_{28}H_{34}O_6$ 28956-89-0



betibeglogenum darolentivecum #
betibeglogene darolentivec

A self-inactivating human immunodeficiency virus-1 (HIV-1)-derived lentiviral vector encoding a T87Q-mutated form of the human hemoglobin subunit beta (HBB, beta-globin) gene under the control of a human β-globin promoter and a 3' β-globin enhancer
gene therapy (beta-thalassemia)

bétibéglogène darolentivec

Vecteur lentiviral auto-inactivant dérivé du virus de l'immunodéficience humaine-1 (HIV-1) codant pour une forme mutée (T87Q) du gène de la sous-unité bêta de l'hémoglobine humaine (HBB, bêta-globine) sous le contrôle d'un promoteur de la β-globine humaine et un activateur de la β-globine en position 3'.
thérapie génique (bêta-thalassémie)

betibeglogén darolentivec

Un vector lentiviral auto-inactivante derivado del virus de la inmunodeficiencia humana 1 (VIH-1) que contiene el gen que codifica para una forma mutada (T87Q) de la subunidad beta de la hemoglobina humana (HBB, beta-globina) bajo el control de un promotor de la β-globina humana y un potenciador (enhancer) de la β-globina en posición 3'.
terapia génica (beta-talasemia)

1905394-85-5

bimiralisibum

bimiralisib

5-[4,6-di(morpholin-4-yl)-1,3,5-triazin-2-yl]-4-(trifluoromethyl)pyridin-2-amine
antineoplastic

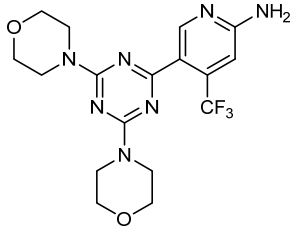
bimiralisib

5-[4,6-di(morpholin-4-yl)-1,3,5-triazin-2-yl]-4-(trifluorométhyl)pyridin-2-amine
antinéoplasique

bimiralisib

5-[4,6-di(morfolin-4-il)-1,3,5-triazin-2-il]-4-(trifluorometil)piridin-2-amino
antineoplásico

$C_{17}H_{20}F_3N_7O_2$ 1225037-39-7



brivoligidum

brivoligide

2'-deoxycytidylyl-(3'→5')-thymidylyl-(5'→3')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-thymidylyl-(5'→3')-2'-deoxyadenylyl-(3'→5')-2'-deoxycytidine duplex

	with 2'-deoxyguanylyl-(5'→3')-2'-deoxyadenylyl-(5'→3')-thymidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxycytidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxycytidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-2'-deoxycytidylyl-(5'→3')-2'-deoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-deoxyadenylyl-(5'→3')-thymidylyl-(5'→3')-2'-deoxyguanosine *analgesic*
brivoligide	2'-désoxycytidylyl-(3'→5')-thymidylyl-(5'→3')-2'-désoxyadénylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyguanylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyadénylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyguanylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyadénylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyguanylyl-(3'→5')-2'-désoxycytidylyl-(3'→5')-2'-désoxyadénylyl-(3'→5')-thymidylyl-(5'→3')-2'-désoxyadénylyl-(3'→5')-2'-désoxycytidine duplex avec 2'-désoxyguanylyl-(5'→3')-2'-désoxyadénylyl-(5'→3')-thymidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxycytidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxycytidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-2'-désoxycytidylyl-(5'→3')-2'-désoxyguanylyl-(5'→3')-thymidylyl-(5'→3')-2'-désoxyadénylyl-(5'→3')-thymidylyl-(5'→3')-2'-désoxyguanosine *analgésique*
brivoligida	2'-desoxicitidilil-(3'→5')-timidilil-(5'→3')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiguanilil-(3'→5')-2'-desoxicitidilil-(3'→5')-2'-desoxiadenilil-(3'→5')-timidilil-(5'→3')-2'-desoxiadenilil-(3'→5')-2'-desoxicitidina dúplex con 2'-desoxiguanilil-(5'→3')-2'-desoxiadenilil-(5'→3')-timidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxicitidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxiguanilil-(5'→3')-timidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxicitidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxiguanilil-(5'→3')-timidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-2'-desoxicitidilil-(5'→3')-2'-desoxiguanilil-(5'→3')-timidilil-(5'→3')-2'-desoxiadenilil-(5'→3')-timidilil-(5'→3')-2'-desoxiguanosina *analgésico*

$C_{444}H_{561}N_{177}O_{272}P_{44}$ 1803075-42-4

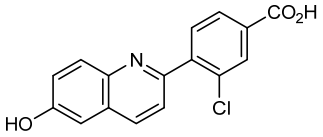
(3'-5') d(C-T-A-C-G-C-C-C-A-C-C-G-C-C-C-A-C-G-C-A-T-A-C)
. . . . . .
(5'-3') d(G-A-T-G-C-G-G-G-T-G-G-C-G-G-G-T-G-C-G-T-A-T-G)

cavosonstatum
cavosonstat — 3-chloro-4-(6-hydroxyquinolin-2-yl)benzoic acid
alcohol dehydrogenase inhibitor

cavosonstat — acide 3-chloro-4-(6-hydroxyquinoléin-2-yl)benzoïque
inhibiteur de l'alcool déshydrogénase

cavosonstat — ácido 3-cloro-4-(6-hidroxiquinolein-2-il)benzoico
inhibidor de la alcohol deshidrogenasa

$C_{16}H_{10}ClNO_3$ 1371587-51-7

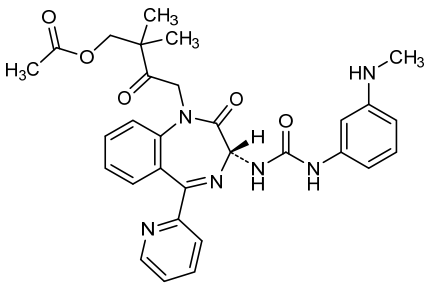


ceclazepidum
ceclazepide — 2,2-dimethyl-4-[(3*R*)-3-({[3-(methylamino)phenyl]carbamoyl}amino)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1*H*-1,4-benzodiazepin-1-yl]-3-oxobutyl acetate
cholecystokinin receptor antagonist

céclazépide — acétate de 2,2-diméthyl-4-[(3*R*)-3-({[3-(méthylamino)phényl]carbamoyl}amino)-2-oxo-5-(pyridin-2-yl)-2,3-dihydro-1*H*-1,4-benzodiazépin-1-yl]-3-oxobutyle
antagoniste des récepteurs des cholécystokinines

ceclazepida — acetato de 2,2-dimetil-4-[(3*R*)-3-({[3-(metilamino)fenil]carbamoil}amino)-2-oxo-5-(piridin-2-il)-2,3-dihidro-1*H*-1,4-benzodiazepin-1-il]-3-oxobutilo
antagonista de los receptores de las colecistoquininas

$C_{30}H_{32}N_6O_5$ 1801749-44-9



citarinostatum
citarinostat — 2-(2-chloro-*N*-phenylanilino)-*N*-[7-(hydroxyamino)-7-oxoheptyl]pyrimidine-5-carboxamide
histone deacetylase inhibitor, antineoplastic

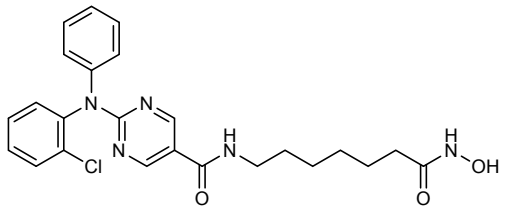
citarinostat

2-(2-chloro-*N*-phénylanilino)-*N*-[7-(hydroxyamino)-7-oxoheptyl]pyrimidine-5-carboxamide
inhibiteur de l'histone désacétylase, antinéoplasique

citarinostat

2-(2-cloro-*N*-fenilanilina)-*N*-[7-(hidroxiamino)-7-oxoheptil]pirimidina-5-carboxamida
inhibidor de la histona desacetilasa, antineoplásico

$C_{24}H_{26}ClN_5O_3$ 1316215-12-9



cosdosiranum

cosdosiran

adenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-cytidylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methylcytidine duplex with [(2*R*,3*S*)-3-hydroxyoxolan-2-yl]methyl hydrogen uridylyl-(5'→3')-2'-deoxycytidylyl-(5'→3')-cytidylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-cytidylyl-(5'→3')-cytidylyl-(5'→3')-5'-guanylate
inhibition of caspase 2 synthesis

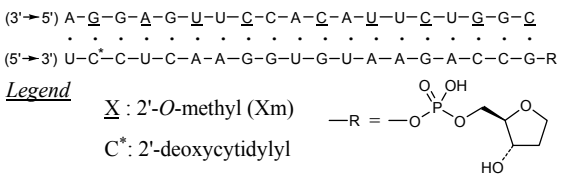
cosdosiran

adénylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-cytidylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthylcytidine duplex avec l'uridylyl-(5'→3')-2'-désoxycytidylyl-(5'→3')-cytidylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-adénylyl-(5'→3')-adénylyl-(5'→3')-guanylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-adénylyl-(5'→3')-adénylyl-(5'→3')-guanylyl-(5'→3')-adénylyl-(5'→3')-cytidylyl-(5'→3')-cytidylyl-(5'→3')-hydrogéno-5'-guanylate de [(2*R*,3*S*)-3-hydroxyoxolan-2-yl]méthyle
inhibition de la synthèse de la caspase 2

cosdosirán

adenilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-citidilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metilcitidina duplex con uridilil-(5'→3')-2'-desoxicitidilil-(5'→3')-citidilil-(5'→3')-uridilil-(5'→3')-citidilil-(5'→3')-adenilil-(5'→3')-adenilil-(5'→3')-guanilil-(5'→3')-guanilil-(5'→3')-uridilil-(5'→3')-guanilil-(5'→3')-uridilil-(5'→3')-adenilil-(5'→3')-adenilil-(5'→3')-guanilil-(5'→3')-adenilil-(5'→3')-citidilil-(5'→3')-citidilil-(5'→3')-hidrógeno -5'-guanilato de [(2*R*,3*S*)-3-hidroxioxolan-2-il]metilo
inhibición de la síntesis de la caspasa 2

$C_{375}H_{476}N_{143}O_{266}P_{37}$ 1834560-88-1



Legend
X : 2'-*O*-methyl (Xm)
C*: 2'-deoxycytidylyl

cosfroviximabum #
cosfroviximab

immunoglobulin G1-kappa, anti-[*Reston ebolavirus, Sudan ebolavirus,Tai Forest ebolavirus, Zaire ebolavirus (Zaire Ebola virus (EBOV))* glycoprotein], chimeric monoclonal antibody;
gamma1 heavy chain (1-452) [*Mus musculus* VH (IGHV8-8*01 (76.50%) -(IGHD) -IGHJ4*01) [10.7.14] (1-122) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (219) (123-220), hinge (221-235), CH2 (236-345), CH3 D12 (361), L14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfide with kappa light chain (1'-213') [*Mus musculus* V-KAPPA (IGKV6-13*01 (94.70%) -IGKJ5*01) [6.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dimer (231-231":234-234")-bisdisulfide
immunomodulator, antiviral

cosfroviximab

immunoglobuline G1-kappa, anti-[glycoprotéine de *Reston ebolavirus, Sudan ebolavirus,Tai Forest ebolavirus, Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-452) [*Mus musculus* VH (IGHV8-8*01(76.50%) -(IGHD) -IGHJ4*01) [10.7.14] (1-122) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (219) (123-220), charnière (221-235), CH2 (236-345), CH3 D12 (361), L14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfure avec la chaîne légère kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV6-13*01 (94.70%) -IGKJ5*01) [6.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dimère (231-231":234-234")-bisdisulfure
immunomodulateur, antiviral

cosfroviximab

inmunoglobulina G1-kappa, anti-[glicoproteína de *Reston ebolavirus, Sudan ebolavirus,Tai Forest ebolavirus, Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-452) [*Mus musculus* VH (IGHV8-8*01(76.50%) -(IGHD) -IGHJ4*01) [10.7.14] (1-122) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (219) (123-220), bisagra (221-235), CH2 (236-345), CH3 D12 (361), L14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfuro con la cadena ligera kappa (1'-213') [*Mus musculus* V-KAPPA (IGKV6-13*01 (94.70%) -IGKJ5*01) [6.3.9] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dímero (231-231'':234-234'')-bisdisulfuro
inmunomodulador, antiviral

1792982-57-0

Heavy chain / Chaîne lourde / Cadena pesada

```
DVKLLESGGG LVQPGGSLKL SCAASGFSLS TSGVGVGWFR QPSGKGLEWL  50
ALIWWDDDKY YNPSLKSQLS ISKDFSRNQV FLKISNVDIA DTATYYCARR 100
DPFGYDNAMG YWGQGTSVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR DELTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
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Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPLS LSTSVGDRVS LTCKASQNVG TAVAWYQQKP GQSPKLLIYS  50
ASNRYTGVPD RFTGSGSGTD FTLTISNMQS EDLADYFCQQ YSSYPLTFGA 100
GTKLELRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                          213
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Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-97 149-205 266-326 372-430
22"-97" 149"-205" 266"-326" 372"-430"
Intra-L (C23-C104) 23'-88' 133'-193'
23'"-88"' 133'"-193'"
Inter-H-L (h 5-CL 126) 225-213' 225"-213'"
Inter-H-H (h 11, h 14) 231-231" 234-234"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Complex bi-antennary (G0 > 75%) and high mannose (< 17%) *Nicotiana benthamiana*-type glycans / glycanes de type *Nicotiana benthamiana* bi-antennaires complexes (G0 > 75%) et riches en mannose (< 17%) / glicanos de tipo *Nicotiana benthamiana* biantenarios complejos (G0 > 75%) y alto contenido de manosa (< 17%).

dasiglucagonum

dasiglucagon

mutated human glucagon analogue:
[16-(2-methylalanine)(S>X),17-L-alanine(R>A),20-L-α-glutamyl(Q>E),21-L-α-glutamyl(D>E),24-L-lysyl(Q>K),27-L-α-glutamyl(M>E),28-L-serine(N>S)]human glucagon
glucagon analogue

dasiglucagon

analogue du glucagon humain muté :
[16-(2-méthylalanine)(S>X),17-L-alanine(R>A),20-L-α-glutamyl(Q>E),21-L-α-glutamyl(D>E),24-L-lysyl(Q>K),27-L-α-glutamyl(M>E),28-L-sérine(N>S)]glucagon humain
analogue du glucagon

dasiglucagón

análogo del glucagón humano mutado: [16-(2-metilalanina)(S>X),17-L-alanina(R>A),20-L-α-glutamil(Q>E),21-L-α-glutamil(D>E),24-L-lisil(Q>K),27-L-α-glutamil(M>E),28-L-serina(N>S)]glucagón humano
análogo de glucagón

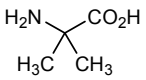
$C_{153}H_{225}N_{43}O_{49}S$ 1544300-84-6

Sequence / Séquence / Secuencia

HSQGTFTSDY SKYLDXARAE EFVKWLEST 29

Modified residue / Résidu modifié / Resto modificado

X(16)
2-methylalanine (Aib)
(aminoisobutyric acid)



delpazolidum

delpazolid

(5*R*)-3-[3-fluoro-4-(1-methyl-5,6-dihydro-1,2,4-triazin-4(1*H*)-yl)phenyl]-5-(hydroxymethyl)-1,3-oxazolidin-2-one
antibacterial

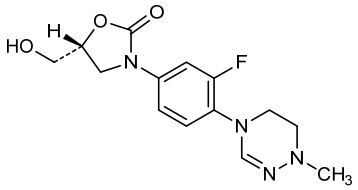
delpazolid

(5*R*)-3-[3-fluoro-4-(1-méthyl-5,6-dihydro-1,2,4-triazin-4(1*H*)-yl)phényl]-5-(hydroxyméthyl)-1,3-oxazolidin-2-one
antibactérien

delpazolid

(5*R*)-3-[3-fluoro-4-(1-metil-5,6-dihidro-1,2,4-triazin-4(1*H*)-il)fenil]-5-(hidroximetil)-1,3-oxazolidin-2-ona
antibacteriano

$C_{14}H_{17}FN_4O_3$ 1219707-39-7



dematirsenum

dematirsen

all-P-ambo-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*,5-*C*-dimethyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,5-*C*-dimethyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-dimethyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,5-*C*-dimethyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-dimethyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-dimethylcytidine
promotion of functional dystrophin synthesis

dématirsen

tout-P-ambo-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*,5-*C*-diméthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,5-*C*-diméthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-diméthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*,5-*C*-diméthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-diméthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*,5-*C*-diméthylcytidine
stimulation de la synthèse de dystrophine fonctionnelle

dematirsén

todo-P-ambo-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*,5-*C*-dimetil-*P*-tiocitidilil-(3'→5')-2'-*O*,5-*C*-dimetil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*,5-*C*-dimetil-*P*-tiocitidilil-(3'→5')-2'-*O*,5-*C*-dimetil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*,5-*C*-dimetil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*,5-*C*-dimetilcitidina
estimulación de la síntesis de distrofina funcional

$C_{266}H_{354}N_{86}O_{156}P_{24}S_{24}$ 1802465-55-9

(3'-5')-(P-thio)[Gm-Um-Um-Gm-m5Cm-m5Cm-Um-m5Cm-m5Cm-Gm-Gm-Um-Um-m5Cm-Um-Gm-Am-Am-Gm-Gm-Um-Gm-Um-Um-m5Cm]

Legend: m as suffix = 2'-*O*-methyl
m5 as prefix = 5-*C*-methyl

derazantinibum

derazantinib

(6*R*)-6-(2-fluorophenyl)-*N*-(3-{2-[(2-methoxyethyl)amino]ethyl}phenyl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine
antineoplastic

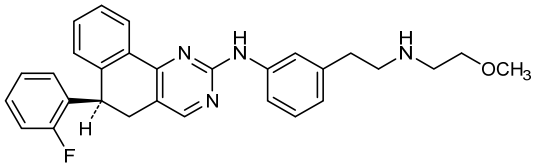
dérazantinib

(6*R*)-6-(2-fluorophényl)-*N*-(3-{2-[(2-méthoxyéthyl)amino]éthyl}phényl)-5,6-dihydrobenzo[*h*]quinazolin-2-amine
antinéoplasique

derazantinib

(6*R*)-6-(2-fluorofenil)-*N*-(3-{2-[(2-metoxietil)amino]etil}fenil)-5,6-dihidrobenzo[*h*]quinazolin-2-amina
antineoplásico

$C_{29}H_{29}FN_4O$ 1234356-69-4



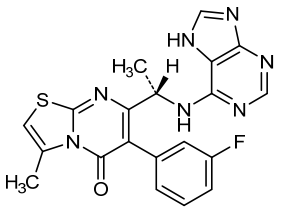
dezapelisibum

dezapelisib — 6-(3-fluorophenyl)-3-methyl-7-[(1*S*)-1-(7*H*-purin-6-ylamino)ethyl]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one
antineoplastic

dézapélisib — 6-(3-fluorophényl)-3-méthyl-7-[(1*S*)-1-(7*H*-purin-6-ylamino)éthyl]-5*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-5-one
antinéoplasique

dezapelisib — 6-(3-fluorofenil)-3-metil-7-[(1*S*)-1-(7*H*-purin-6-ilamino)etil]-5*H*-[1,3]tiazolo[3,2-*a*]pirimidin-5-ona
antineoplásico

$C_{20}H_{16}FN_7OS$ 1262440-25-4



donaperminogenum seltoplasmidum #

donaperminogene seltoplasmid — Plasmid DNA vector (pCK) containing a genomic-cDNA hybrid of the human hepatocyte growth factor (HGF) gene, HGF-X7, expressing two wild-type isoforms of HGF, HGF_{723} and HGF_{728}, under the control of the promoter and enhancer of the immediate-early (IE) gene of the human cytomegalovirus (HCMV).
gene therapy (angiogenesis stimulator)

donaperminogène seltoplasmide — Vecteur constitué d'ADN plasmidique (pCK) contenant un hybride de l'ADN génomique complémentaire (cDNA) du gène du facteur de croissance des hépatocytes humain (HGF), HGF-7, qui exprime deux isoformes sauvages de HGF, HGF_{723} et HGF_{728}, sous le contrôle du promoteur et activateur du gène immédiat-précoce du cytomégalovirus humain (CMV)
thérapie génique (stimulateur de l'angiogénèse)

donapermingén seltoplásmido

Vector de DNA plasmídico (pCK) que contiene un híbrido de DNA genómico-DNA complementario (cDNA) del gen del factor de crecimiento de hepatocitos humano (HGF), HGF-X7, que expresa dos isoformas salvajes/silvestres de HGF, HGF_{723} y HGF_{728}, bajo el control del promotor y el potenciador (enhancer) del gen inmediato-temprano (IE) del citomegalovirus humano
terapia génica (estimulador de la angiogénesis)

1787232-87-4

dorzagliatinum

dorzagliatin

(2*S*)-2-[4-(2-chlorophenoxy)-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl]-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-1*H*-pyrazol-3-yl}-4-methylpentanamide
antidiabetic

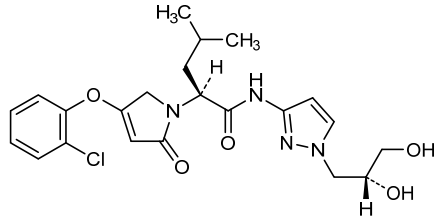
dorzagliatine

(2*S*)-2-[4-(2-chlorophénoxy)-2-oxo-2,5-dihydro-1*H*-pyrrol-1-yl]-*N*-{1-[(2*R*)-2,3-dihydroxypropyl]-1*H*-pyrazol-3-yl}-4-méthylpentanamide
antidiabétique

dorzagliatina

(2*S*)-2-[4-(2-clorofenoxi)-2-oxo-2,5-dihidro-1*H*-pirrol-1-il]-*N*-{1-[(2*R*)-2,3-dihidroxipropil]-1*H*-pirazol-3-il}-4-metilpentanamida
hipoglucemiante

$C_{22}H_{27}ClN_4O_5$ 1191995-00-2



dotinuradum

dotinurad

(3,5-dichloro-4-hydroxyphenyl)(1,1-dioxo-1,2-dihydro-3*H*-1λ^6-1,3-benzothiazol-3-yl)methanone
urate transporter inhibitor

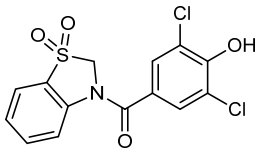
dotinurad

(3,5-dichloro-4-hydroxyphényl)(1,1-dioxo-1,2-dihydro-3*H*-1λ^6-1,3-benzothiazol-3-yl)méthanone
inhibiteur du transporteur de l'urate

dotinurad

(3,5-dicloro-4-hidroxifenil)(1,1-dioxo-1,2-dihidro-3*H*-1λ^6-1,3-benzotiazol-3-il)metanona
inhibidor del transportador del urato

$C_{14}H_9Cl_2NO_4S$ 1285572-51-1



duvortuxizumabum #
duvortuxizumab

immunoglobulin G1 scFv-h-CH2-CH3(_scFv)_h-CH2-CH3, bispecific, anti-[*Homo sapiens* CD19 (B lymphocyte surface antigen B4, Leu-12)] and anti-[*Homo sapiens* CD3 epsilon (CD3E, Leu-4)], humanized and chimeric monoclonal antibody;
scFv-h-CH2-CH3 chain (1-502) [humanized V-KAPPA anti-CD19 (IGKV3D-11*02 (79.30%) -IGKJ2*02) [5.3.9] (1-106)-8-mer triglycyl-seryl-tetraglycyl linker (107-114) -*Mus musculus* VH anti-CD3 (IGHV10-1*02 (88.90%) -(IGHD) -IGHJ3*01) [8.10.16] (115-239)-5-mer alanyl-seryl-threonyl-lysyl-glycyl linker (240-244) -E-coil motif (245-272) -3-mer triglycyl linker (273-275) -*Homo sapiens* IGHG1*03, nG1m1 hinge-CH2-CH3 (hinge 6-15 (276-285), CH2 L1.3>A (289), L1.2>A (290) (286-395), CH3 E12 (411), M14 (413), T22>W (421) (knob) (396-500), CHS (501-502)) (276-502)];
(249-248')-disulfide with the scFv chain (1'-271') [*Musmusculus* V-LAMBDA anti-CD3 (IGLV1*01 (81.20%) -IGKJ1*01) [9.3.9](1'-109') -9-mer tetraglycyl-seryl-tetraglycyl linker (110'-118') -humanized VH anti-CD19 (*Homo sapiens* IGHV2-5*08 (90.80%) -(IGHD) -IGHJ4*01 L123>T (233) [10.7.12](119'-238') -5-mer alanyl-seryl-threonyl-lysyl-glycyl linker -(239'-243') -K-coil motif(244'-271')];
(281-6'':284-9'')-bisdisulfide with the *Homo sapiens* IGHG1*03, nG1m1 hinge-CH2-CH3 chain (1-227) [hinge 6-15 (1-10), CH2 L1.3>A (4), L1.2>A (5) (11-120), CH3 E12 (136), M14 (138), T22>S (146) / L24>A (148) / Y86>V (187) (hole), H115>R (215) (121-225), CHS (226-227)]
immunomodulator, antineoplastic

duvortuxizumab	immunoglobuline G1 scFv-h-CH2-CH3(_scFv)_h-CH2-CH3, bispécifique, anti-[*Homo sapiens* CD19 (antigène de surface B4 des lymphocytes B, Leu-12)] et anti-[*Homo sapiens* CD3 epsilon (CD3E, Leu-4)], anticorps monoclonal humanisé et chimérique; chaîne scFv-h-CH2-CH3 (1-502) [V-KAPPA humanisé anti-CD19 (IGKV3D-11*02 (79.30%) -IGKJ2*02) [5.3.9] (1-106) -8-mer triglycyl-séryl-tétraglycyl linker (107-114) -*Mus musculus* VH anti-CD3 (IGHV10-1*02 (88.90%) -(IGHD) -IGHJ3*01) [8.10.16] (115-239)-5-mer alanyl-séryl-thréonyl-lysyl-glycyl linker (240-244) -motif E-coil (245-272) -3-mer triglycyl linker (273-275) -*Homo sapiens* IGHG1*03, nG1m1 charnière-CH2-CH3 (charnière 6-15 (276-285), CH2 L1.3>A (289), L1.2>A (290) (286-395), CH3 E12 (411), M14 (413), T22>W (421) (*knob*) (396-500), CHS (501-502)) (276-502)]; (249-248')-disulfure avec la chaîne scFv (1'-271') [*Mus musculus* V-LAMBDA anti-CD3 (IGLV1*01 (81.20%) -IGKJ1*01) [9.3.9] (1'-109') -9-mer tétraglycyl-séryl-tétraglycyl linker (110'-118') -VH humanisé anti-CD19 (*Homo sapiens* IGHV2-5*08 (90.80%) -(IGHD) -IGHJ4*01 L123>T (233) [10.7.12] (119'-238') -5-mer alanyl-séryl-thréonyl-lysyl-glycyl linker -(239'-243') -motif K-coil(244'-271')]; (281-6'':284-9'')-bisdisulfure avec la chaîne *Homo sapiens* IGHG1*03, nG1m1 charnière-CH2-CH3 (1-227) [charnière 6-15 (1-10), CH2 L1.3>A (4), L1.2>A (5) (11-120), CH3 E12 (136), M14 (138), T22>S (146) / L24>A (148) / Y86>V (187) (*hole*), H115>R (215) (121-225), CHS (226-227)] *immunomodulateur, antinéoplasique*
duvortuxizumab	inmunoglobulina G1 scFv-h-CH2-CH3(_scFv)_h-CH2-CH3, biespecífica, anti-[*Homo sapiens* CD19 (antígeno de superficie B4 de los linfocitos B, Leu-12)] y anti-[*Homo sapiens* CD3 epsilon (CD3E, Leu-4)], anticuerpo monoclonal humanizado y quimérico; cadena scFv-h-CH2-CH3 (1-502) [V-KAPPA humanizado anti-CD19 (IGKV3D-11*02 (79.30%) -IGKJ2*02) [5.3.9] (1-106) -8-mer triglicil-seril-tetraglicil conector (107-114) -*Mus musculus* VH anti-CD3 (IGHV10-1*02 (88.90%) -(IGHD) -IGHJ3*01) [8.10.16] (115-239)-5-mer alanil-seril-treonil-lisil-glicil conector (240-244) -secuencia E-coil (245-272) -3-mer triglicil conector (273-275) -*Homo sapiens* IGHG1*03, nG1m1 bisagra-CH2-CH3 (bisagra 6-15 (276-285), CH2 L1.3>A (289), L1.2>A (290) (286-395), CH3 E12 (411), M14 (413), T22>W (421) (*knob*) (396-500), CHS (501-502)) (276-502)]; (249-248')-disulfuro con la cadena scFv (1'-271') [*Mus musculus* V-LAMBDA anti-CD3 (IGLV1*01 (81.20%) -IGKJ1*01) [9.3.9] (1'-109') -9-mer tetraglicil-seril-tetraglicil conector (110'-118') -VH humanizado anti-CD19 (*Homo sapiens* IGHV2-5*08 (90.80%) -(IGHD) -IGHJ4*01 L123>T (233) [10.7.12] (119'-238') -5-mer alanil-seril-treonil-lisil-glicil conector -(239'-243') -secuencia K-coil(244'-271')]; (281-6'':284-9'')-bisdisulfuro con la cadena *Homo sapiens* IGHG1*03, nG1m1 bisagra-CH2-CH3 (1-227) [bisagra 6-15 (1-10), CH2 L1.3>A (4), L1.2>A (5) (11-120), CH3 E12 (136), M14 (138), T22>S (146) / L24>A (148) / Y86>V (187) (*hole*), H115>R (215) (121-225), CHS (226-227)] *inmunomodulador, antineoplásico*

1831098-91-9

Chain 1 scFv h-CH2-CH3 (VL anti-CD19, VH anti-CD3)

```
ENVLTQSPAT LSVTPGEKAT ITCRASQSVS YMHWYQQKPG QAPRLLIYDA  50
SNRASGVPSR FSGSGSGTDH TLTISSLEAE DAATYYCFQG SVYPFTFGQG 100
TKLEIKGGGS GGGGEVQLVE SGGGLVQPGG SLRLSCAASG FTFSTYAMNW 150
VRQAPGKGLE WVGRIRSKYN NYATYYADSV KGRFTISRDD SKNSLYLQMN 200
SLKTEDTAVY YCVRHGNFGN SYVSWFAYWG QGTLVTVSSA STKGEVAACE 250
KEVAALEKEV AALEKEVAAL EKGGGDKTHT CPPCPAPEAA GGPSVFLFPP 300
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 350
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 400
PQVYTLPPSR EEMTKNQVSL WCLVKGFYPS DIAVEWESNG QPENNYKTTP 450
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 500
GK                                                      502
```

Chain 2 scFv (VL anti-CD3, VH anti-CD19)

```
QAVVTQEPSL TVSPGGTVTL TCRSSTGAVT TSNYANWVQQ KPGQAPRGLI  50
GGTNKRAPWT PARFSGSLLG GKAALTITGA QAEDEADYYC ALWYSNLWVF 100
GGGTKLTVLG GGGSGGGGQV TLRESGPALV KPTQTLTLTC TFSGFSLSTS 150
GMGVGWIRQP PGKALEWLAH IWWDDDKRYN PALKSRLTIS KDTSKNQVFL 200
TMTNMDPVDT ATYYCARMEL WSYYFDYWGQ GTTVTVSSAS TKGKVAACKE 250
KVAALKEKVA ALKEKVAALK E                                 271
```

Chain 3 h-CH2-CH3

```
DKTHTCPPCP APEAAGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED  50
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 100
CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLSCAVK 150
GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLVSKL TVDKSRWQQG 200
NVFSCSVMHE ALHNRYTQKS LSLSPGK                           227
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-chain 1 (C23-C104) 23-87 136-212 316-376 422-480
Intra-chain 2 (C23-C104) 22'-90' 140'-215'
Intra-chain 3 (C23-C104) 41"-101" 147"-205"
Inter-chain 1 - chain 2 249-248'
Inter-chain 1 (h 11) - chain 3 (h 11) 281-6"
Inter-chain 1 (h 14) - chain 3 (h 14) 284-9"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
352, 77'"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
502, 227'"

efgartigimodum alfa #

efgartigimod alfa

mutated human immunoglobulin G1 Fc fragment, covalent dimer, produced in Chinese hamster ovary (CHO) cells, glycoform alfa;
[37-L-tyrosine(M>Y(32)),39-L-threonine(S>T(34)),41-L-α-glutamic acid(T>E(36)),218-L-lysine(H>K(213)),219-L-phenylalanine(N>F(214))]Fc fragment of human immunoglobulin heavy constant gamma 1-(6-232)-peptide, dimer (6-6':9-9')-bisdisulfide
immunomodulator

efgartigimod alfa

fragment Fc de l'immunoglobuline G1 humaine mutée, dimère covalent, produit par des cellules ovariennes de hamsters chinois (CHO), glycoforme alfa ;
[37-L-tyrosine(M>Y(32)),39-L-thréonine(S>T(34)),41-L-acide α-glutamique(T>E(36)),218-L-lysine(H>K(213)),219-L-phénylalanine(N>F(214))]fragment Fc de la chaîne lourde constante gamma 1 de l'immunoglobuline humaine-(6-232)-peptide, (6-6':9-9')-bisdisulfide du dimère
immunomodulateur

efgartigimod alfa

fragmento Fc de la inmunoglobulina G1 humana mutada, dímero covalente, producido por las células ováricas de hamsters chinos (CHO), glicoforma alfa; [37-L-tirosina(M>Y(32)),39-L-treonina(S>T(34)),41-L-ácido α-glutámico(T>E(36)),218-L-lisina(H>K(213)),219-L-fenilalanina(N>F(214))]fragmento Fc de la cadena pesada constante gamma 1 de la inmunoglobulina humana-(6-232)-péptido, (6-6':9-9')-bisdisulfuro del dímero
inmunomodulador

1821402-21-4

Monomer sequence / Séquence du monomère / Secuencia del monómero
DKTHTCPPCP APELLGGPSV FLFPPKPKDT LYITREPEVT CVVVDVSHED 50
PEVKFNWYVD GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK 100
CKVSNKALPA PIEKTISKAK GQPREPQVYT LPPSRDELTK NQVSLTCLVK 150
GFYPSDIAVE WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG 200
NVFSCSVMHE ALKFHYTQKS LSLSPGK 227

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
6-6' 9-9' 41-101 41'-101' 147-205 147'-205'

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-77 Asn-77"

eftilagimodum alfa #
eftilagimod alfa

human lymphocyte activation gene 3 protein extracellular domains fused to human immunoglobulin G1 Fc fragment through a linker peptide, covalent dimer, produced in Chinese hamster ovary (CHO) cells, glycoform alfa; human lymphocyte activation gene 3 protein (LAG-3, protein FDC, CD223 antigen) precursor-(23-434)-peptidyltetrakis(L-α-aspartyl)-L-lysylbis(glycyl-L-seryl)glycylFc fragment of human immunoglobulin heavy constant G1*01, dimer (427-427':433-433':436-436')-trisdisulfide
immunomodulator

eftilagimod alfa

domaines extracellulaires de la protéine d'activation du gène 3 lymphocytaire humain fusionnés au fragment Fc de l'immunoglobuline G1 humaine via un lien peptidique, dimère covalent, produit par des cellules ovariennes de hamster chinois (CHO), glycoforme alfa; précurseur de la protéine d'activation du gène 3 lymphocytaire humain (LAG-3, protéine FDC, antigène CD223)-(23-434)-peptidyltétrakis(L-α-aspartyl)-L-lysylbis(glycyl-L-séryl)glycylfragment Fc de la partie lourde constante de l'immunoglobuline G1*01, (427-427':433-433':436-436')-trisdisulfure du dimère
immunomodulateur

eftilagimod alfa

dominios extracelulares de la proteína de activación del gen 3 linfocitario humano fusionados con el fragmento Fc de la inmunoglobulina G1 mediante un vínculo peptídico, dímero covalente, producido por las células ováricas de hamsters chinos (CHO), glicoforma alfa;

precursor de la proteína de activación del gen 3 linfocitario humano (LAG-3, proteína FDC, antígeno CD223)-(23-434)-peptidiltetrakis(L-α-aspartil)-L-lisilbis(glicil-L-seril)glicilfragmento Fc de la parte pesada constante de la inmunoglobulina G1*01, (427-427':433-433':436-436')-trisdisulfuro del dímero
inmunomodulador

1800476-36-1

Monomer sequence / Séquence du monomère / Secuencia del monómero

```
LQPGAEVPVV WAQEGAPAQL PCSPTIPLQD LSLLRRAGVT WQHQPDSGPP 50
AAAPGHPLAP GPHPAAPSSW GPRPRRYTVL SVGPGGLRSG RLPLQPRVQL 100
DERGRQRGDF SLWLRPARRA DAGEYRAAVH LRDRALSCRL RLRLGQASMT 150
ASPPGSLRAS DWVILNCSFS RPDRPASVHW FRNRGQGRVP VRESPHHHLA 200
ESFLFLPQVS PMDSGPWGCI LTYRDGFNVS IMYNLTVLGL EPPTPLTVYA 250
GAGSRVGLPC RLPAGVGTRS FLTAKWTPPG GGPDLLVTGD NGDFTLRLED 300
VSQAQAGTYT CHIHLQEQQL NATVTLAIIT VTPKSFGSPG SLGKLLCEVT 350
PVSGQERFVW SSLDTPSQRS FSGPWLEAQE AQLLSQPWQC QLYQGERLLG 400
AAVYFTELSS PGDDDDKGSG SGEPKSCDKT HTCPPCPAPE LLGGPSVFLF 450
PPKPKDTLMI SRTPEVTCVV VDVSHEDPEV KFNWYVDGVE VHNAKTKPRE 500
EQYNSTYRVV SVLTVLHQDW LNGKEYKCKV SNKALPAPIE KTISKAKGQP 550
REPQVYTLPP SRDELTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT 600
TPPVLDSDGS FFLYSKLTVD KSRWQQGNVF SCSVMHEALH NHYTQKSLSL 650
SPGK                                                   654
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
22-138 22'-138' 167-219 167'-219' 260-311 260'-311' 347-390 347'-390'
427-427' 433-433' 436-436' 468-528 468'-528' 574-632 574'-632'

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-166 Asn-166' Asn-228 Asn-228' Asn-234
Asn-234' Asn-321 Asn-321' Asn-504 Asn-504'

eltanexorum
eltanexor

(2*E*)-3-{3-[3,5-bis(trifluoromethyl)phenyl]-1*H*-1,2,4-triazol-1-yl}-2-(pyrimidin-5-yl)prop-2-enamide
antineoplastic

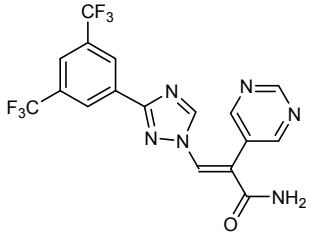
eltanexor

(2*E*)-3-{3-[3,5-bis(trifluorométhyl)phényl]-1*H*-1,2,4-triazol-1-yl}-2-(pyrimidin-5-yl)prop-2-énamide
antinéoplasique

eltanexor

(2*E*)-3-{3-[3,5-bis(trifluorometil)fenil]-1*H*-1,2,4-triazol-1-il}-2-(pirimidin-5-il)prop-2-enamida
antineoplásico

$C_{17}H_{10}F_6O$ 1642300-52-4



empesertibum
empesertib

(2*R*)-2-(4-fluorophenyl)-*N*-[4-(2-{[4-(methanesulfonyl)-2-methoxyphenyl]amino}[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)phenyl]propanamide
antineoplastic

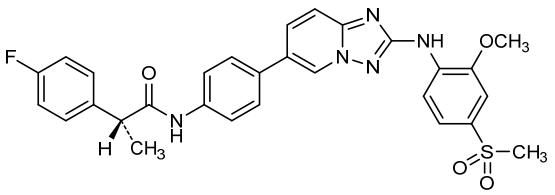
empésertib

(2*R*)-2-(4-fluorophényl)-*N*-[4-(2-{[4-(méthanesulfonyl)-2-méthoxyphényl]amino}[1,2,4]triazolo[1,5-*a*]pyridin-6-yl)phényl]propanamide
antinéoplasique

empesertib

(2*R*)-2-(4-fluorofenil)-*N*-[4-(2-{[4-(metanosulfonil)-2-metoxifenil]amino}[1,2,4]triazolo[1,5-*a*]piridin-6-il)fenil]propanamida
antineoplásico

$C_{29}H_{26}FN_5O_4S$ 1443763-60-7



estetrolum

estetrol

estra-1,3,5(10)-triene-3,15α,16α,17β-tetrol
estrogen

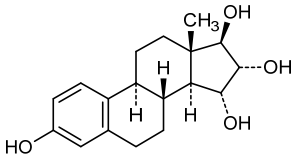
estétrol

estra-1,3,5(10)-triène-3,15α,16α,17β-tétrol
estrogène

estetrol

estra-1,3,5(10)-trieno-3,15α,16α,17β-tetrol
estrógeno

$C_{18}H_{24}N_4$ 15183-37-6



etoposidi toniribas

etoposide toniribate

[(4*RS*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl 4-[(5*R*,5a*R*,8a*R*,9*S*)-9-({4,6-*O*-[(1*R*)-ethane-1,1-diyl]-β-D-glucopyranosyl}oxy)-6-oxo-5,5a,6,8,8a,9-hexahydro-2*H*-furo[3',4':6,7]naphtho[2,3-*d*][1,3]dioxol-5-yl]-2,6-dimethoxyphenyl carbonate
antineoplastic

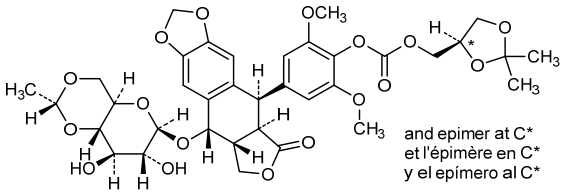
toniribate d'étoposide

carbonate de [(4*RS*)-2,2-diméthyl-1,3-dioxolan-4-yl]méthyle et de 4-[(5*R*,5a*R*,8a*R*,9*S*)-9-({4,6-*O*-[(1*R*)-éthane-1,1-diyl]-β-D-glocopyranosyl}oxy)-6-oxo-5,5a,6,8,8a,9-hexahydro-2*H*-furo[3',4'-6,7]naphto[2,3-*d*][1,3]dioxol-5-yl]-2,6-diméthoxyphényle
antinéoplasique

toniribato de etopósido

carbonato de [(4*RS*)-2,2-dimetil-1,3-dioxolan-4-il]metilo y de 4-[(5*R*,5a*R*,8a*R*,9*S*)-9-({4,6-*O*-[(1*R*)-etano-1,1-diil]-β-D-glocopiranosil}oxi)-6-oxo-5,5a,6,8,8a,9-hexahidro-2*H*-furo[3',4'-6,7]nafto[2,3-*d*][1,3]dioxol-5-il]-2,6-dimetoxifenilo
antineoplásico

$C_{36}H_{42}O_{17}$ 433304-61-1



etrasimodum
etrasimod

[(3*R*)-7-{[4-cyclopentyl-3-(trifluoromethyl)phenyl]methoxy}-1,2,3,4-tetrahydrocyclopenta[*b*]indol-3-yl]acetic acid
immunomodulator

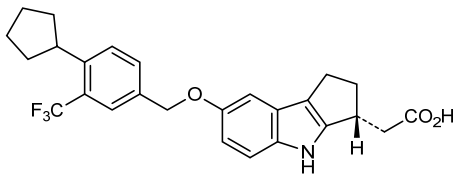
étrasimod

acide [(3*R*)-7-{[4-cyclopentyl-3-(trifluorométhyl)phényl]méthoxy}-1,2,3,4-tétrahydrocyclopenta[*b*]indol-3-yl]acétique
immunomodulateur

etrasimod

ácido [(3*R*)-7-{[4-ciclopentil-3-(trifluorometil)fenil]metoxi}-1,2,3,4-tetrahidrociclopenta[*b*]indol-3-il]acético
inmunomodulador

$C_{26}H_{26}F_3NO_3$ 1206123-37-6

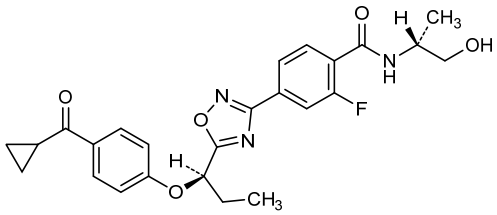


evagenretcelum
evagenretcel

Cell-based gene therapy consisting of a genetically modified cell line, derived from human donor-derived retinal pigment epithelial (RPE) cells. The cell line was transfected sequentially with two plasmids (p834 and p910) expressing the same fusion protein composed of: signal peptide and domain 2 of VEGFR1 (vascular endothelial growth factor receptor 1, FLT1) (VEGFR1(D2)); domain 3 of VEGFR2 (vascular endothelial growth factor receptor 2, KDR) (VEGFR2(D3)); and hinge domain, CH2 region and CH3 region of human immunoglobulin G1 (IgG1) under the control of a promoter containing a mouse cytomegalovirus (mCMV) enhancer, the human elongation factor 1-alpha (EF1-alpha) core promoter and a synthetic intron (I 126).
cell therapy (macular degeneration)

évagenretcel	Thérapie génique basée sur des cellules, consistant en une lignée cellulaire génétiquement modifiée, dérivée de cellules de l'épithélium pigmentaire rétinien d'un donneur humain. La lignée cellulaire a été transfectée de manière séquentielle avec deux plasmides (p834 et p910) qui expriment la même protéine de fusion composée de: un peptide signal et le domaine 2 du VEGFR1 (facteur de croissance de l'endothélium vasculaire 1, FLT1) (VEGFR1(D2)); le domaine 3 du VEGFR2 (facteur de croissance de l'endothélium vasculaire 2, KDR) (VEGFR2(D3)); et le domaine charnière, la région CH2 et la région CH3 de l'immunoglobuline G1 (IgG1) humaine. L'expression est sous le contrôle d'un promoteur qui contient un activateur d'un cytomégalovirus murin (mCMV), le promoteur nucléaire du facteur d'élongation humain 1-alpha (EF1-alpha) et un intron synthétique (I 126). *thérapie cellulaire (dégénerescence de la macula)*
evagenretcel	Terapia génica basada en células, consistente en una línea celular modificada genéticamente, derivada de células de donante humano del epitelio pigmentario de la retina. La línea celular se transfectó de forma secuencial con dos plásmidos (p834 y p910) que expresan la misma proteína de fusión compuesta por: un péptido señal y el domino 2 de VEGFR1 (receptor 1 del factor de crecimiento del endotelio vascular, FLT1) (VEGFR1(D2)); el dominio 3 de VEGFR2 (receptor 2 del factor de crecimiento del endotelio vascular, KDR) (VEGFR2(D3)); y el dominio bisagra, la región CH2 y la región CH3 de inmunoglobulina G1 (IgG1) humana. La expresión está bajo el control de un promotor que contiene un potenciador (enhancer) de uno citomegalovirus de ratón, el promotor nuclear del factor de elongación humano 1-alpha (EF1-alpha) y un intrón sintético (I 126). *terapia celular (degeneración macular)*
firuglipelum	
firuglipel	4-(5-{(1*R*)-1-[4-(cyclopropanecarbonyl)phenoxy]propyl}-1,2,4-oxadiazol-3-yl)-2-fluoro-*N*-[(2*R*)-1-hydroxypropan-2-yl]benzamide *antidiabetic*
firuglipel	4-(5-{(1*R*)-1-[4-(cyclopropanecarbonyl)phénoxy]propyl}-1,2,4-oxadiazol-3-yl)-2-fluoro-*N*-[(2*R*)-1-hydroxypropan-2-yl]benzamide *antidiabétique*
firuglipel	4-(5-{(1*R*)-1-[4-(ciclopropanocarbonil)fenoxi]propil}-1,2,4-oxadiazol-3-il)-2-fluoro-*N*-[(2*R*)-1-hidroxipropan-2-il]benzamida *hipoglucemiante*

$C_{25}H_{26}FN_3O_5$ 1371591-51-3



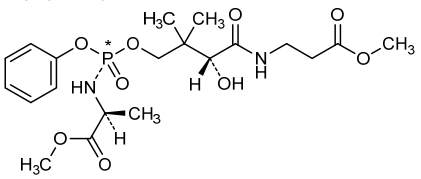
fosmetpantotenatum

fosmetpantotenate — dimethyl 4-*ambo*-(2*S*,8*R*)-8-hydroxy-2,7,7-trimethyl-4,9-dioxo-4-phenoxy-5-oxa-3,10-diaza-4λ^5-phosphatridecanedioate
immunomodulator

fosmetpantoténate — 4-*ambo*-(2*S*,8*R*)-8-hydroxy-2,7,7-triméthyl-4,9-dioxo-4-phénoxy-5-oxa-3,10-diaza-4λ^5-phosphatridécanedioate de diméthyle
immunomodulateur

fosmetpantotenato — 4-*ambo*-(2*S*,8*R*)-8-hidroxi-2,7,7-trimetil-4,9-dioxo-4-fenoxi-5-oxa-3,10-diaza-4λ^5-fosfatridecanodioato de dimetilo
inmunomodulador

$C_{20}H_{31}N_2O_9P$ 1858268-66-2



and epimer at P*
et l'épimère en P*
y el epímero al P*

frunevetmabum #

frunevetmab — immunoglobulin G1-kappa, anti-[*Mus musculus* NGF (nerve growth factor, nerve growth factor beta polypeptide, NGFB, beta-NGF)], felinized monoclonal antibody; gamma1 heavy chain (1-457) [felinized VH (*Rattus norvegicus* IGHV2-45*01 (77.30%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) -*Felis catus* IGHG1*01 (CH1 (123-220), hinge (221-239), CH2 (240-348), CH3 (349-455), CHS (456-457)) (123-457)], (137-214')-disulfide with kappa light chain (1'-217') [felinized V-KAPPA (*Rattus norvegicus* IGKV12S34*01 (70.50%) -IGKJ2-3*01) [6.3.9] (1'-107') -*Felis catus* IGKC*01 (108'-214') -glutaminyl-arginyl-glutamate (215'-217')]; dimer (232-232":234-234":237-237")-trisdisulfide
analgesic (veterinary use)

frunévetmab — immunoglobuline G1-kappa, anti-[*Mus musculus* NGF (facteur de croissance du nerf, facteur de croissance du nerf polypeptide bêta, NGFB, bêta-NGF)], anticorps monoclonal félinisé;

chaîne lourde gamma1 (1-457) [VH félinisé (*Rattus norvegicus* IGHV2-45*01 (77.30%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) - *Felis catus* IGHG1*01 (CH1 (123-220), charnière (221-239), CH2 (240-348), CH3 (349-455), CHS (456-457) (123-457)], (137-214')-disulfure avec la chaîne légère kappa (1'-217') [V-KAPPA félinisé (*Rattus norvegicus* IGKV12S34*01 (70.50%) - IGKJ2-3*01) [6.3.9] (1'-107') -*Felis catus* IGKC*01 (108'-214') - glutaminyl-arginyl-glutamate (215'-217')]; dimère (232-232'':234-234'':237-237'')-trisdisulfure
analgesique (usage vétérinaire)

frunevetmab

inmunoglobulina G1-kappa, anti-[*Mus musculus* NGF (factor de crecimiento del nervio, factor de crecimiento del nervio polipéptido beta, NGFB, bêta-NGF)], anticuerpo monoclonal felinizado;
cadena pesada gamma1 (1-457) [VH felinizado (*Rattus norvegicus* IGHV2-45*01 (77.30%) -(IGHD)-IGHJ4*01) [8.7.16] (1-122) -*Felis catus* IGHG1*01 (CH1 (123-220), bisagra (221-239), CH2 (240-348), CH3 (349-455), CHS (456-457) (123-457)], (137-214')-disulfuro con la cadena ligera kappa (1'-217') [V-KAPPA felinizado (*Rattus norvegicus* IGKV12S34*01 (70.50%) -IGKJ2-3*01) [6.3.9] (1'-107') -*Felis catus* IGKC*01 (108'-214') -glutaminil-arginil-glutamato (215'-217')]; dímero (232-232'':234-234'':237-237'')-trisdisulfuro
analgésico (uso veterinario)

1708936-80-4

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVESGAE LVQPGESLRL TCAASGFSLT NNNVNWVRQA PGKGLEWMGG  50
VWAGGATDYN SALKSRLTIT RDTSKNTVFL QMHSLQSEDT ATYYCARDGG 100
YSSSTLYAMD AWGQGTTVTV SAASTTAPSV FPLAPSCGTT SGATVALACL 150
VLGYFPEPVT VSWNSGALTS GVHTFPAVLQ ASGLYSLSSM VTVPSSRWLS 200
DTFTCNVAHP PSNTKVDKTV RKTDHPPGPK PCDCPKCPPP EMLGGPSIFI 250
FPPKPKDTLS ISRTPEVTCL VVDLGPDDSD VQITWFVDNT QVYTAKTSPR 300
EEQFNSTYRV VSVLPILHQD WLKGKEFKCK VNSKSLPSPI ERTISKAKGQ 350
PHEPQVYVLP PAQEELSRNK VSVTCLIKSF HPPDIAVEWE ITGQPEPENN 400
YRTTPPQLDS DGTYFVYSKL SVDRSHWQRG NTYTCSVSHE ALHSHHTQKS 450
LTQSPGK                                               457
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Light chain / Chaîne légère / Cadena ligera

```
DIEMTQSPLS LSVTPGESVS ISCRASEDIY NALAWYLQKP GRSPRLLIYN  50
TDTLHTGVPD RFSGSGSGTD FTLKISRVQT EDVGVYFCQH YFHYPRTFGQ 100
GTKLELKRSD AQPSVFLFQP SLDELHTGSA SIVCILNDFY PKEVNVKWKV 150
DGVVQNKGIQ ESTTEQNSKD STYSLSSTLT MSSTEYQSHE KFSCEVTHKS 200
LASTLVKSFN RSECQRE                                    217
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-95 149-205 269-329 375-435
22"-95" 149"-205" 269"-329" 375"-435"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (CH1 11-CL 126) 137-214' 137"-214'"
Inter-H-H (h12, h 14, h 17) 232-232" 234-234" 237-237"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
305, 305"
L CL N122
210',210'"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados.

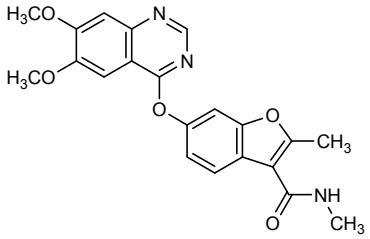
fruquintinibum

fruquintinib — 6-[(6,7-dimethoxyquinazolin-4-yl)oxy]-*N*,2-dimethyl-1-benzofuran-3-carboxamide
antineoplastic

fruquintinib — 6-[(6,7-diméthoxyquinazolin-4-yl)oxy]-*N*,2-diméthyl-1-benzofurane-3-carboxamide
antinéoplasique

fruquintinib — 6-[(6,7-dimetoxiquinazolin-4-il)oxi]-*N*,2-dimetil-1-benzofurano-3-carboxamida
antineoplásico

$C_{21}H_{19}N_3O_5$ 1194506-26-7



gatipotuzumabum #

gatipotuzumab — immunoglobulin G1-kappa, anti-[*Homo sapiens* MUC1 (mucin 1, polymorphic epithelial mucin, PEM, episialin, CD227) tumor antigen TA-MUC1 conformational epitope O-glycosylated on the threonine of the immunodominant PDTRP motif of the tandem repeats], humanized monoclonal antibody;
gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-72*01 (85.00%) -(IGHD)-IGHJ4*01) [8.10.8] (1-117) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (214) (118-215), hinge (216-230), CH2 (231-340), CH3 D12 (356), L14 (358), G110 (431) (341-445), CHS (446-447)) (118-447)], (220-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-28*01 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dimer (226-226":229-229")-bisdisulfide
immunomodulator, antineoplastic

gatipotuzumab — immunoglobuline G1-kappa, anti-[*Homo sapiens* MUC1 (mucine 1, mucine épithéliale polymorphique, PEM, CD227) épitope conformationnel O-glycosylé sur la thréonine du motif immunodominant PDTRP des répétitions en tandem de l'antigène tumoral TA-MUC1], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-447) [VH humanisé (*Homo sapiens* IGHV3-72*01 (85.00%) -(IGHD)-IGHJ4*01) [8.10.8] (1-117) -*Homo sapiens* IGHG1*07p, G1m17,1, 2 (CH1 K120 (214) (118-215), charnière (216-230), CH2 (231-340), CH3 D12 (356), L14 (358), G110 (431) (341-445), CHS (446-447)) (118-447)], (220-219')-disulfure avec la chaîne légère kappa (1'-219') [V-KAPPA humanisé (*Homo sapiens* IGKV2-28*01 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dimère (226-226":229-229")-bisdisulfure
immunomodulateur, antinéoplasique

gatipotuzumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* MUC1 (mucina 1, mucina epitelial polimórfica, PEM, CD227) epítopo conformacional O-glicosilado en la treonina del espaciador inmunodominante PDTRP de las repeticiones en tandem del antígeno tumoral TA-MUC1], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-447) [VH humanizado (*Homo sapiens* IGHV3-72*01 (85.00%) -(IGHD)-IGHJ4*01) [8.10.8] (1-117) -*Homo sapiens* IGHG1*07p, G1m17,1, 2 (CH1 K120 (214) (118-215), bisagra (216-230), CH2 (231-340), CH3 D12 (356), L14 (358), G110 (431) (341-445), CHS (446-447)) (118-447)], (220-219')-disulfuro con la cadena ligera kappa (1'-219') [V-KAPPA humanizado (*Homo sapiens* IGKV2-28*01 (86.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dímero (226-226":229-229")-bisdisulfuro
inmunomodulador, antineoplásico

1264737-26-9

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSMRL SCVASGFPFS NYWMNWVRQA PGKGLEWVGE  50
IRLKSNNYTT HYAESVKGRF TISRDDSKNS LYLQMNSLKT EDTAVYYCTR 100
HYYFDYWGQG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKKVEPKSC DKTHTCPPCP APELLGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA PIEKTISKAK GQPREPQVYT 350
LPPSRDELTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE GLHNHYTQKS LSLSPGK    447
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPLS NPVTPGEPAS ISCRSSKSLL HSNGITYFFW YLQKPGQSPQ  50
LLIYQMSNLA SGVPDRFSGS GSGTDFTLRI SRVEAEDVGV YYCAQNLELP 100
PTFGQGTKVE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                   219
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

```
Intra-H (C23-C104)  22-98     144-200    261-321    367-425
                    22"-98"   144"-200"  261"-321"  367"-425"
Intra-L (C23-C104)  23'-93'   139'-199'
                    23'"-93'" 139'"-199'"
Inter-H-L (h 5-CL 126)  220-219'  220"-219'"
Inter-H-H (h 11, h 14)  226-226"  229-229"
```

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H VH 62:
57, 57"
H CH2 N84.4:
297, 297"

Produced in human erythroleukemia (K562) cell line. Glycans are mostly biantennary complex glycans with <30% high mannose and high degree of galactosylation. They have >5% sialylated glycans, <50% fucosylation, >10% bisecting N-acetylglucosamine bearing glycans and no N-glycolylneuraminic acid./ Produit par des cellules humaines d'érythroleucémie (K562). Les glycanes sont principalement complexes bi-antennaires avec <30% de mannose de haut poinds moléculaire et de haut degré de galactosilation. Ils contiennent >5% de glycanes sialylés, <50% de fucosylation, >10% de glycanes présentant des N-acétylglucosamines bisectionnées et pas d'acide N-glycolylneuraminique./ Producido en la línea celular humana de eritroleucemia (K562). Los glicanos son principalmente glicanos complejos biantenarios con <30% de manosas de alto peso molecular y alto grado de galactosilación. Contienen >5% de glicanos sialilados, <50% de fucosilación, >10% de glicanos que llevan N-acetilglucosaminas biseccionadas y ningún ácido N-glicolilneuramínico.

gedivumabum #

gedivumab	immunoglobulin G1-kappa, anti-[influenza A virus hemagglutinin HA], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-455) [*Homo sapiens* VH (IGHV3-30*01 (89.70%) -(IGHD) -IGHJ4*01 T122>I (119)) [8.8.18] (1-125) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (222) (126-223), hinge (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455)) (1-455)], (228-216')-disulfide with kappa light chain (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (89.50%) -IGKJ4*01) [6.3.11] (1'-109') -*Homo sapiens* IGKC*01, Km3 A45.1 (155), V101 (193) (110'-216')]; dimer (234-234":237-237")-bisdisulfide *immunomodulator, antiviral*
gédivumab	immunoglobuline G1-kappa, anti-[hémagglutinine HA du virus de la grippe A], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-455) [*Homo sapiens* VH (IGHV3-30*01 (89.70%) -(IGHD) -IGHJ4*01 T122>I (119)) [8.8.18] (1-125) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (222) (126-223), charnière (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455)) (1-455)], (228-216')-disulfure avec la chaîne légère (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (89.50%) -IGKJ4*01) [6.3.11] (1'-109') -*Homo sapiens* IGKC*01, Km3 A45.1 (155), V101 (193) (110'-216')]; dimère (234-234":237-237")-bisdisulfure *immunomodulateur, antiviral*
gedivumab	inmunoglobulina G1-kappa, anti-[hemaglutinina HA del virus de la gripe A], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-455) [*Homo sapiens* VH (IGHV3-30*01 (89.70%) -(IGHD) -IGHJ4*01 T122>I (119)) [8.8.18] (1-125) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (222) (126-223), bisagra (224-238), CH2 (239-348), CH3 E12 (364), M14 (366) (349-453), CHS (454-455)) (1-455)], (228-216')-disulfuro con la cadena ligera (1'-216') [*Homo sapiens* V-KAPPA (IGKV3-15*01 (89.50%) -IGKJ4*01) [6.3.11] (1'-109') -*Homo sapiens* IGKC*01, Km3 A45.1 (155), V101 (193) (110'-216')]; dímero (234-234":237-237")-bisdisulfuro *inmunomodulador, antiviral*

1807954-17-1

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG VVQPGKSLRL SCAASGLTFS SYAVHWVRQA PGKGLEWVTL  50
ISYDGANQYY ADSVKGRFTI SRDNSKNTVY LQMNSLRPED TAVYYCAVPG 100
PVFGIFPPWS YFDNWGQGIL VTVSSASTKG PSVFPLAPSS KSTSGGTAAL 150
GCLVKDYFPE PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS 200
LGTQTYICNV NHKPSNTKVD KKVEPKSCDK THTCPPCPAP ELLGGPSVFL 250
FPPKPKDTLM ISRTPEVTCV VVDVSHEDPE VKFNWYVDGV EVHNAKTKPR 300
EEQYNSTYRV VSVLTVLHQD WLNGKEYKCK VSNKALPAPI EKTISKAKGQ 350
PREPQVYTLP PSREEMTKNQ VSLTCLVKGF YPSDIAVEWE SNGQPENNYK 400
TTPPVLDSDG SFFLYSKLTV DKSRWQQGNV FSCSVMHEAL HNHYTQKSLS 450
LSPGK                                                   455
```

Light chain / Chaîne légère / Cadena ligera

```
EIVLTQSPAT LSVSPGERAT LSCRASQVIS HNLAWYQQKP GQAPRLLIYG  50
ASTRASGIPA RFSGSGSGTD YTLTITSLQS EDFAVYYCQH YSNWPPRLTF 100
GGGTKVEIKR TVAAPSVFIF PPSDEQLKSG TASVVCLLNN FYPREAKVQW 150
KVDNALQSGN SQESVTEQDS KDSTYSLSST LTLSKADYEK HKVYACEVTH 200
QGLSSPVTKS FNRGEC                                      216
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 152-208 269-329 375-433
22"-96" 152"-208" 269'-329" 375"-433"
Intra-L (C23-C104) 23'-88' 136'-196'
23'"-88'" 136'"-196'"
Inter-H-L (h 5-CL 126) 228-216' 228"-216'"
Inter-H-H (h 11, h 14) 234-234" 237-237"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
305, 305"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

gilvetmabum #

gilvetmab

immunoglobulin G2-kappa, anti-[*Canis familiaris* PDCD1 (programmed cell death 1, PD-1, PD1, CD279)], caninized monoclonal antibody;
gamma2 heavy chain (1-455) [caninized VH (*Mus musculus* IGHV14-3*02 (76.00%) -(IGHD)-IGHJ3*01) [8.8.13] (1-120) -*Canis lupus familiaris* IGHG2*02 (CH1 (121-217), hinge (218-236), CH2 D27>A (271), N84.4>A (303)) (237-346), CH3 (347-453), CHS (454-455)) (121-455)], (135-214')-disulfide with kappa light chain (1'-218') [caninized V-KAPPA (*Mus musculus* IGKV1-117*01 (69.00%) -IGKJ2*03) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-214') -glutaminyl-arginyl-valyl-aspartate (215'-218')]; dimer (232-232":235-235")-bisdisulfide
antineoplastic (veterinary use)

gilvetmab

immunoglobuline G2-kappa, anti-[*Canis familiaris* PDCD1 (protéine 1 de mort cellulaire programmée, PD-1, PD1, CD279)], anticorps monoclonal caninisé;
chaîne lourde gamma2 (1-455) [VH caninisé ((*Mus musculus* IGHV14-3*02 (76.00%) -(IGHD)-IGHJ3*01) [8.8.13] (1-120) -*Canis lupus familiaris* IGHG2*02 (CH1 (121-217), charnière (218-236), CH2 D27>A (271), N84.4>A (303)) (237-346), CH3 (347-453), CHS (454-455)) (121-455)], (135-214')-disulfure avec la chaîne légère kappa (1'-218') [V-KAPPA caninisé (*Mus musculus* IGKV1-117*01 (69.00%) -IGKJ2*03) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-214') -glutaminyl-arginyl-valyl-aspartate (215'-218')]; dimère (232-232":235-235")-bisdisulfure
antinéoplasique (usage vétérinaire)

gilvetmab

inmunoglobulina G2-kappa, anti-[*Canis familiaris* PDCD1 (proteína 1 de muerte celular programada, PD-1, PD1, CD279)], anticuerpo monoclonal caninizado; cadena pesada gamma2 (1-455) [VH caninizado ((*Mus musculus* IGHV14-3*02 (76.00%) -(IGHD)-IGHJ3*01) [8.8.13] (1-120) -*Canis lupus familiaris* IGHG2*02 (CH1 (121-217), bisagra (218-236), CH2 D27>A (271), N84.4>A (303)) (237-346), CH3 (347-453), CHS (454-455)) (121-455)], (135-214')-disulfuro con la cadena ligera kappa (1'-218') [V-KAPPA caninizado (*Mus musculus* IGKV1-117*01 (69.00%) -IGKJ2*03) [6.3.9] (1'-107') -*Canis lupus familiaris* IGKC*01 (108'-214') -glutaminil-arginil-valil-aspartato (215'-218')]; dímero (232-232":235-235")-bisdisulfuro
antineoplásico (uso veterinario)

1808081-43-7

Heavy chain / Chaîne lourde / Cadena pesada
```
EVQLVQSGGD LVKPGGSVRL SCVASGFNIK NTYMHWVRQA PGKGLQWIGR  50
IAPANVDTKY APKFQGKATI SADTAKNTAY MQLNSLRAED TAVYYCVLIY 100
YDYDGDIDVW GQGTLVTVSS ASTTAPSVFP LAPSCGSTSG STVALACLVS 150
GYFPEPVTVS WNSGSLTSGV HTFPSVLQSS GLYSLSSMVT VPSSRWPSET 200
FTCNVAHPAS KTKVDKPVPK RENGRVPRPP DCPKCPAPEM LGGPSVFIFP 250
PKPKDTLLIA RTPEVTCVVV ALDPEDPEVQ ISWFVDGKQM QTAKTQPREE 300
QFAGTYRVVS VLPIGHQDWL KGKQFTCKVN NKALPSPIER TISKARGQAH 350
QPSVYVLPPS REELSKNTVS LTCLIKDFFP PDIDVEWQSN GQQEPESKYR 400
TTPPQLDEDG SYFLYSKLSV DKSRWQRGDT FICAVMHEAL HNHYTQESLS 450
HSPGK                                                   455
```

Light chain / Chaîne légère / Cadena ligera
```
DIVMTQTPLS LSVSLGEPAS ISCHASQNIN VWLSWYRQKP GQIPQLLIYK  50
ASHLHTGVPD RFSGSGSGTD FTLRISRVEA DDAGVYYCQQ GQSWPLTFGQ 100
GTKVEIKRND AQPAVYLFQP SPDQLHTGSA SVVCLLNSFY PKDINVKWKV 150
DGVIQDTGIQ ESVTEQDSKD STYSLSSTLT MSSTEYLSHE LYSCEITHKS 200
LPSTLIKSFQ RSECQRVD                                     218
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	147-203	267-327	373-433
	22"-96"	147"-203"	267"-327"	373"-433"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (CH1 11-CL 126)	135-214'	135"-214'"		
Inter-H-H (h 14, h 17)	232-232"	235-235"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4>A:
303, 303"
No N-glycosylation sites / pas de sites de N-glycosylation /ningúna posición de N-glicosilación

glepaglutidum
glepaglutide

mutated human glucagon like peptide-2 (GLP-2) analogue with a C-terminal hexa-lysine addition; [2-glycine(A>G),3-glutamic acid(D>E),5-threonine(S>T),8-serine(D>S),10-leucine(M>L),11-alanine(N>A),16-alanine(N>A),24-alanine(N>A),28-alanine(Q>A)]human glucagon-like peptide 2 (GLP-2) fusion peptide with hexalysinamide
antidiabetic

glépaglutide	analogue du peptide 2 semblable au glucagon (GLP-2) humain muté, à l'extrémité C-terminale duquel sont ajoutées 6 lysines; [2-glycine(A>G),3-acide glutamique(D>E),5-thréonine(S>T),8-sérine(D>S),10-leucine(M>L),11-alanine(N>A),16-alanine(N>A),24-alanine(N>A),28-alanine(Q>A)]peptide 2 semblable au glucagon humain (GLP-2) peptide de fusion avec l'hexalysinamide *antidiabétique*
glepaglutida	análogo del péptido 2 semejante al glucagón (GLP-2) humano mutado, con una adición de 6 lisinas en la extremidad C-terminal; [2-glicina(A>G),3-ácido glutámico(D>E),5-treonina(S>T),8-serina(D>S),10-leucina(M>L),11-alanina(N>A),16-alanina(N>A),24-alanina(N>A),28-alanina(Q>A)]péptido 2 semejante al glucagón humano (GLP-2) proteína de fusión con la hexalisinamida *hipoglucemiante*

$C_{197}H_{325}N_{53}O_{55}$ 914009-86-2

Sequence / Séquence/ Secuencia
HGEGTFSSEL ATILDALAAR DFIAWLIATK ITDKKKKKK 39

Modified residue / Résidu modifié / Resto modificado
K lysinamide

ilixadencelum

ilixadencel	Cell therapy consisting of pro-inflammatory monocyte-derived dendritic cells (MoDCs), isolated from an allogeneic human healthy blood donor and *ex-vivo* stimulated with resiquimod (R848), polyinosinic-polycytidylic acid (poly(I:C)) and interferon gamma (IFN-γ). Contains at least 70% of dendritic cells (DC). These cells express T-lymphocyte activation antigen CD86 and the major histocompatibility complex (MHC) class II molecule HLA-DR, and secrete pro-inflammatory soluble factors, including interleukin 12 (IL-12) and C-C motif chemokine 5 (CCL5; also known as RANTES). *cell therapy (antineoplastic)*
ilixadencel	Thérapie cellulaire allogénique consistant en des cellules dendritiques pro-inflammatoires humaines dérivées de monocytes isolés du sang d'un donneur sain et stimulées *ex vivo* avec du résiquimod (R848), l'acide polyinosinique-polycytidylique (poly(I:C)) et de l'interféron gamma (IFN-γ). La thérapie cellulaire contient au moins 70% de cellules dendritiques. Ces cellules expriment l'antigène d'activation des lymphocytes T CD86 et la molécule du complexe majeur d'histocompatibilité (CMH) de classe II HLA-DR et secrètent des facteurs solubles pro-inflammatoires, dont l'interleukine 12 (IL-12) et la chimioquine à motif C-C 5 (CCL5; aussi connue comme RANTES). *thérapie cellulaire (antinéoplasique)*

ilixadencel

Terapia celular consistente en células dendríticas pro-inflamatorias humanas derivadas a partir de monocitos aislados de un donante de sangre sano y estimuladas *ex-vivo* con resiquimod (R848), ácido poliinosinico-policitidilico acid (poli(I:C) e interferón gamma (IFN-γ). La terapia celular contiene al menos un 70% de células dendríticas. Estas células expresan antígeno de activación de linfocitos T CD86 y la molécula del complejo principal de histocompatibilidad de clase II HLA-DR, y secretan factores solubles pro-inflamatorios, incluyendo interleukina 12 (IL-12) y quimiocina C-C 5 (CCL5, también conocida como RANTES).
terapia celular (antineoplásico)

imarikirenum

imarikiren

1-(4-methoxybutyl)-*N*-(2-methylpropyl)-*N*-[(3*S*,5*R*)-5-(morpholine-4-carbonyl)piperidin-3-yl]-1*H*-benzimidazole-2-carboxamide
renin inhibitor

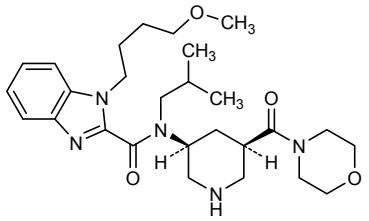
imarikirène

1-(4-méthoxybutyl)-*N*-(2-méthylpropyl)-*N*-[(3*S*,5*R*)-5-(morpholine-4-carbonyl)pipéridin-3-yl]-1*H*-benzimidazole-2-carboxamide
inhibiteur de la rénine

imarikireno

1-(4-metoxibutil)-*N*-(2-metilpropil)-*N*-[(3*S*,5*R*)-5-(morfolina-4-carbonil)piperidin-3-il]-1*H*-benzoimidazol-2-carboxamida
inhibidor de la renina

$C_{27}H_{41}N_5O_4$ 1202265-63-1



inarigivirum soproxilum

inarigivir soproxil

P-ambo-2'-*O*-methyl-S^P-({[(propan-2-yloxy)carbonyl]oxy}methyl)-*P*-thiouridylyl-(3'→5')-2'-deoxyadenosine
antiviral

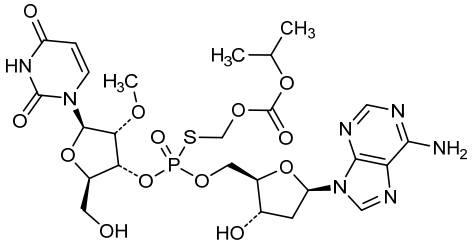
inarigivir soproxil

P-ambo-2'-*O*-méthyl-S^P-({[(propan-2-yloxy)carbonyl]oxy}méthyl)-*P*-thiouridylyl-(3'→5')-2'-désoxyadénosine
antiviral

inarigivir soproxilo

P-ambo-2'-*O*-metil-S^P-({[(propan-2-iloxi)carbonil]oxi}metil)-*P*-tiouridilil-(3'→5')-2'-desoxiadenosina
antiviral

$C_{25}H_{34}N_7O_{13}PS$ 942123-43-5



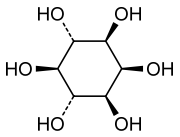
inositolum

inositol *myo*-inositol (cyclohexane-1,2,3,5/4,6-hexol)
vitamin

inositol *myo*-inositol (cyclohexane-1,2,3,5/4,6-hexol)
*vitamin*e

inositol *mio*-inositol (ciclohexano-1,2,3,5/4,6-hexol)
vitamina

$C_6H_{12}O_6$ 87-89-8



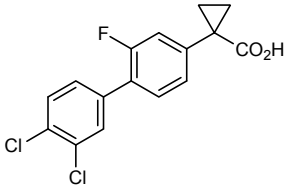
itanapracedum

itanapraced 1-(3',4'-dichloro-2-fluoro[1,1'-biphenyl]-4-yl)cyclopropane-1-carboxylic acid
immunomodulator, acting on microglia

itanapraced acide 1-(3',4'-dichloro-2-fluoro[1,1'-biphényl]-4-yl)cyclopropane-1-carboxylique
immunomodulateur, agissant sur la microglie

itanapraced ácido 1-(3',4'-dicloro-2-fluoro[1,1'-bifenil]-4-il)ciclopropano-1-carboxílico
inmunomodulador, que interacciona sobre la microglia

$C_{16}H_{11}Cl_2FO_2$ 749269-83-8



lacnotuzumabum #

lacnotuzumab	immunoglobulin G1-kappa, anti-[*Homo sapiens* CSF1 (colony stimulating factor 1, colony stimulating factor 1 (macrophage), M-CSF, macrophage colony stimulating factor 1, MCSF)], humanized monoclonal antibody; gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV4-30-4*01 (85.70%) -(IGHD)-IGHJ4*01) [9.7.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (215) (119-216), hinge (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS (447-448)) (119-448)], (221-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV6-21*02 (80.00%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dimer (227-227":230-230")-bisdisulfide *immunomodulator, antineoplastic*
lacnotuzumab	immunoglobuline G1-kappa, anti-[*Homo sapiens* CSF1 (facteur 1 de stimulation de colonie, facteur 1 de stimulation des colonies (macrophage), M-CSF, facteur 1 de stimulation des colonies de macrophages, MCSF)], anticorps monoclonal humanisé; chaîne lourde gamma1 (1-448) [VH humanisé (*Homo sapiens* IGHV4-30-4*01 (85.70%) -(IGHD)-IGHJ4*01) [9.7.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (215) (119-216), charnière (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS (447-448)) (119-448)], (221-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV6-21*02 (80.00%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dimère (227-227":230-230")-bisdisulfure *immunomodulateur, antinéoplasique*
lacnotuzumab	inmunoglobulina G1-kappa, anti-[*Homo sapiens* CSF1 (factor 1 de estimulación de colonias, factor 1 de estimulación de las colonias (macrofago), M-CSF, factor 1 de estimulación de las colonias de macrofagos, MCSF)], anticuerpo monoclonal humanizado; cadena pesada gamma1 (1-448) [VH humanizado (*Homo sapiens* IGHV4-30-4*01 (85.70%) -(IGHD)-IGHJ4*01) [9.7.11] (1-118) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (215) (119-216), charnière (217-231), CH2 (232-341), CH3 E12 (357), M14 (359) (342-446), CHS (447-448)) (119-448)], (221-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV6-21*02 (80.00%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dímero (227-227":230-230")-bisdisulfuro *inmunomodulador, antineoplásico*

1831128-32-5

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLQESGPG LVKPSQTLSL TCTVSDYSIT SDYAWNWIRQ FPGKGLEWMG  50
YISYSGSTSY NPSLKSRITI SRDTSKNQFS LQLNSVTAAD TAVYYCASFD 100
YAHAMDYWGQ GTTVTVSSAS TKGPSVFPLA PSSKSTSGGT AALGCLVKDY 150
FPEPVTVSWN SGALTSGVHT FPAVLQSSGL YSLSSVVTVP SSSLGTQTYI 200
CNVNHKPSNT KVDKRVEPKS CDKTHTCPPC PAPELLGGPS VFLFPPKPKD 250
TLMISRTPEV TCVVVDVSHE DPEVKFNWYV DGVEVHNAKT KPREEQYNST 300
YRVVSVLTVL HQDWLNGKEY KCKVSNKALP APIEKTISKA KGQPREPQVY 350
TLPPSREEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD 400
SDGSFFLYSK LTVDKSRWQQ GNVFSCSVMH EALHNHYTQK SLSLSPGK   448
```

Light chain / Chaîne légère / Cadena ligera

```
DIVLTQSPAF LSVTPGEKVT FTCQASQSIG TSIHWYQQKT DQAPKLLIKY  50
ASESISGIPS RFSGSGSGTD FTLTISSVEA EDAADYYCQQ INSWPTTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 145-201 262-322 368-426
22"-96" 145"-201" 262"-322" 368"-426"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 221-214' 221"-214'"
Inter-H-H (h 11, h 14) 227-227" 230-230"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4 :
298, 298"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados.

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales

H CHS K2 C-terminal lysine clipping:
448, 448"

lanabecestatum

lanabecestat

(1,4-*trans*,1'*R*)-4-methoxy-5"-methyl-6'-[5-(prop-1-yn-1-yl)pyridin-3-yl]-3'*H*-dispiro[cyclohexane-1,2'-indene-1',2"-imidazol]-4"-amine
beta-secretase inhibitor

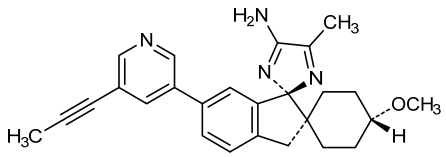
lanabécestat

(1,4-*trans*,1'*R*)-4-méthoxy-5"-méthyl-6'-[5-(prop-1-yn-1-yl)pyridin-3-yl]-3'*H*-dispiro[cyclohexane-1,2'-indène-1',2"-imidazol]-4"-amine
inhibiteur de la secrétase bêta

lanabecestat

(1,4-*trans*,1'*R*)-4-metoxi-5"-metil-6'-[5-(prop-1-in-1-il)piridin-3-il]-3'*H*-dispiro[ciclohexano-1,2'-indeno-1',2"-imidazol]-4"-amino
inhibidor de la secretasa beta

$C_{26}H_{28}N_4O$ 1383982-64-6



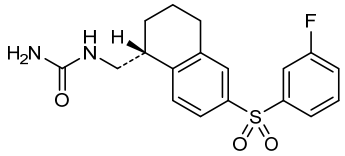
landipirdinum

landipirdine — {[(1*R*)-6-(3-fluorobenzenesulfonyl)-1,2,3,4-tetrahydronaphthalen-1-yl]methyl}urea
serotonin receptor antagonist

landipirdine — {[(1*R*)-6-(3-fluorobenzènesulfonyl)-1,2,3,4-tétrahydronaphthalèn-1-yl]méthyl}urée
antagoniste des récepteurs de la sérotonine

landipirdina — {[(1*R*)-6-(3-fluorobencenosulfonil)-1,2,3,4-tetrahidronaftalen-1-il]metil}urea
antagonista del receptor de la serotonina

$C_{18}H_{19}FN_2O_3S$ 1000308-25-7



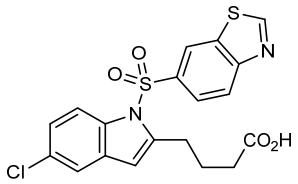
lanifibranorum

lanifibranor — 4-[1-(1,3-benzothiazole-6-sulfonyl)-5-chloro-1*H*-indol-2-yl]butanoic acid
peroxisome proliferator-activated receptors (PPAR) agonist

lanifibranor — acide 4-[1-(1,3-benzothiazole-6-sulfonyl)-5-chloro-1*H*-indol-2-yl]butanoïque
agoniste des récepteurs activés par les proliférateurs de peroxysomes

lanifibranor — ácido 4-[1-(1,3-benzotiazol-6-sulfonil)-5-cloro-1*H*-indol-2-il]butanoico
agonista de los receptores activados por los factores de proliferación de peroxisomas

$C_{19}H_{15}ClN_2O_4S_2$ 927961-18-0



larcaviximabum #

larcaviximab — immunoglobulin G1-kappa, anti-[*Zaire ebolavirus* (Zaire Ebola virus (EBOV)) glycoprotein], chimeric monoclonal antibody;
gamma1 heavy chain (1-449) [*Mus musculus* VH (IGHV1-42*01 (85.70%) -(IGHD) -IGHJ3*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (216) (120-217), hinge (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS (448-449) (120-449)], (222-214')-disulfide with kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV12-44*01 (96.80%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228":231-231")-bisdisulfide
immunomodulator, antiviral

larcaviximab

immunoglobuline G1-kappa, anti-[glycoprotéine de *Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-449) [VH *Mus musculus* (IGHV1-42*01 (85.70%) -(IGHD) -IGHJ3*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (216) (120-217), charnière (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS (448-449) (120-449)], (222-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA *Mus musculus* (IGKV12-44*01 (96.80%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228'':231-231'')-bisdisulfure
immunomodulateur, antiviral

larcaviximab

inmunoglobulina G1-kappa, anti-[glicoproteína de *Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-449) [VH *Mus musculus* (IGHV1-42*01 (85.70%) -(IGHD) -IGHJ3*01) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (216) (120-217), bisagra (218-232), CH2 (233-342), CH3 D12 (358), L14 (360) (343-447), CHS (448-449) (120-449)], (222-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA *Mus musculus* (IGKV12-44*01 (96.80%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (228-228'':231-231'')-bisdisulfuro
inmunomodulador, antiviral

1792982-56-9

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLQESGPE LEMPGASVKI SCKASGSSFT GFSMNWVKQS NGKSLEWIGN  50
IDTYYGGTTY NQKFKGKATL TVDKSSSTAY MQLKSLTSED SAVYYCARSA 100
YYGSTFAYWG QGTLVTVSAA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKRVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEALHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPAS LSASVGETVT ITCRASENIY SYLAWYQQKQ GKSPQLLVYN  50
AKTLIEGVPS RFSGSGSGTQ FSLKINSLQP EDFGSYFCQH HFGTPFTFGS 100
GTELEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	146-202	263-323	369-427
	22''-96''	146''-202''	263''-323''	369''-427''
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'''-88'''	134'''-194'''		
Inter-H-L (h 5-CL 126)	222-214'	222''-214'''		
Inter-H-H (h 11, h 14)	228-228''	231-231''		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
299, 299''
Complex bi-antennary (G0 > 85%) and high mannose (< 10%) *Nicotiana benthamiana*-type glycans / glycanes de type *Nicotiana benthamiana* bi-antennaires complexes (G0 > 85%) et riches en mannose (< 10%) / glicanos de tipo *Nicotiana benthamiana* biantenarios complejos (G0 > 85%) y alto contenido de manosa (< 10%).

lesinidasum alfa #

lesinidase alfa

human alpha-*N*-acetylglucosaminidase, extracted from egg white of transgenic chickens, glycoform alfa
enzyme replacement therapy

lésinidase alfa

alpha-*N*-acétylglucosaminidase humaine, extraite du blanc d'œuf de poules transgéniques, glycoforme alfa
traitement enzymatique substitutif

lesinidasa alfa

alfa-*N*-acetilglucosaminidasa humana, extraída del huevo blanco de gallinas transgénicas, glicoforma alfa
tratamiento enzimático de sustitución

1522433-40-4

Sequence / séquence / secuencia

```
DEAREAAAVR ALVARLLGPG PAADFSVSVE RALAAKPGLD TYSLGGGGAA 50
RVRVRGSTGV AAAAGLHRYL RDFCGCHVAW SGSQLRLPRP LPAVPGELTE 100
ATPNRYRYYQ NVCTQSYSFV WWDWARWERE IDWMALNGIN LALAWSGQEA 150
IWQRVYLALG LTQAEINEFF TGPAFLAWGR MGNLHTWDGP LPPSWHIKQL 200
YLQHRVLDQM RSFGMTPVLP AFAGHVPEAV TRVFPQVNVT KMGSWGHFNC 250
SYSCSFLLAP EDPIFPIIGS LFLRELIKEF GTDHIYGADT FNEMQPPSSE 300
PSYLAAATTA VYEAMTAVDT EAVWLLQGWL FQHQPQFWGP AQIRAVLGAV 350
PRGRLLVLDL FAESQPVYTR TASFQGQPFI WCMLHNFGGN HGLFGALEAV 400
NGGPEAARLF PNSTMVGTGM APEGISQNEV VYSLMAELGW RKDPVPDLAA 450
WVTSFAARRY GVSHPDAGAA WRLLLRSVYN CSGEACRGHN RSPLVRRPSL 500
QMNTSIWYNR SDVFEAWRLL LTSAPSLATS PAFRYDLLDL TRQAVQELVS 550
LYYEEARSAY LSKELASLLR AGGVLAYELL PALDEVLASD SRFLLGSWLE 600
QARAAAVSEA EADFYEQNSR YQLTLWGPEG NILDYANKQL AGLVANYYTP 650
RWRLFLEALV DSVAQGIPFQ QHQFDKNVFQ LEQAFVLSKQ RYPSQPRGDT 700
VDLAKKIFLK YYPRWVAGSW                                  720
```

Disulfide bridges location
250-254 481-486

Glycosylation sites (N)
Asn-238 Asn-249 Asn-412 Asn-480 Asn-503 Asn-509

lesofavumabum #

lesofavumab

immunoglobulin G1-kappa, anti-[influenza B virus hemagglutinin HA], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-453) [*Homo sapiens* VH (IGHV5-51*01 (89.70%) -(IGHD) -IGHJ5*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (220) (124-221), hinge (222-236), CH2 (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)) (124-453)], (226-219')-disulfide with kappa light chain (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (99.90%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dimer (232-232'':235-235'')-bisdisulfide
immunomodulator, antiviral

lésofavumab

immunoglobuline G1-kappa, anti-[hémagglutinine HA du virus de la grippe B], *Homo sapiens* anticorps monoclonal;

chaîne lourde gamma1 (1-453) [*Homo sapiens* VH (IGHV5-51*01 (89.70%) -(IGHD) -IGHJ5*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (220) (124-221), charnière (222-236), CH2 (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)) (124-453)], (226-219')-disulfure avec la chaîne légère kappa (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (99.90%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dimère (232-232":235-235")-bisdisulfure
immunomodulateur, antiviral

lesofavumab

inmunoglobulina G1-kappa, anti-[hemaglutinina HA del virus de la grippe B], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-453) [*Homo sapiens* VH (IGHV5-51*01 (89.70%) -(IGHD) -IGHJ5*01) [8.8.16] (1-123) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (220) (124-221), bisagra (222-236), CH2 (237-346), CH3 E12 (362), M14 (364) (347-451), CHS (452-453)) (124-453)], (226-219')-disulfuro con la cadena ligera kappa (1'-219') [*Homo sapiens* V-KAPPA (IGKV2-28*01 (99.90%) -IGKJ2*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01, Km3 A45.1 (158), V101 (196) (113'-219')]; dímero (232-232":235-235")-bisdisulfuro
inmunomodulador, antiviral

1807960-57-1

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVQSGAE VKKPGESLKI SCKVSGYSFT SQWIGWVRQM PGKGLEWIGM  50
MYPGESETIY SPSFQGQVTI SADNSISTAY LQWSSLKASD TAIYYCASGP 100
GYSGYHYGWF DTWGQGTLVT VSSASTKGPS VFPLAPSSKS TSGGTAALGC 150
LVKDYFPEPV TVSWNSGALT SGVHTFPAVL QSSGLYSLSS VVTVPSSSLG 200
TQTYICNVNH KPSNTKVDKK VEPKSCDKTH TCPPCPAPEL LGGPSVFLFP 250
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 300
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 350
EPQVYTLPPS REEMTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 400
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 450
PGK                                                     453
```

Light chain / Chaîne légère / Cadena ligera

```
DIVMTQSPLS LPVTPGEPAS ISCRSSQSLL RSNGYNYLDW YLQKPGQSPQ  50
LLIYLGSNRA SGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCMQALQTP 100
YTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK 150
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE 200
VTHQGLSSPV TKSFNRGEC                                    219
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	150-206	267-327	373-431
	22"-96"	150"-206"	267'-327"	373"-431"
Intra-L (C23-C104)	23'-93'	139'-199'		
	23'"-93'"	139'"-199'"		
Inter-H-L (h 5-CL 126)	226-219'	226"-219'"		
Inter-H-H (h 11, h 14)	232-232"	235-235"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
303, 303"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

letolizumabum #

letolizumab

immunoglobulin G1 VH-CH2-CH3 chain, anti-[*Homo sapiens* CD40LG (CD40 ligand, CD40L, tumor necrosis factor ligand superfamily member 5, TNFSF5, tumor necrosis factor related activation protein, TRAP, CD154)], humanized monoclonal antibody;
VH-CH2-CH3 chain (1-353) [humanized VH (IGHV3-23*01 (87.80%) -(IGHD) -IGHJ1*01) [8.8.11] (1-118) -IGHG1*01, G1m1 (CH1 (119-121), hinge C5>S (126), C11>S (132), C14>S (135) (122-136), CH2 P2>S (144) (137-246), CH3 D12 (262), L14 (264) (247-351), CHS (352-353)) (119-353)]; noncovalently linked dimer
immunomodulator

létolizumab

immunoglobuline G1 chaîne VH-CH2-CH3, anti-[*Homo sapiens* CD40LG (CD40 ligand, CD40L, membre 5 de la superfamille des ligands facteurs de nécrose tumorale, TNFSF5, protéine d'activation apparentée au facteur de nécrose tumorale, TRAP, CD154)], anticorps monoclonal humanisé;
chaîne VH-CH2-CH3 (1-353) [VH humanisé (IGHV3-23*01 (87.80%) -(IGHD) -IGHJ1*01) [8.8.11] (1-118) -IGHG1*01, G1m1 (CH1 (119-121), charnière C5>S (126), C11>S (132), C14>S (135) (122-136), CH2 P2>S (144) (137-246), CH3 D12 (262), L14 (264) (247-351), CHS (352-353)) (119-353)]; dimère lié de manière non covalente
immunomodulateur

letolizumab

inmunoglobulina G1 cadena VH-CH2-CH3, anti-[*Homo sapiens* CD40LG (CD40 ligando, CD40L, miembro 5 de la superfamilia de los ligandos factores de necrosis tumoral, TNFSF5, proteína de activación relacionada con el factor de necrosis tumoral, TRAP, CD154)], anticuerpo monoclonal humanizado;
cadena VH-CH2-CH3 (1-353) [VH humanizado (IGHV3-23*01 (87.80%) -(IGHD) -IGHJ1*01) [8.8.11] (1-118) -IGHG1*01, G1m1 (CH1 (119-121), bisagra C5>S (126), C11>S (132), C14>S (135) (122-136), CH2 P2>S (144) (137-246), CH3 D12 (262), L14 (264) (247-351), CHS (352-353)) (119-353)]; dímero unido no covalentemente
inmunomodulador

1450981-87-9

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFN WELMGWARQA PGKGLEWVSG  50
IEGPGDVTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCVKVG 100
KDAKSDYRGQ GTLVTVSSAS TEPKSSDKTH TSPPSPAPEL LGGSSVFLFP 150
PKPKDTLMIS RTPEVTCVVV DVSHEDPEVK FNWYVDGVEV HNAKTKPREE 200
QYNSTYRVVS VLTVLHQDWL NGKEYKCKVS NKALPAPIEK TISKAKGQPR 250
EPQVYTLPPS RDELTKNQVS LTCLVKGFYP SDIAVEWESN GQPENNYKTT 300
PPVLDSDGSF FLYSKLTVDK SRWQQGNVFS CSVMHEALHN HYTQKSLSLS 350
PGK                                                     353
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 167-227 273-331
22"-96" 167"-227" 273'-331"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
203, 203"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

losatuxizumabum #

losatuxizumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB) delta 2-7 isoform (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], humanized and chimeric monoclonal antibody;
humanized gamma1 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV4-30-4*01 (81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), hinge (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfide with chimeric kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (225-225'':228-228'')-bisdisulfide
immunomodulator, antineoplastic

losatuxizumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB) isoforme delta 2-7 (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], anticorps monoclonal humanisé et chimérique;
chaîne lourde gamma1 humanisée (1-446) [VH humanisé (*Homo sapiens* IGHV4-30-4*01(81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), charnière (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfure avec la chaîne légère kappa chimérique (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (225-225'':228-228'')-bisdisulfure
immunomodulateur, antinéoplasique

losatuxizumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* EGFR (receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB) isoforma delta 2-7 (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], anticuerpo monoclonal humanizado y quimérico;
cadena pesada gamma1 humanizada (1-446) [VH humanizado (*Homo sapiens* IGHV4-30-4*01(81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), bisagra (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfuro con la cadena ligera kappa quimérica (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (225-225'':228-228'')-bisdisulfuro
inmunomodulador, antineoplásico

1801544-27-3

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLQESGPG LVKPSQTLSL TCTVSGYSIS RDFAWNWIRQ PPGKGLEWMG  50
YISYNGNTRY QPSLKSRITI SRDTSKNQFF LKLNSVTAAD TATYYCVTAS 100
RGFPYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200
VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS MSVSVGDRVT ITCHSSQDIN SNIGWLQQKP GKSFKGLIYH  50
GTNLDDGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCVQ YAQFPWTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	143-199	260-320	366-424
	22"-96"	143"-199"	260"-320"	366"-424"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)	219-214'	219"-214'"		
Inter-H-H (h 11, h 14)	225-225"	228-228"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
446, 446"

losatuxizumabum vedotinum #
losatuxizumab vedotin

immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB) delta 2-7 isoform (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], humanized and chimeric monoclonal antibody conjugated to auristatin E;
humanized gamma1 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV4-30-4*01 (81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), hinge (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfide with chimeric kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (225-225":228-228")-bisdisulfide; conjugated, on an average of 3 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker
For the *vedotin* part, please refer to the document *"INN for pharmaceutical substances: Names for radicals, groups and others"*.*
immunomodulator, antineoplastic

losatuxizumab védotine	immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB) isoforme delta 2-7 (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], anticorps monoclonal humanisé et chimérique conjugué à l'auristatine E; chaîne lourde gamma1 humanisée (1-446) [VH humanisé (*Homo sapiens* IGHV4-30-4*01(81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), charnière (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfure avec la chaîne légère kappa chimérique (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (225-225'':228-228'')-bisdisulfure; conjugué, sur 3 cystéinyl en moyenne, au monométhylauristatine E (MMAE), via un linker clivable de type maléimidocaproyl-valyl-citrullinyl-p-aminobenzyloxycarbonyl (mc-val-cit-PABC) Pour la partie *védotine*, veuillez-vous référer au document *"INN for pharmaceutical substances: Names for radicals, groups and others"*. *immunomodulateur, antinéoplasique*
losatuxizumab vedotina	inmunoglobulina G1-kappa, anti-[*Homo sapiens* EGFR (receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB) isoforma delta 2-7 (delta2-7EGFR, de2-7 EGFR, EGFRvIII)], anticuerpo monoclonal humanizado y quimérico conjugado con la auristatina E; cadena pesada gamma1 humanizada (1-446) [VH humanizado (*Homo sapiens* IGHV4-30-4*01(81.40%) -(IGHD) -IGHJ4*01) [9.7.9] (1-116) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (213) (117-214), bisagra (215-229), CH2 (230-339), CH3 E12 (355), M14 (357) (340-444), CHS (445-446)) (117-446)], (219-214')-disulfuro con la cadena ligera kappa quimérica (1'-214') [*Mus musculus* V-KAPPA (IGKV14-100*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (225-225'':228-228'')-bisdisulfuro; conjugado en 3 restos cisteinil, por término medio, con monometilauristatina E (MMAE), mediante un enlace de tipo maleimidocaproil-valil-citrulinil-p-aminobenziloxicarbonil (mc-val-cit-PABC) escindible Para la fracción *vedotina*, se pueden referir al documento *"INN for pharmaceutical substances: Names for radicals, groups and others"*. *inmunomodulador, antineoplásico*

1685249-67-5

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLQESGPG LVKPSQTLSL TCTVSGYSIS RDFAWNWIRQ PPGKGLEWMG  50
YISYNGNTRY QPSLKSRITI SRDTSKNQFF LKLNSVTAAD TATYYCVTAS 100
RGFPYWGQGT LVTVSSASTK GPSVFPLAPS SKSTSGGTAA LGCLVKDYFP 150
EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS SLGTQTYICN 200
VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF LFPPKPKDTL 250
MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP REEQYNSTYR 300
VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG QPREPQVYTL 350
PPSREEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD 400
GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL SLSPGK     446
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS MSVSVGDRVT ITCHSSQDIN SNIGWLQQKP GKSFKGLIYH  50
GTNLDDGVPS RFSGSGSGTD YTLTISSLQP EDFATYYCVQ YAQFPWTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 143-199 260-320 366-424
22"-96" 143"-199" 260"-320" 366"-424"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126)* 219-214' 219"-214'"
Inter-H-H (h 11, h 14) * 225-225" 228-228"
*Two or three of the inter-chain disulfide bridges are not present, an average of 3 cysteinyl being conjugated each via a thioether bond to a drug linker.
*Deux ou trois des ponts disulfures inter-chaînes ne sont pas présents, 3 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif.
*Faltan dos o tres puentes disulfuro inter-catenarios, una media de 3 cisteinil está conjugada a conectores de principio activo.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
296, 296"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
446, 446"

lutetium (^{177}Lu) oxodotreotidum
lutetium (^{177}Lu) oxodotreotide

hydrogen [*N*-{[4,7,10-tris(carboxylato-κ*O*-methyl)-1,4,7,10-tetraazacyclododecan-1-yl-κ^4*N*^{1},*N*^{4},*N*^{7},*N*^{10}]acetyl-κ*O*}-D-phenylalanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-threonyl-L-cysteinyl-L-threoninato cyclic (2→7)-disulfide(4-)](^{177}Lu)lutetate(1-)
antineoplastic

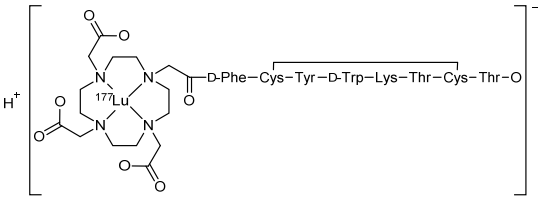
lutécium (^{177}Lu) oxodotréotide

hydrogéno[(2→7)-disulfure cyclique de *N*-{[4,7,10-tris(carboxylato-κ*O*-méthyl)-1,4,7,10-tétraazacyclododécan-1-yl-κ^4*N*^{1},*N*^{4},*N*^{7},*N*^{10}]acétyl-κ*O*}-D-phénylalanyl-L-cystéinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-thréonyl-L-cystéinyl-L-thréoninato(4-)](^{177}Lu)lutétate(1-)
antinéoplasique

lutecio (^{177}Lu) oxodotreotida

hidrógeno[(2→7)-disulfuro cíclico de *N*-{[4,7,10-tris(carboxilato-κ*O*-metil)-1,4,7,10-tetraazaciclododecano-1-il-κ^4*N*^{1},*N*^{4},*N*^{7},*N*^{10}]acetil-κ*O*}-D-fenilalanil-L-cisteinil-L-tirosil-D-triptofil-L-lisil-L-treonil-L-cisteinil-L-treoninato(4-)](^{177}Lu)lutetato(1-)
antineoplásico

$C_{65}H_{87}{}^{177}LuN_{14}O_{19}S_2$ 437608-50-9



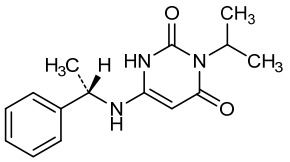
mavacamtenum

mavacamten 6-{[(1*S*)-1-phenylethyl]amino}-3-(propan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione
positive inotropic agent

mavacamten 6-{[(1*S*)-1-phényléthyl]amino}-3-(propan-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione
agent inotrope positif

mavacamten 6-{[(1*S*)-1-feniletil]amino}-3-(propan-2-il)pirimidina-2,4(1*H*,3*H*)-diona
agente inotrópico positivo

$C_{15}H_{19}N_3O_2$ 1642288-47-8



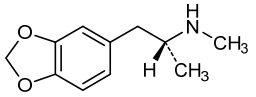
midomafetaminum

midomafetamine *rac*-(2*R*)-1-(2*H*-1,3-benzodioxol-5-yl)-*N*-methylpropan-2-amine
central nervous system stimulant

midomafétamine *rac*-(2*R*)-1-(2*H*-1,3-benzodioxol-5-yl)-*N*-méthylpropan-2-amine
stimulant du système nerveux central

midomafetamina *rac*-(2*R*)-1-(2*H*-1,3-benzodioxol-5-il)-*N*-metilpropan-2-amina
estimulante del sistema nervioso central

$C_{11}H_{15}NO_2$ 42542-10-9

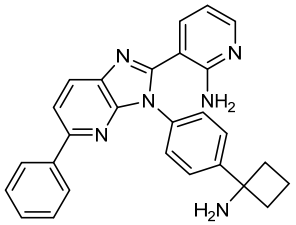


and enantiomer
et énantiomère
y enantiómero

miransertibum

miransertib	3-{3-[4-(1-aminocyclobutyl)phenyl]-5-phenyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyridin-2-amine *antineoplastic*
miransertib	3-{3-[4-(1-aminocyclobutyl)phényl]-5-phényl-3*H*-imidazo[4,5-*b*]pyridin-2-yl}pyridin-2-amine *antinéoplasique*
miransertib	3-{3-[4-(1-aminociclobutil)fenil]-5-fenil-3*H*-imidazo[4,5-*b*]piridin-2-il}piridin-2-amina *antineoplásico*

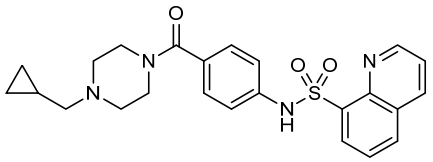
$C_{27}H_{24}N_6$ 1313881-70-7



mitapivatum

mitapivat	*N*-{4-[4-(cyclopropylmethyl)piperazine-1-carbonyl]phenyl}quinoline-8-sulfonamide *pyruvate kinase activator (treatment of pyruvate kinase deficiency)*
mitapivat	*N*-{4-[4-(cyclopropylméthyl)pipérazine-1-carbonyl]phényl}quinoline-8-sulfonamide *activateur de la pyruvate kinase (traitement des déficiences en pyruvate kinase)*
mitapivat	*N*-{4-[4-(ciclopropilmetil)piperazina-1-carbonil]fenil}quinolina-8-sulfonamida *activador de la piruvato kinasa (tratamiento de las deficiencias en piruvato kinasa)*

$C_{24}H_{26}N_4O_3S$ 1260075-17-9



mocravimodum

mocravimod	2-amino-2-[2-(2-chloro-4-{[3-(phenylmethoxy)phenyl]sulfanyl}phenyl)ethyl]propane-1,3-diol *immunomodulator*

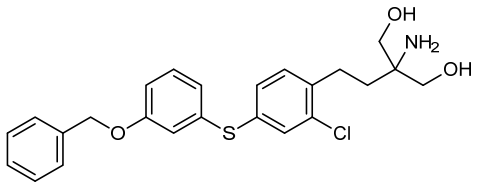
mocravimod

2-amino-2-[2-(2-chloro-4-{[3-(phénylméthoxy)phényl] sulfanyl}phényl)éthyl]propane-1,3-diol
immunomodulateur

mocravimod

2-amino-2-[2-(2-cloro-4-{[3-(fenilmetoxi)fenil] sulfanil}fenil)etil]propano-1,3-diol
inmunomodulador

$C_{24}H_{26}ClNO_3S$ 509092-16-4



molibresibum

molibresib

2-[(4*S*)-6-(4-chlorophenyl)-8-methoxy-1-methyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-4-yl]-*N*-ethylacetamide
antineoplastic

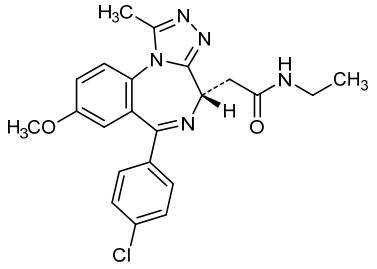
molibrésib

2-[(4*S*)-6-(4-chlorophényl)-8-méthoxy-1-méthyl-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazépin-4-yl]-*N*-éthylacétamide
antinéoplasique

molibresib

2-[(4*S*)-6-(4-clorofenil)-8-metoxi-1-metil-4*H*-[1,2,4]triazolo[4,3-*a*][1,4]benzodiazepin-4-il]-*N*-etilacetamida
antineoplásico

$C_{22}H_{22}ClN_5O_2$ 1260907-17-2



neflamapimodum

neflamapimod

5-(2,6-dichlorophenyl)-2-[(2,4-difluorophenyl)sulfanyl]-6*H*-pyrimido[1,6-*b*]pyridazin-6-one
immunomodulator

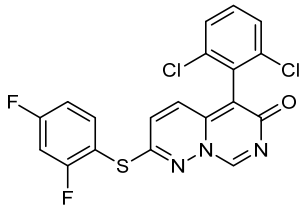
néflamapimod

5-(2,6-dichlorophényl)-2-[(2,4-difluorophényl)sulfanyl]-6*H*-pyrimido[1,6-*b*]pyridazin-6-one
immunomodulateur

neflamapimod

5-(2,6-diclorofenil)-2-[(2,4-difluorofenil)sulfanil]-6*H*-pirimido[1,6-*b*]piridazin-6-ona
inmunomodulador

$C_{19}H_9Cl_2F_2N_3OS$ 209410-46-8



nemiralisibum

nemiralisib

6-(1*H*-indol-4-yl)-4-(5-{[4-(propan-2-yl)piperazin-1-yl]methyl}-1,3-oxazol-2-yl)-1*H*-indazole
antineoplastic

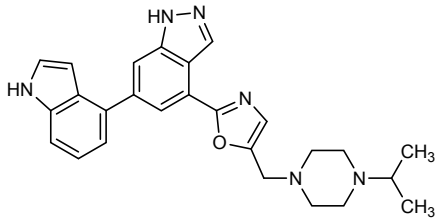
némiralisib

6-(1*H*-indol-4-yl)-4-(5-{[4-(propan-2-yl)pipérazin-1-yl]méthyl}-1,3-oxazol-2-yl)-1*H*-indazole
antinéoplasique

nemiralisib

6-(1*H*-indol-4-il)-4-(5-{[4-(propan-2-il)piperazin-1-il]metil}-1,3-oxazol-2-il)-1*H*-indazol
antineoplásico

$C_{26}H_{28}N_6O$ 1254036-71-9



olamkiceptum #

olamkicept

extracellular domains of glycoprotein 130 (gp130) fused to human immunoglobulin G1 Fc fragment, covalent dimer, produced in Chinese hamster ovary (CHO) cells; human interleukin-6 receptor subunit beta (IL-6RB, interleukin-6 signal transducer, membrane glycoprotein 130, CD130 antigen) precursor-(23-617)-peptide fusion protein with [19-L-alanine(L>A(609)),20-L-α-glutamic acid(L>E(610)),22-L-alanine(G>A(612))]human immunoglobulin G1*03 Fc fragment-(6-232)-peptide, dimer (601-601':604-604')-bisdisulfide
immunosuppressant

olamkicept

domaines extracellulaires de la glycoprotéine 130 (gp130) humaine fusionnés au fragment Fc de l'immunoglobuline G1 humaine, dimère covalent, produit par des cellules ovariennes de hamster chinois (CHO);
sous-unité bêta du récepteur humain de l'interleukine-6 (IL-6RB, transducteur du signal de l'interleukine-6, glycoprotéine130 membranaire, antigène CD130) précurseur-(23-617)-peptide protéine de fusion avec le [19-L-alanine(L>A(609)),20-acide L-α-glutamique (L>E(610)),22-L-alanine(G>A(612))]fragment Fc de l'immunoglobuline G1*03 humaine-(6-232)-peptide, (601-601':604-604')-bisdisulfure du dimère
immunosuppresseur

olamkicept

dominios extracelulares de la glicoproteína 130 (gp130) fusionados con el fragmento Fc de la inmunoglobulina G1 humana, dímero covalente, producido por las células ováricas de hamster chino (CHO);
subunidad beta del receptor humano de la interleukina-6 (IL-6RB, transductor de la señal de la interleukina-6, glicoproteína130 membranaria, antígeno CD130) precursor-(23-617)-péptido proteína de fusión con el [19-L-alanina(L>A(609)),20-ácido L-α-glutámico (L>E(610)),22-L-alanina(G>A(612))]fragmento Fc de la inmunoglobulina G1*03 humana-(6-232)-péptido, (601-601':604-604')-bisdisulfuro del dímero
inmunosupresor

1702282-14-1

Monomer sequence / Séquence du monomère / Secuencia del monómero

```
ELLDPCGYIS PESPVVQLHS NFTAVCVLKE KCMDYFHVNA NYIVWKTNHF 50
TIPKEQYTII NRTASSVTFT DIASLNIQLT CNILTFGQLE QNVYGITIIS 100
GLPPEKPKNL SCIVNEGKKM RCEWDGGRET HLETNFTLKS EWATHKFADC 150
KAKRDTPTSC TVDYSTVYFV NIEVWVEAEN ALGKVTSDHI NFDPVYKVKP 200
NPPHNLSVIN SEELSSILKL TWTNPSIKSV IILKYNIQYR TKDASTWSQI 250
PPEDTASTRS SFTVQDLKPF TEYVFRIRCM KEDGKGYWSD WSEEASGITY 300
EDRPSKAPSF WYKIDPSHTQ GYRTVQLVWK TLPPFEANGK ILDYEVTLTR 350
WKSHLQNYTV NATKLTVNLT NDRYLATLTV RNLVGKSDAA VLTIPACDFQ 400
ATHPVMDLKA FPKDNMLWVE WTTPRESVKK YILEWCVLSD KAPCITDWQQ 450
EDGTVHRTYL RGNLAESKCY LITVTPVYAD GPGSPESIKA YLKQAPPSKG 500
PTVRTKKVGK NEAVLEWDQL PVDVQNGFIR NYTIFYRTII GNETAVNVDS 550
SHTEYTLSSL TSDTLYMVRM AAYTDEGGKD GPEFTFTTPK FAQGEDKTHT 600
CPPCPAPEAE GAPSVFLFPP KPKDTLMISR TPEVTCVVVD VSHEDPEVKF 650
NWYVDGVEVH NAKTKPREEQ YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN 700
KALPAPIEKT ISKAKGQPRE PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS 750
DIAVEWESNG QPENNYKTTP PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC 800
SVMHEALHNH YTQKSLSLSP GK                               822
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

6-32	6'-32'	26-81	26'-81'	112-122	112'-122'	150-160	150'-160'
436-444	436'-444'	601-601'	604-604'	636-696	636'-696'	742-800	742'-800'

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)

Asn-21	Asn-21'	Asn-61	Asn-61'	Asn-109	Asn-109'	Asn-135	Asn-135'
Asn-205	Asn-205'	Asn-357	Asn-357'	Asn-361	Asn-361'	Asn-368	Asn-368'
Asn-531	Asn-531'	Asn-542	Asn-542'	Asn-672	Asn-672'		

oleclumabum #

oleclumab

immunoglobulin G1-lambda1, anti-[*Homo sapiens* NT5E (5'-nucleotidase ecto, 5' nucleotidase, NT5, eN, eNT NTE, CALJA, CD73)], *Homo sapiens* monoclonal antibody; gamma1 heavy chain (1-447) [*Homo sapiens* VH (IGHV3-23*01 (96.90%) -(IGHD) -IGHJ1*01 Q120>R (109)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (214) (118-215), hinge (216-230), CH2 L1.3>F (234), L1.2>E (235), P116>S (331), (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-447)) (118-447)], (220-215')-disulfide with lambda1 light chain (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-44*01 (89.80%) -IGLJ2*01) [8.3.11] (1'-110') -*Homo sapiens* IGLC2*01 (111'-216')]; dimer (226-226'':229-229'')-bisdisulfide
immunomodulator, antineoplastic

oléclumab

immunoglobuline G1-lambda1, anti-[*Homo sapiens* NT5E (5' ecto nucléotidase, 5' nucléotidase, NT5, eN, eNT NTE, CALJA, CD73)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma1 (1-447) [*Homo sapiens* VH (IGHV3-23*01 (96.90%) -(IGHD) -IGHJ1*01 Q120>R (109)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (214) (118-215), charnière (216-230), CH2 L1.3>F (234), L1.2>E (235), P116>S (331), (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-447)) (118-447)], (220-215')-disulfure avec la chaîne légère lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-44*01 (89.80%) -IGLJ2*01) [8.3.11] (1'-110') -*Homo sapiens* IGLC2*01 (111'-216')]; dimère (226-226'':229-229'')-bisdisulfure
immunomodulateur, antinéoplasique

oleclumab

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* NT5E (5' ecto nucleotidasa, 5' nucleotidasa, NT5, eN, eNT NTE, CALJA, CD73)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-447) [*Homo sapiens* VH (IGHV3-23*01 (96.90%) -(IGHD) -IGHJ1*01 Q120>R (109)) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (214) (118-215), bisagra (216-230), CH2 L1.3>F (234), L1.2>E (235), P116>S (331), (231-340), CH3 E12 (356), M14 (358) (341-445), CHS (446-447)) (118-447)], (220-215')-disulfuro con la cadena ligera lambda1 (1'-216') [*Homo sapiens* V-LAMBDA (IGLV1-44*01 (89.80%) -IGLJ2*01) [8.3.11] (1'-110') -*Homo sapiens* IGLC2*01 (111'-216')]; dímero (226-226'':229-229'')-bisdisulfuro
inmunomodulador, antineoplásico

1803176-05-7

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAYSWVRQA PGKGLEWVSA  50
ISGSGGRTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARLG 100
YGRVDEWGRG TLVTVSSAST KGPSVFPLAP SSKSTSGGTA ALGCLVKDYF 150
PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTQTYIC 200
NVNHKPSNTK VDKRVEPKSC DKTHTCPPCP APEFEGGPSV FLFPPKPKDT 250
LMISRTPEVT CVVVDVSHED PEVKFNWYVD GVEVHNAKTK PREEQYNSTY 300
RVVSVLTVLH QDWLNGKEYK CKVSNKALPA SIEKTISKAK GQPREPQVYT 350
LPPSREEMTK NQVSLTCLVK GFYPSDIAVE WESNGQPENN YKTTPPVLDS 400
DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE ALHNHYTQKS LSLSPGK    447
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Light chain / Chaîne légère / Cadena ligera

```
QSVLTQPPSA SGTPGQRVTI SCSGSLSNIG RNPVNWYQQL PGTAPKLLIY  50
LDNLRLSGVP DRFSGSKSGT SASLAISGLQ SEDEADYYCA TWDDSHPGWT 100
FGGGTKLTVL GQPKAAPSVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV 150
AWKADSSPVK AGVETTTPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT 200
HEGSTVEKTV APTECS                                      216
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 144-200 261-321 367-425
22"-96" 144"-200" 261"-321" 367"-425"
Intra-L (C23-C104) 22'-89' 138'-197'
22"'-89"' 138"'-197"'
Inter-H-L (h 5-CL 126) 220-215' 220"-215"'
Inter-H-H (h 11, h 14) 226-226' 229-229"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
297, 297"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

olodanriganum
olodanrigan

(3*S*)-5-(benzyloxy)-2-(diphenylacetyl)-6-methoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid
analgesic

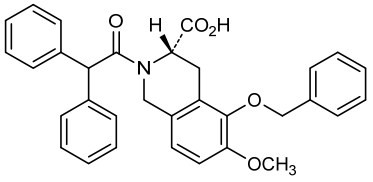
olodanrigan

acide (3*S*)-5-(benzyloxy)-2-(diphénylacétyl)-6-méthoxy-1,2,3,4-tétrahydroisoquinoline-3-carboxylique
analgésique

olodanrigán

ácido (3*S*)-5-(benciloxi)-2-(difenilacetil)-6-metoxi-1,2,3,4-tetrahidroisoquinolina-3-carboxílico
analgésico

$C_{32}H_{29}NO_5$ 1316755-16-4



pegapamodutidum
pegapamodutide

$S^{3.38}$,$S^{3.39}$-bis{(3*RS*)-1-[3-({3-[ω-methoxypoly(oxyethylene-1,2-diyl)]propyl}amino)-3-oxopropyl]-2,5-dioxopyrrolidin-3-yl}-[2-Aib(S>2-methylA),17-Lys(R>K),18-Lys(R>K),21-Glu(D>E),27-Leu(M>L),29-Aib(T>2-methylA),30-Gly(K>G)]human oxyntomodulinyl-L-cysteinyl-L-cysteinamide
oxyntomodulin analogue

pégapamodutide

$S^{3.38}$,$S^{3.39}$-bis{(3*RS*)-1-[3-({3-[ω-méthoxypoly(oxyéthylène-1,2-diyl)]propyl}amino)-3-oxopropyl]-2,5-dioxopyrrolidin-3-yl}-[2-Aib(S>2-méthylA),17-Lys(R>K),18-Lys(R>K),21-Glu(D>E),27-Leu(M>L),29-Aib(T>2-méthylA),30-Gly(K>G)]oxyntomodulinyl humain-L-cystéinyl-L-cystéinamide
analogue de l'oxyntomoduline

pegapamodutida

$S^{3.38}$,$S^{3.39}$-bis{(3*RS*)-1-[3-({3-[ω-metoxipoli(oxietileno-1,2-diil)]propil}amino)-3-oxopropil]-2,5-dioxopirrolidin-3-il}-[2-Aib(S>2-metilA),17-Lys(R>K),18-Lys(R>K),21-Glu(D>E),27-Leu(M>L),29-Aib(T>2-metilA),30-Gly(K>G)]oxintomodulinil humano-L-cisteinil-L-cisteinamida
análogo de la oxintomodulina

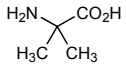
$C_{219}H_{335}N_{63}O_{67}S_2[C_2H_4O]_{2n}$ 1492924-65-8

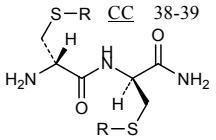
Sequence / Séquence / Secuencia

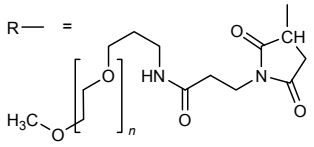
HBQGTFTSDY SKYLDSKKAQ EFVQWLLNBG RNRNNIACC 39

Modified residues / Résidus modifiés / Restos modificados

B(2 , 29)
2-methylalanine (Aib)
(aminoisobutyric acid)







peginterferonum alfacon-2 #

peginterferon alfacon-2

mutated human interferon alpha with pegylated N-terminal GSGGG addition, produced in *Escherichia coli*; *N*-{3-[ω-methoxypoly(oxyethylene)]propyl}glycyl-L-seryltrisglycyl-[22-L-arginine(G>R),76-L-alanine(T>A),78-L-aspartic acid(E>D),79-L-glutamic acid(Q>E),86-L-tyrosine(S>Y),90-L-tyrosine(N>Y),121-L-arginine(K>R),156-L-threonine(K>T),157-L-asparagine(I>N),158-L-leucine(F>L),166-L-aspartic acid(E>D)]human interferon alpha-21 (IFN-alpha-21, interferon alpha-F)
immunomodulator

péginterféron alfacon-2

interféron alpha humain muté pégylé sur l'extrémité N-terminale via un peptide GSGGG, produit par *Escherichia coli*; *N*-{3-[ω-méthoxypoly(oxyéthylène)]propyl}glycyl-L-séryltrisglycyl-[22-L-arginine(G>R),76-L-alanine(T>A),78-L-acide aspartique(E>D),79-L-acide glutamique(Q>E),86-L-tyrosine(S>Y),90-L-tyrosine(N>Y),121-L-arginine(K>R),156-L-thréonine(K>T),157-L-asparagine(I>N),158-L-leucine(F>L),166-L-acide aspartique(E>D)]interféron alpha-21 humain (IFN-alpha-21, interféron alpha-F)
immunomodulateur

peginterferon alfacon-2

interferón alfa humano mutado pegilado en el extremo N-terminal mediante un péptido GSGGG, producido por *Escherichia coli*;
N-{3-[ω-metoxipoli(oxietileno)]propil}glicil-L-seriltrisglicil-[22-L-arginina(G>R),76-L-alanina(T>A),78-L-ácido aspártico(E>D),79-L-ácido glutámico(Q>E),86-L-tirosina(S>Y),90-L-tirosina(N>Y),121-L-arginina(K>R),156-L-treonina(K>T),157-L-asparagina(I>N),158-L-leucina(F>L),166-L-ácido aspártico(E>D)]interferón alfa-21 humano (IFN-alfa-21, interferón alfa-F)

inmunomodulador

1848968-91-1

Sequence / Séquence / Secuencia

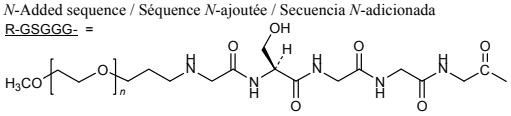
R-GSGGG

```
CDLPQTHSLG NRRALILLAQ MRRISPFSCL KDRHDFGFPQ EEFDGNQFQK  50
AQAISVLHEM IQQTFNLFST KDSSAAWDES LLEKFYTELY QQLNDLEACV 100
IQEVGVEETP LMNVDSILAV RKYFQRITLY LTEKKYSPCA WEVVRAEIMR 200
SFSLSTNLQE RLRRKD                                      216
```

Disulfide bridges location / Position des ponts disulfure / Posición de los puentes disulfuro
1-99 29-139

N-Added sequence / Séquence *N*-ajoutée / Secuencia *N*-adicionada

R-GSGGG- =



porgaviximabum #
porgaviximab

immunoglobulin G1-kappa, anti-[*Zaire ebolavirus* (Zaire Ebola virus (EBOV)) glycoprotein], chimeric monoclonal antibody;
gamma1 heavy chain (1-451) [*Mus musculus* VH (IGHV6-6*02 (95.00%) -(IGHD) -IGHJ4*01) [8.10.12] (1-121) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (218) (122-219), hinge (220-234), CH2 (235-344), CH3 D12 (360), L14 (362) (345-449), CHS (450-451) (122-451)], (224-214')-disulfide with kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV12-46*01 (94.70%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (230-230":233-233")-bisdisulfide
immunomodulator, antiviral

porgaviximab

immunoglobuline G1-kappa, anti-[glycoprotéine de *Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-451) [VH *Mus musculus* (IGHV6-6*02 (95.00%) -(IGHD) -IGHJ4*01) [8.10.12] (1-121) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (218) (122-219), charnière (220-234), CH2 (235-344), CH3 D12 (360), L14 (362) (345-449), CHS (450-451) (122-451)], (224-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA *Mus musculus* (IGKV12-46*01 (94.70%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (230-230":233-233")-bisdisulfure
immunomodulateur, antiviral

porgaviximab

inmunoglobulina G1-kappa, anti-[glicoproteína de *Zaire ebolavirus* (virus Ebola Zaïre (EBOV))], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-451) [VH *Mus musculus* (IGHV6-6*02 (95.00%) -(IGHD) -IGHJ4*01) [8.10.12] (1-121) -*Homo sapiens* IGHG1*01v, G1m17>G1m3, G1m1 (CH1 K120>R (218) (122-219), bisagra (220-234), CH2 (235-344), CH3 D12 (360), L14 (362) (345-449), CHS (450-451) (122-451)], (224-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA *Mus musculus* (IGKV12-46*01 (94.70%) -IGKJ2*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')];
dímero (230-230":233-233")-bisdisulfuro
inmunomodulador, antiviral

1792982-55-8

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLQESGGG LMQPGGSMKL SCVASGFTFS NYWMNWVRQS PEKGLEWVAE  50
IRLKSNNYAT HYAESVKGRF TISRDDSKRS VYLQMNTLRA EDTGIYYCTR 100
GNGNYRAMDY WGQGTSVTVS SASTKGPSVF PLAPSSKSTS GGTAALGCLV 150
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTQ 200
TYICNVNHKP SNTKVDKRVE PKSCDKTHTC PPCPAPELLG GPSVFLFPPK 250
PKDTLMISRT PEVTCVVVDV SHEDPEVKFN WYVDGVEVHN AKTKPREEQY 300
NSTYRVVSVL TVLHQDWLNG KEYKCKVSNK ALPAPIEKTI SKAKGQPREP 350
QVYTLPPSRD ELTKNQVSLT CLVKGFYPSD IAVEWESNGQ PENNYKTTPP 400
VLDSDGSFFL YSKLTVDKSR WQQGNVFSCS VMHEALHNHY TQKSLSLSPG 450
K                                                       451
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPAS LSVSVGETVS ITCRASENIY SSLAWYQQKQ GKSPQLLVYS  50
ATILADGVPS RFSGSGSGTQ YSLKINSLQS EDFGTYYCQH FWGTPYTFGG 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-98 148-204 265-325 371-429
22"-98" 148"-204" 265"-325" 371"-429"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 224-214' 224"-214'"
Inter-H-H (h 11, h 14) 230-230" 233-233"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
301, 301"
Complex bi-antennary (G0 > 85%) and high mannose (< 10%) *Nicotiana benthamiana*-type glycans / glycanes de type *Nicotiana benthamiana* bi-antennaires complexes (G0 > 85%) et riches en mannose (< 10%) / glicanos de tipo *Nicotiana benthamiana* biantenarios complejos (G0 >85%) y alto contenido de manosa (< 10%).

praliciguatum

praliciguat

1,1,1,3,3,3-hexafluoro-2-{[(5-fluoro-2-{1-[(2-fluorophenyl)methyl]-5-(1,2-oxazol-3-yl)-1*H*-pyrazol-3-yl}pyrimidin-4-yl)amino]methyl}propan-2-ol
guanylate cyclase activator, vasodilator

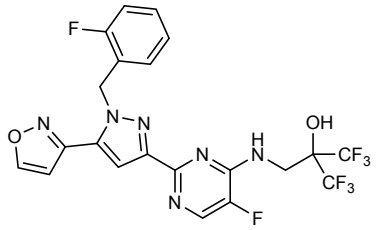
praliciguat

1,1,1,3,3,3-hexafluoro-2-{[(5-fluoro-2-{1-[(2-fluorophényl)méthyl]-5-(1,2-oxazol-3-yl)-1*H*-pyrazol-3-yl}pyrimidin-4-yl)amino]méthyl}propan-2-ol
activateur de la guanylate cyclase, vasodilatateur

praliciguat

1,1,1,3,3,3-hexafluoro-2-{[(5-fluoro-2-{1-[(2-fluorofenil)metil]-5-(1,2-oxazol-3-il)-1*H*-pirazol-3-il}pirimidin-4-il)amino]metil}propan-2-ol
activador de la guanilato ciclasa, vasodilatador

$C_{21}H_{14}F_8N_6O_2$ 1628730-49-3



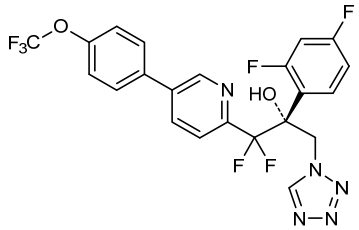
quilseconazolum

quilseconazole (2*R*)-2-(2,4-difluorophenyl)-1,1-difluoro-3-(1*H*-tetrazol-1-yl)-1-{5-[4-(trifluoromethoxy)phenyl]pyridin-2-yl}propan-2-ol
antifungal

quilséconazole (2*R*)-2-(2,4-difluorophényl)-1,1-difluoro-3-(1*H*-tétrazol-1-yl)-1-{5-[4-(trifluorométhoxy)phényl]pyridin-2-yl}propan-2-ol
antifongique

quilseconazol (2*R*)-2-(2,4-difluorofenil)-1,1-difluoro-3-(1*H*-tetrazol-1-il)-1-{5-[4-(trifluorometoxi)fenil]piridin-2-il}propan-2-ol
antifúngico

$C_{22}H_{14}F_7N_5O_2$ 1340593-70-5



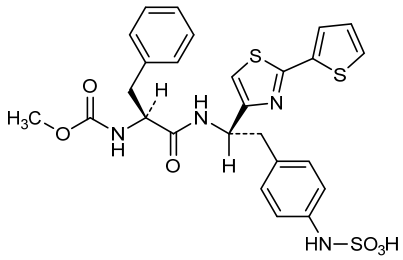
razuprotafibum

razuprotafib *N*-(4-{(2*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-phenylpropanamido}-2-[2-(thiophen-2-yl)-1,3-thiazol-4-yl]ethyl}phenyl)sulfamic acid
protein tyrosine phosphatase ß (HPTPß) inhibitor

razuprotafib acide *N*-(4-{(2*S*)-2-{(2*S*)-2-[(méthoxycarbonyl)amino]-3-phénylpropanamido}-2-[2-(thiophén-2-yl)-1,3-thiazol-4-yl]éthyl}phényl)sulfamique
inhibiteur de la protéine tyrosine phosphatase ß

razuprotafib ácido *N*-(4-{(2*S*)-2-{(2*S*)-2-[(metoxicarbonil)amino]-3-fenilpropanamido}-2-[2-(tiofen-2-il)-1,3-tiazol-4-il]etil}fenil)sulfámico
inhibidor de la proteína tirosina fosfatasa ß

$C_{26}H_{26}N_4O_6S_3$ 1008510-37-9



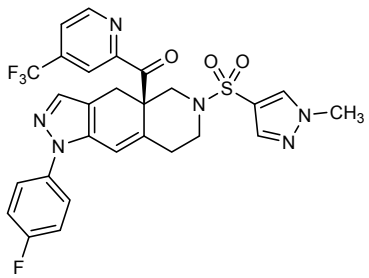
relacorilantum

relacorilant [(4a*R*)-1-(4-fluorophenyl)-6-(1-methyl-1*H*-pyrazole-4-sulfonyl)-1,4,5,6,7,8-hexahydro-4a*H*-pyrazolo[3,4-*g*]isoquinolin-4a-yl][4-(trifluoromethyl)pyridin-2-yl]methanone
glucocorticoid receptor antagonist

rélacorilant [(4a*R*)-1-(4-fluorophényl)-6-(1-méthyl-1*H*-pyrazole-4-sulfonyl)-1,4,5,6,7,8-hexahydro-4a*H*-pyrazolo[3,4-*g*]isoquinoléin-4a-yl][4-(trifluorométhyl)pyridin-2-yl]méthanone
antagoniste du récepteur des glucocorticoïdes

relacorilant [(4a*R*)-1-(4-fluorofenil)-6-(1-metil-1*H*-pirazolo-4-sulfonil)-1,4,5,6,7,8-hexahidro-4a*H*-pirazolo[3,4-*g*]isoquinolein-4a-il][4-(trifluorometil)piridin-2-il]metanona
antagonista del receptor de los glucocorticoides

$C_{27}H_{22}F_4N_6O_3S$ 1496510-51-0



remdesivirum

remdesivir 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,5-anhydro-D-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate
antiviral

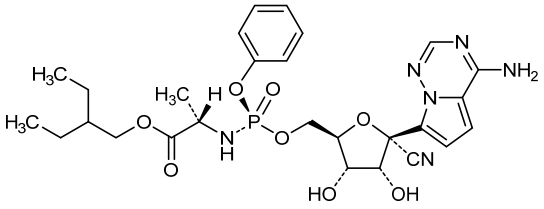
remdésivir

N-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-2,5-anhydro-D-altrononitril-6-*O*-yl]phénoxyphosphoryl}-L-alaninate de 2-éthylbutyle
antiviral

remdesivir

N-{(*S*)-[2-*C*-(4-aminopirrolo[2,1-*f*][1,2,4]triazin-7-il)-2,5-anhidro-D-altrononitril-6-*O*-il]fenoxifosforil}-L-alaninato de 2-etilbutilo
antiviral

$C_{27}H_{35}N_6O_8P$ 1809249-37-3



ribaxamasum #

ribaxamase

truncated beta-lactamase from *Bacillus licheniformis* (penicillinase)-peptide (des-1-lysine-small exopenicillinase), produced in *Escherichia coli*; [262-asparagine(D>N)]beta-lactamase from *Bacillus licheniformis* (penicillinase, EC=3.5.2.6)-(18-281)-peptide
enzyme

ribaxamase

peptide tronqué de la bêta-lactamase de *Bacillus licheniformis* (pénicillinase) (dès-1-lysine-exopénicillinase racourcie), produit par *Escherichia coli;* [262-asparagine(D>N)]*Bacillus licheniformis* bêta-lactamase (pénicillinase, EC=3.5.2.6)-(18-281)-peptide
enzyme

ribaxamasa

péptido truncado de la beta-lactamasa de *Bacillus licheniformis* (penicilinasa) (des-1-lisina-exopenicilinasa acortada), producido por *Escherichia coli;* [262-asparagina(D>N)]*Bacillus licheniformis* beta-lactamasa (penicilinasa, EC=3.5.2.6)-(18-281)-péptido
enzima

1792207-66-9

```
                  TEM KDDFAKLEEQ FDAKLGIFAL DTGTNRTVAY 50
RPDERFAFAS TIKALTVGVL LQQKSIEDLN QRITYTRDDL VNYNPITEKH 100
VDTGMTLKEL ADASLRYSDN AAQNLILKQI GGPESLKKEL RKIGDEVTNP 150
ERFEPELNEV NPGETQDTST ARALVTSLRA FALEDKLPSE KRELLIDWMK 200
RNTTGDALIR AGVPDGWEVA DKTGAASYGT RNDIAIIWPP KGDPVVLAVL 250
SSRDKKDAKY DNKLIAEATK VVMKALNMNG K                    281
```

rimigorsenum

rimigorsen

all-P-ambo-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methylguanosine

promotion of functional dystrophin synthesis

rimigorsen

tout-P-ambo-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthylguanosine

stimulation de la synthèse de dystrophine fonctionnelle

rimigorsén

todo-P-ambo-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metilguanosina

estimulación de la síntesis de distrofina funcional

$C_{207}H_{274}N_{67}O_{123}P_{19}S_{19}$ 1196915-71-5

(3'-5')-(P-thio)[Um-Cm-Am-Gm-Cm-Um-Um-Cm-Um-Gm-Um-Um-Am-Gm-Cm-Cm-Am-Cm-Um-Gm]

Legend: m as suffix = 2'-*O*-methyl

rislenemdazum

rislenemdaz

(4-methylphenyl)methyl (3*S*,4*R*)-3-fluoro-4-{[(pyrimidin-2-yl)amino]methyl}piperidine-1-carboxylate

N-methyl-D-aspartate (NMDA) receptor antagonist

rislénemdaz

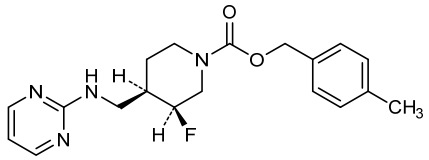
(3*S*,4*R*)-3-fluoro-4-{[(pyrimidin-2-yl)amino]méthyl}pipéridine-1-carboxylate de (4-méthylphényl)méthyle

antagoniste des récepteurs du NMDA

rislenemdaz

(3*S*,4*R*)-3-fluoro-4-{[(pirimidin-2-il)amino]metil}piperidina-1-carboxilato de (4-metilfenil)metilo
antagonista del receptor de NMDA

$C_{19}H_{23}FN_4O_2$ 808732-98-1



sampeginterferonum beta-1a #
sampeginterferon beta-1a

$N^{2.1}$-{-4-[ω-methoxypoly(oxyethylene)]butyl}-human interferon beta (fibroblast interferon, IFN-beta), expressed in Chinese hamster ovary (CHO) cells, glycoform alfa
immunomodulator

sampèginterféron bêta-1a

$N^{2.1}$-{-4-[ω-méthoxypoly(oxyéthylène)]butyl}-interféron bêta humain (interféron fibroblastique, IFN-bêta), produit par des cellules ovariennes de hamsters chinois (CHO), glycoforme alfa
immunomodulateur

sampeginterferón beta-1a

$N^{2.1}$-{-4-[ω-metoxipoli(oxietileno)]butil}-interferón beta humano (interferón fibroblástico, IFN-beta), producido por las células ováricas de hamster chino (CHO), glicoforma alfa
inmunomodulador

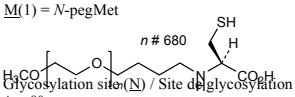
1796570-07-4

Sequence / Séquence / Secuencia

```
MSYNLLGFLQ RSSNFQCQKL LWQLNGRLEY CLKDRMNFDI PEEIKQLQQF  50
QKEDAALTIY EMLQNIFAIF RQDSSSTGWN ETIVENLLAN VYHQINHLKT 100
VLEEKLEKED FTRGKLMSSL HLKRYYGRIL HYLKAKEYSH CAWTIVRVEI 150
LRNFYFINRL TGYLRN                                      166
```

Disulfide bridge location / Position du pont disulfure / Posición del puente disulfuro
31-141
Modified residue / Résidu modifié / Resto modificado

M(1) = *N*-pegMet



Glycosylation site (N) / Site de glycosylation (N) / Posición de glicosilación (N)
Asn-80

selicrelumabum #
selicrelumab

immunoglobulin G2-kappa, anti-[*Homo sapiens* CD40 (tumor necrosis factor receptor superfamily member 5, TNFRSF5)], *Homo sapiens* monoclonal antibody; gamma2 heavy chain (1-452) [*Homo sapiens* VH (IGHV1-2*02 (98.00%) -(IGHD) -IGHJ4*01) [8.8.19] (1-126) -*Homo sapiens* IGHG2*01, G2m.. (CH1 (127-224), hinge (225-236), CH2 V45.1 (287) (237-345), CH3 (346-450), CHS (451-452)) (127-452)], (140-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-12*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228'':229-229'':232-232'':235-235'')-tetrakisdisulfide
immunomodulator, antineoplastic

sélicrélumab

immunoglobuline G2-kappa, anti-[*Homo sapiens* CD40 (membre 5 de la superfamille des récepteurs du TNF, TNFRSF5)], *Homo sapiens* anticorps monoclonal; chaîne lourde gamma2 (1-452) [*Homo sapiens* VH (IGHV1-2*02 (98.00%) -(IGHD) -IGHJ4*01) [8.8.19] (1-126) -*Homo sapiens* IGHG2*01, G2m.. (CH1 (127-224), charnière (225-236), CH2 V45.1 (287) (237-345), CH3 (346-450), CHS (451-452)) (127-452)], (140-214')-disulfure avec la chaîne légère (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-12*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228":229-229":232-232":235-235")-tétrakisdisulfure
immunomodulateur, antinéoplasique

selicrelumab

inmunoglobulina G2-kappa, anti-[*Homo sapiens* CD40 (miembro 5 de la superfamilia de los receptores del TNF, TNFRSF5)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma2 (1-452) [*Homo sapiens* VH (IGHV1-2*02 (98.00%) -(IGHD) -IGHJ4*01) [8.8.19] (1-126) -*Homo sapiens* IGHG2*01, G2m.. (CH1 (127-224), bisagra (225-236), CH2 V45.1 (287) (237-345), CH3 (346-450), CHS (451-452)) (127-452)], (140-214')-disulfuro con la cadena ligera (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-12*01 (94.70%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (228-228":229-229":232-232":235-235")-tetrakisdisulfuro
inmunomodulador, antineoplásico

1622140-49-1

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT GYYMHWVRQA PGQGLEWMGW  50
INPDSGGTNY AQKFQGRVTM TRDTSISTAY MELNRLRSDD TAVYYCARDQ 100
PLGYCTNGVC SYFDYWGQGT LVTVSSASTK GPSVFPLAPC SRSTSESTAA 150
LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS 200
NFGTQTYTCN VDHKPSNTKV DKTVERKCCV ECPPCPAPPV AGPSVFLFPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVQF NWYVDGVEVH NAKTKPREEQ 300
FNSTFRVVSV LTVVHQDWLN GKEYKCKVSN KGLPAPIEKT ISKTKGQPRE 350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PMLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
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Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS VSASVGDRVT ITCRASQGIY SWLAWYQQKP GKAPNLLIYT  50
ASTLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ ANIFPLTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 105-110 153-209 266-326 372-430
22"-96" 105"-210" 153"-206" 266"-326" 372"-430"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (CH1 10-CL 126) 140-214' 140"-214'"
Inter-H-H (h 4, h 5, h 8, h 11) 228-228" 229-229" 232-232" 235-235"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

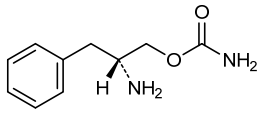
solriamfetolum

solriamfetol — (2*R*)-2-amino-3-phenylpropyl carbamate
dopamine and norepinephrine reuptake inhibitor

solriamfétol — carbamate de (2*R*)-2-amino-3-phénylpropyle
inhibiteur de la recapture de la dopamine et de la norépinephrine

solriamfetol — carbamato de (2*R*)-2-amino-3-fenilpropilo
inhibidor de la recaptación de dopamina y de norepinefrina

$C_{10}H_{14}N_2O_2$ 178429-62-4



suvratoxumabum #

suvratoxumab — immunoglobulin G1-kappa, anti-[*Staphylococcus aureus* alpha toxin (AT, alpha-hemolysin, alpha-HL, hly, hla)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-452) [*Homo sapiens* VH (IGHV3-13*01 (96.90%) -(IGHD) -IGHJ6*01) [8.7.16] (1-122) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (219) (123-220), hinge (221-235), CH2 M15.1>Y (257), S16>T (259), T18>E (261) (236-345), CH3 E12 (361), M14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfide with kappa light chain (1'-213') [*Homo sapiens* V-KAPPA (IGKV1-5*03 (96.80%) -IGKJ1*01) [6.3.8] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dimer (231-231":234-234")-bisdisulfide
immunomodulator

suvratoxumab — immunoglobuline G1-kappa, anti-[*Staphylococcus aureus* toxine alpha (AT, hémolysine alpha, HL-alpha, hly, hla)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-452) [*Homo sapiens* VH (IGHV3-13*01 (96.90%) -(IGHD) -IGHJ6*01) [8.7.16] (1-122) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (219) (123-220), charnière (221-235), CH2 M15.1>Y (257), S16>T (259), T18>E (261) (236-345), CH3 E12 (361), M14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfure avec la chaîne légère kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV1-5*03 (96.80%) -IGKJ1*01) [6.3.8] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dimère (231-231":234-234")-bisdisulfure
immunomodulateur

suvratoxumab — inmunoglobulina G1-kappa, anti-[*Staphylococcus aureus* toxina alfa (AT, hemolisina alfa, HL-alfa, hly, hla)], *Homo sapiens* anticuerpo monoclonal;

cadena pesada gamma1 (1-452) [*Homo sapiens* VH (IGHV3-13*01 (96.90%) -(IGHD) -IGHJ6*01) [8.7.16] (1-122) -*Homo sapiens* IGHG1*03, G1m3, nG1m1 (CH1 R120 (219) (123-220), bisagra (221-235), CH2 M15.1>Y (257), S16>T (259), T18>E (261) (236-345), CH3 E12 (361), M14 (363) (346-450), CHS (451-452)) (123-452)], (225-213')-disulfuro con la cadena ligera kappa (1'-213') [*Homo sapiens* V-KAPPA (IGKV1-5*03 (96.80%) -IGKJ1*01) [6.3.8] (1'-106') -*Homo sapiens* IGKC*01, Km3 A45.1 (152), V101 (190) (107'-213')]; dímero (231-231''':234-234'')-bisdisulfuro
inmunomodulador

1629620-18-3

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SHDMHWVRQA TGKGLEWVSG  50
IGTAGDTYYP DSVKGRFTIS RENAKNSLYL QMNSLRAGDT AVYYCARDRY 100
SPTGHYYGMD VWGQGTTVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP 250
KPKDTLYITR EPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ 300
YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
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Light chain / Chaîne légère / Cadena ligera

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DIQMTQSPST LSASVGDRVT ITCRASQSIS SWLAWYQQKP GKAPKLLIYK  50
ASSLESGVPS RFSGSGSGTE FTLTISSLQP DDFATYYCKQ YADYWTFGQG 100
TKVEIKRTVA APSVFIFPPS DEQLKSGTAS VVCLLNNFYP REAKVQWKVD 150
NALQSGNSQE SVTEQDSKDS TYSLSSTLTL SKADYEKHKV YACEVTHQGL 200
SSPVTKSFNR GEC                                          213
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-95 149-205 266-326 372-430
22''-95'' 149''-205'' 266'-326'' 372''-430''
Intra-L (C23-C104) 23'-88' 133'-193'
23'''-88''' 133'''-193'''
Inter-H-L (h 5-CL 126) 225-213' 225''-213'''
Inter-H-H (h 11, h 14) 231-231'' 234-234''

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302''
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

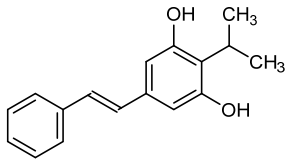
tapinarofum

tapinarof — 5-[(1*E*)-2-phenylethen-1-yl]-2-(propan-2-yl)benzene-1,3-diol
anti-inflammatory

tapinarof — 5-[(1*E*)-2-phényléthén-1-yl]-2-(propan-2-yl)benzène-1,3-diol
anti-inflammatoire

tapinarof — 5-[(1*E*)-2-fenileten-1-il]-2-(propan-2-il)benceno-1,3-diol
antiinflamatorio

$C_{17}H_{18}O_2$ 79338-84-4



teprasiranum

teprasiran

guanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-adenosine duplex with 2'-*O*-methyluridylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-methylcytidine
inhibition of cellular tumor antigen p53 expression

téprasiran

guanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-cytidylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-adénosine duplex avec la 2'-*O*-méthyluridylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylguanylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyladénylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-adénylyl-(3'→5')-2'-*O*-méthyluridylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylcytidylyl-(3'→5')-uridylyl-(3'→5')-2'-*O*-méthylcytidine
inhibition de l'expression de l'antigène tumoral cellulaire p53

teprasirán

guanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-citidilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-citidilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-citidilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-adenosina dúplex con la 2'-*O*-metiluridilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-guanilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilguanilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiladenilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-adenilil-(3'→5')-2'-*O*-metiluridilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilcitidilil-(3'→5')-uridilil-(3'→5')-2'-*O*-metilcitidina
inhibición de la expresión del antígeno tumoral celular p53

$C_{380}H_{484}N_{140}O_{262}P_{36}$ 1231737-88-4

(3'→5') G–A–G–A–A–U–A–U–U–U–C–A–C–C–C–U–U–C–A

(5'→3') C–U–C–U–U–A–U–A–A–A–G–U–G–G–G–A–A–G–U

Legend X : 2'-*O*-methyl (Xm)

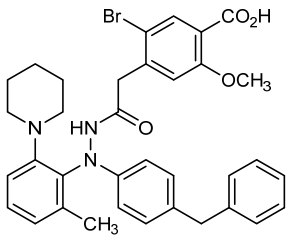
teslexivirum

teslexivir — 4-(2-{2-(4-benzylphenyl)-2-[2-methyl-6-(piperidin-1-yl)phenyl]hydrazin-1-yl}-2-oxoethyl)-5-bromo-2-methoxybenzoic acid
antiviral

teslexivir — acide 4-(2-{2-(4-benzylphényl)-2-[2-méthyl-6-(pipéridin-1-yl)phényl]hydrazin-1-yl}-2-oxoéthyl)-5-bromo-2-méthoxybenzoïque
antiviral

teslexivir — ácido 4-(2-{2-(4-bencilfenil)-2-[2-metil-6-(piperidin-1-il)fenil]hidrazin-1-il}-2-oxoetil)-5-bromo-2-metoxibenzoico
antiviral

$C_{35}H_{36}BrN_3O_4$ 1075798-37-6



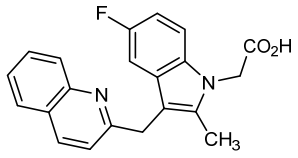
timapiprantum

timapiprant — {5-fluoro-2-methyl-3-[(quinolin-2-yl)methyl]-1*H*-indol-1-yl}acetic acid
prostaglandin receptor antagonist

timapiprant — acide {5-fluoro-2-méthyl-3-[(quinolin-2-yl)méthyl]-1*H*-indol-1-yl}acétique
antagoniste du récepteur des prostaglandines

timapiprant — ácido {5-fluoro-2-metil-3-[(quinolin-2-il)metil]-1*H*-indol-1-il}acético
agonista del receptor de las prostaglandinas

$C_{21}H_{17}FN_2O_2$ 851723-84-7



timigutuzumabum #

timigutuzumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB2 (epidermal growth factor receptor 2, receptor tyrosine-protein kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], humanized monoclonal antibody; gamma1 heavy chain (1-450) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (217) (121-218), hinge (219-233), CH2 (234-343), CH3 D12 (359), L14 (361), G110 (434) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (229-229":232-232")-bisdisulfide
immunomodulator, antineoplastic

timigutuzumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* ERBB2 (récepteur 2 du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticorps monoclonal humanisé;
chaîne lourde gamma1 (1-450) [VH humanisé (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (217) (121-218), charnière (219-233), CH2 (234-343), CH3 D12 (359), L14 (361), G110 (434) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (229-229":232-232")-bisdisulfure
immunomodulateur, antinéoplasique

timigutuzumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* ERBB2 (receptor 2 del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticuerpo monoclonal humanizado;
cadena pesada gamma1 (1-450) [VH humanizado (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (217) (121-218), bisagra (219-233), CH2 (234-343), CH3 D12 (359), L14 (361), G110 (434) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (229-229":232-232")-bisdisulfuro
inmunomodulador, antineoplásico

1665274-14-5

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR  50
IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG 100
GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEGLHNHYT QKSLSLSPGK 450
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Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS  50
ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	147-203	264-324	370-428
	22"-96"	147"-203"	264"-324"	370"-428"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)	223-214'	223"-214'"		
Inter-H-H (h 11, h 14)	229-229"	232-232"		

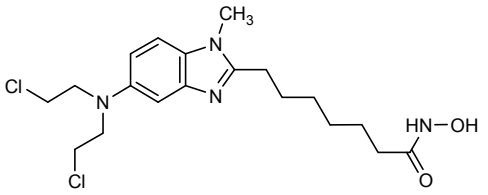
N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
300, 300"

Produced in human erythroleukemia (K562) cell line. Glycans are mostly biantennary complex glycans with <30% high mannose and high degree of galactosylation. They have <40% sialylated glycans, <50% fucosylated glycans, <50% bisecting N-acetylglucosamine bearing glycans and no N-glycolylneuraminic acid/ Produit par des cellules humaines d'érythroleucémie (K562). Les glycanes sont principalement complexes bi-antennaires avec <30% de mannose de haut poinds moléculaire et de haut degré de galactosylation. Ils contiennent <40% de glycanes sialylés, <50% de glycanes fucosylés, <50% de glycanes présentant des N-acétylglucosamines bisectionnées et pas d'acide N-glycolylneuraminique. / Producido en la línea celular humana de eritroleucemia (K562). Los glicanos son principalmente glicanos complejos biantenarios con <30% de manosas de alto peso molecular y alto grado de galactosilación. Contienen <40% de glicanos sialilados, <50% de fucosilación, <50% de glicanos que llevan N-acetilglucosaminas biseccionadas y ningún ácido N-glicolilneuramínico

tinostamustinum

tinostamustine	7-{5-[bis(2-chloroethyl)amino]-1-methyl-1*H*-benzimidazol-2-yl}-*N*-hydroxyheptanamide *antineoplastic*
tinostamustine	7-{5-[bis(2-chloroéthyl)amino]-1-méthyl-1*H*-benzimidazol-2-yl}-*N*-hydroxyheptanamide *antinéoplasique*
tinostamustina	7-{5-[bis(2-cloroetil)amino]-1-metil-1*H*-benzoimidazol-2-il}-*N*-hidroxiheptanamida *antineoplásico*

$C_{19}H_{28}Cl_2N_4O_2$ 1236199-60-2



tivanisiranum

tivanisiran

duplex of adenylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-adenylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-adenylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-adenosine and uridylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-uridylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')uridine
analgesic

tivanisiran

duplex d'adénylyl-(3'→5')-adénylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-adénylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-adénylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-adénosine et d'uridylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-adénylyl-(5'→3')-guanylyl-(5'→3')-adénylyl-(5'→3')-adénylyl-(5'→3')-guanylyl-(5'→3')-adénylyl-(5'→3')-uridylyl-(5'→3')-guanylyl-(5'→3')-adénylyl-(5'→3')-adénylyl-(5'→3')-guanylyl-(5'→3')uridine
analgésique

tivanisirán

dúplex de adenilil-(3'→5')-adenilil-(3'→5')-guanilil-(3'→5')-citidilil-(3'→5')-guanilil-(3'→5')-citidilil-(3'→5')-adenilil-(3'→5')-uridilil-(3'→5')-citidilil-(3'→5')-uridilil-(3'→5')-uridilil-(3'→5')-citidilil-(3'→5')-uridilil-(3'→5')-adinilil-(3'→5')-citidilil-(3'→5')-uridilil-(3'→5')-uridilil-(3'→5')-citidilil-(3'→5')-adenosina y de uridilil-(5'→3')-uridilil-(5'→3')-citidilil-(5'→3')-guanilil-(5'→3')-citidilil-(5'→3')-guanilil-(5'→3')-uridilil-(5'→3')-adinilil-(5'→3')-guanilil-(5'→3')-adenilil-(5'→3')-adenilil-(5'→3')-guanilil-(5'→3')-adenilil-(5'→3')-uridilil-(5'→3')-guanilil-(5'→3')-adenilil-(5'→3')-adenilil-(5'→3')-guanilil-(5'→3')uridina
analgésico

$C_{361}H_{447}N_{141}O_{262}P_{19}$ 1848224-71-4

(3'-5')-[A-A-G-C-G-C-A-U-C-U-U-C-U-A-C-U-U-C-A]
° °
(5'-3')-[U-U-C-G-C-G-U-A-G-A-A-G-A-U-G-A-A-G-U]

tomuzotuximabum #

tomuzotuximab

immunoglobulin G1-kappa, anti-[*Homo sapiens* EGFR (epidermal growth factor receptor, receptor tyrosine-protein kinase erbB-1, ERBB1, HER1, HER-1, ERBB)], chimeric monoclonal antibody;
gamma1 heavy chain (1-448) [*Mus musculus* VH (IGHV2-2*03 -(IGHD) -IGHJ3*01 A128>T (119)) [8.7.13] (1-119) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (216) (120-217), hinge (218-232), CH2 (233-342), CH3 D12 (358), L14 (360), G110 (433) (343-447), CHS (448-449)) (120-449)], (222-214')-disulfide with kappa light chain (1'-214') [*Mus musculus* V-KAPPA (IGKV5-48*01 -IGKJ5*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (228-228'':231-231'')-bisdisulfide
immunomodulator, antineoplastic

tomuzotuximab

immunoglobuline G1-kappa, anti-[*Homo sapiens* EGFR (récepteur du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erb-1, ERBB1, HER1, HER-1, ERBB)], anticorps monoclonal chimérique;
chaîne lourde gamma1 (1-448) [*Mus musculus* VH (IGHV2-2*03 -(IGHD) -IGHJ3*01 A128>T (119)) [8.7.13] (1-119) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (216) (120-217), charnière (218-232), CH2 (233-342), CH3 D12 (358), L14 (360), G110 (433) (343-447), CHS (448-449)) (120-449)], (222-214')-disulfure avec la chaîne légère kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV5-48*01 -IGKJ5*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (228-228'':231-231'')-bisdisulfure
immunomodulateur, antinéoplasique

tomuzotuximab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* EGFR (receptor del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erb-1, ERBB1, HER1, HER-1, ERBB)], anticuerpo monoclonal quimérico;
cadena pesada gamma1 (1-448) [*Mus musculus* VH (IGHV2-2*03 -(IGHD) -IGHJ3*01 A128>T (119)) [8.7.13] (1-119) -*Homo sapiens* IGHG1*07p, G1m17,1,2 (CH1 K120 (216) (120-217), bisagra (218-232), CH2 (233-342), CH3 D12 (358), L14 (360), G110 (433) (343-447), CHS (448-449)) (120-449)], (222-214')-disulfuro con la cadena ligera kappa (1'-214') [*Mus musculus* V-KAPPA (IGKV5-48*01 -IGKJ5*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (228-228'':231-231'')-bisdisulfuro
inmunomodulador, antineoplásico

1646321-00-7

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLKQSGPG LVQPSQSLSI TCTVSGFSLT NYGVHWVRQS PGKGLEWLGV  50
IWSGGNTDYN TPFTSRLSIN KDNSKSQVFF KMNSLQSNDT AIYYCARALT 100
YYDYEFAYWG QGTLVTVSTA STKGPSVFPL APSSKSTSGG TAALGCLVKD 150
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTQTY 200
ICNVNHKPSN TKVDKKVEPK SCDKTHTCPP CPAPELLGGP SVFLFPPKPK 250
DTLMISRTPE VTCVVVDVSH EDPEVKFNWY VDGVEVHNAK TKPREEQYNS 300
TYRVVSVLTV LHQDWLNGKE YKCKVSNKAL PAPIEKTISK AKGQPREPQV 350
YTLPPSRDEL TKNQVSLTCL VKGFYPSDIA VEWESNGQPE NNYKTTPPVL 400
DSDGSFFLYS KLTVDKSRWQ QGNVFSCSVM HEGLHNHYTQ KSLSLSPGK  449
```

Light chain / Chaîne légère / Cadena ligera

```
DILLTQSPVI LSVSPGERVS FSCRASQSIG TNIHWYQQRT NGSPRLLIKY  50
ASESISGIPS RFSGSGSGTD FTLSINSVES EDIADYYCQQ NNNWPTTFGA 100
GTKLELKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-95	146-202	263-323	369-427
	22"-95"	146"-202"	263"-323"	369"-427"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88"'	134'"-194"'		
Inter-H-L (h 5-CL 126)	222-214'	222"-214"'		
Inter-H-H (h 11, h 14)	228-228"	231-231"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
L V-KAPPA N47:
41', 41"
Unglycosylated
H VH N97:
88, 88"
H CH2 N84.4:
299, 299"

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales
H CHS K2 C-terminal lysine clipping:
449, 449"

Produced in human erythroleukemia (K562) cell line. Glycans are mostly biantennary complex glycans with <30% high mannose and high degree of galactosylation. They have >5% sialylated glycans, <50% fucosylation, >10% bisecting N-acetylglucosamine bearing glycans and no N-glycolylneuraminic acid. Produit par des cellules humaines d'érythroleucémie (K562). Les glycanes sont principalement complexes bi-antennaires avec <30% de mannose de haut poinds moléculaire et de haut degré de galactosilation. Ils contiennent >5% de glycanes sialylés, <50% de fucosylation, >10% de glycanes présentant des N-acétylglucosamines bisectionnées et pas d'acide N-glycolylneuraminique. Producido en la línea celular humana de eritroleucemia (K562). Los glicanos son principalmente glicanos complejos biantenarios con <30% de manosas de alto peso molecular y alto grado de galactosilación. Contienen >5% de glicanos sialilados, <50% de fucosilación, >10% de glicanos que llevan N-acetilglucosaminas biseccionadas y ningún ácido N-glicolilneuramínico.

trastuzumabum deruxtecanum #
trastuzumab deruxtecan

immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB2 (epidermal growth factor receptor 2, receptor tyrosine-protein kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], humanized monoclonal antibody conjugated to deruxtecan, comprising a linker and a camptothecin derivative;

	gamma1 heavy chain (1-450) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ4*02) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (217) (121-218), hinge (219-233),CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.20%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 8 cysteinyl, to deruxtecan, comprising a linker and a camptothecin derivative *immunomodulator, antineoplastic*
trastuzumab déruxtécan	immunoglobuline G1-kappa, anti-[*Homo sapiens* ERBB2 (récepteur 2 du facteur de croissance épidermique, récepteur tyrosine-protéine kinase erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticorps monoclonal humanisé conjugué au déruxtécan, comprenant un linker et un dérivé de la camptothécine; chaîne lourde gamma1 (1-450) [VH humanisé (*Homo sapiens* (IGHV3-66-*01 (81.60%) -(IGHD)-IGHJ4*02) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (217) (121-218), charnière (219-233),CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfure avec la chaîne légère kappa (1'-214') [V-KAPPA humanisé (*Homo sapiens* IGKV1-39*01 (86.20%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dimère (229-229":232-232")-bisdisulfure, conjugué sur une moyenne de 8 cystéines au déruxtécan, comprenant un linker et un dérivé de la camptothécine *immunomodulateur, antinéoplasique*
trastuzumab deruxtecán	inmunoglobulina G1-kappa, anti-[*Homo sapiens* ERBB2 (receptor 2 del factor de crecimiento epidérmico, receptor tirosina-proteína kinasa erbB-2, EGFR2, HER2, HER-2, p185c-erbB2, NEU, CD340)], anticuerpo monoclonal humanizado conjugado con deruxtecán, que comprende un linker y un derivado de la camptotecina; cadena pesada gamma1 (1-450) [VH humanizado (*Homo sapiens* (IGHV3-66-*01 (81.60%) -(IGHD)-IGHJ4*02) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03v, G1m3>G1m17, nG1m1 (CH1 R120>K (217) (121-218), bisagra (219-233),CH2 (234-343), CH3 E12 (359), M14 (361) (344-448), CHS (449-450)) (121-450)], (223-214')-disulfuro con la cadena ligera kappa (1'-214') [V-KAPPA humanizado (*Homo sapiens* IGKV1-39*01 (86.20%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1, V101 (108'-214')]; dímero (229-229":232-232")-bisdisulfuro, conjugado en 8 cisteínas, por término medio, con deruxtecán, que comprende un linker y un derivado de la camptotecina *inmunomodulador, antineoplásico*

1826843-81-5

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFNIK DTYIHWVRQA PGKGLEWVAR  50
IYPTNGYTRY ADSVKGRFTI SADTSKNTAY LQMNSLRAED TAVYYCSRWG 100
GDGFYAMDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK 150
DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT 200
YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP 250
KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN 300
STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ 350
VYTLPPSREE MTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV 400
LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK 450
```

Light chain / Chaîne légère / Cadena ligera

```
DIQMTQSPSS LSASVGDRVT ITCRASQDVN TAVAWYQQKP GKAPKLLIYS  50
ASFLYSGVPS RFSGSRSGTD FTLTISSLQP EDFATYYCQQ HYTTPPTFGQ 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104) 22-96 147-203 264-324 370-428
22"-96" 147"-203" 264"-324" 370"-428"

Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"

Inter-H-L (h 5-CL 126)* 223-214' 223"-214'"

Inter-H-H (h 11, h 14)* 229-229" 232-232"

*The four inter-chain disulfide bridges are not present, an average of 8 cysteinyl being conjugated each via a thioether bond to a drug linker. *Les quatre ponts disulfures inter-chaînes ne sont pas présents, 8 cystéinyl en moyenne étant chacun conjugué via une liaison thioéther à un linker-principe actif. *Faltan los cuatro puentes disulfuro inter-catenarios, una media de 8 cisteinil está conjugada a conectores de principio activo.

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación

H CH2 N84.4 :
300, 300"

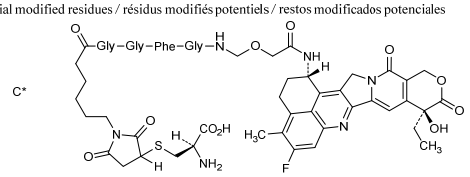
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

Peak area ratio / rapport des aires des pics / relación de áreas de los picos: G0F > 75%, G1F/G1F' <12%, G2F <1%, M5 <2%

Other post-translational modifications / Autres modifications post-traductionnelles / Otras modificaciones post-traduccionales

H CHS K2 C-terminal lysine clipping:
450, 450"

Potential modified residues / résidus modifiés potentiels / restos modificados potenciales



tropifexorum

tropifexor

2-[(1*R*,3*r*,5*S*)-3-({5-cyclopropyl-3-[2-(trifluoromethoxy) phenyl]-1,2-oxazol-4-yl}methoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylic acid
farnesoid X receptor agonist

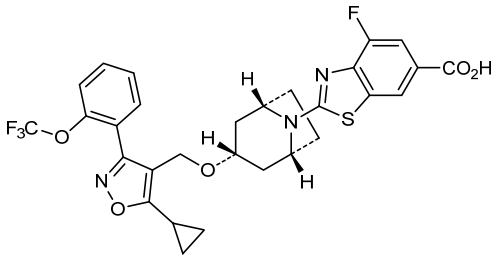
tropifexor

acide 2-[(1*R*,3*r*,5*S*)-3-({5-cyclopropyl-3-[2-(trifluorométhoxy)phényl]-1,2-oxazol-4-yl}méthoxy)-8-azabicyclo[3.2.1]octan-8-yl]-4-fluoro-1,3-benzothiazole-6-carboxylique
agoniste du récepteur farnésoide X

tropifexor

ácido 2-[(1*R*,3*r*,5*S*)-3-({5-ciclopropil-3-[2-(trifluorometoxi) fenil]-1,2-oxazol-4-il}metoxi)-8-azabiciclo[3.2.1]octan-8-il]-4-fluoro-1,3-benzotiazol-6-carboxílico
agonista del receptor farnesoide X

$C_{29}H_{25}F_4N_3O_5S$ 1383816-29-2



tulinerceptum #

tulinercept

human tumor necrosis factor receptor superfamily member 1B (TNF receptor 2, TNF receptor II, p75, p80 TNF-alpha receptor, CD120b antigen)-(1-235)-peptide (extracellular domain), fusion protein with heavy chain constant region of the human immunoglobulin gamma1*03-(99-330)-peptide (Fc fragment) (236-467), fusion protein with C-terminal endoplasmic reticulum hexapeptide Ser-Glu-Lys-Asp-Glu-Leu; dimer (240-240':246-246':249-249')-trisdisulfide, produced in *Nicotiana tabacum* Bright Yellow-2 cells
immunomodulator

tulinercept

membre 1B de la superfamille des récepteurs du facteur de nécrose tumorale humain (TNF récepteur 2, TNF récepteur II, p75, p80 TNF-alpha récepteur, antigène CD120b)-(1-235)-peptide (domaine extracellulaire), protéine de fusion avec la partie constante de la chaîne lourde de l'immunoglobuline G1 humaine gamma1*03-(99-330)-peptide (fragment Fc) (236-467), protéine de fusion avec l'hexapeptide C-terminal du réticulum endoplasmique Ser-Glu-Lys-Asp-Glu-Leu; (240-240':246-246':249-249')-trisdisulfure du dimère, produit par la cellule de *Nicotiana tabacum* Bright Yellow-2
immunomodulateur

tulinercept

miembro 1B de la superfamilia de los receptores del factor de necrosis tumoral humano (TNF receptor2, TNF receptor II, p75, p80 TNF-alfa receptor, antígeno CD120b)-(1-235)-péptido (dominio extracelular), proteína de fusión con la parte constante de la cadena pesada de la inmunoglobulina humana gamma1*03-(99-330)-péptido (fragmento Fc) (236-467), proteína de fusión con el hexapéptido C-terminal del retículo endoplásmico Ser-Glu-Lys-Asp-Glu-Leu; (240-240':246-246':249-249')-trisdisulfuro del dímero, producido por la célula de *Nicotiana tabacum* Bright Yellow-2
inmunomodulador

1623177-41-2

Monomer sequence / Séquence du monomère/ Secuencia del monómero

```
LPAQVAFTPY APEPGSTCRL REYYDQTAQM CCSKCSPGQH AKVFCTKTSD 50
TVCDSCEDST YTQLWNWVPE CLSCGSRCSS DQVETQACTR EQNRICTCRP 100
GWYCALSKQE GCRLCAPLRK CRPGFGVARP GTETSDVVCK PCAPGTFSNT 150
TSSTDICRPH QICNVVAIPG NASMDAVCTS TSPTRSMAPG AVHLPQPVST 200
RSQHTQPTPE PSTAPSTSFL LPMGPSPPAE GSTGDEPKSC DKTHTCPPCP 250
APELLGGPSV FLFPPKPKDT LMISRTPEVT CVVVDVSHED PEVKFNWYVD 300
GVEVHNAKTK PREEQYNSTY RVVSVLTVLH QDWLNGKEYK CKVSNKALPA 350
PIEKTISKAK GQPREPQVYT LPPSREEMTK NQVSLTCLVK GFYPSDIAVE 400
WESNGQPENN YKTTPPVLDS DGSFFLYSKL TVDKSRWQQG NVFSCSVMHE 450
ALHNHYTQKS LSLSPGKSEK DEL                              473
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

18-31	18'-31'	32-45	32'-45'	35-53	35'-53'	56-71	56'-71'
74-88	74'-88'	78-96	78'-96'	98-104	98'-104'	112-121	112'-121'
115-139	115'-139'	142-157	142'-157'	163-178	163'-178'	240-240'	246-246'
249-249'	281-341	281'-341'	387-445	387'-445'			

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-149 Asn-171 Asn-317

tulrampatorum

tulrampator

8-cyclopropyl-3-[2-(3-fluorophenyl)ethyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione
antipsychotic

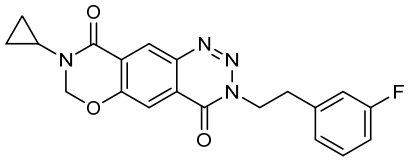
tulrampator

8-cyclopropyl-3-[2-(3-fluorophényl)éthyl]-7,8-dihydro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazine-4,9-dione
antipsychotique

tulrampator

8-ciclopropil-3-[2-(3-fluorofenil)etil]-7,8-dihidro-3*H*-[1,3]oxazino[6,5-*g*][1,2,3]benzotriazina-4,9-diona
antipsicótico

$C_{20}H_{17}FN_4O_3$ 1038984-31-4



valoctocogenum roxaparvovecum #

valoctocogene roxaparvovec

Recombinant adeno-associated virus serotype 5 (rAAV-5) vector encoding the SQ variant of human blood coagulation factor VIII (F8, FVIII), hFVIII-SQ, under the control of a hybrid liver-specific promoter (HLP). The hFVIII-SQ cDNA is B domain deleted with the A2 and A3 domains linked by a DNA sequence encoding a 14-amino acid (SQ) peptide from the B domain.
gene therapy (hemophilia)

valoctocogène roxaparvovec

Vecteur viral adéno-associé de type 5 recombinant (rAAV-5) qui code pour la variante SQ du facteur VIII de coagulation humain (F8, FVIII), hFVIII-SQ, sous le contrôle d'un promoteur hybride spécifique du foie (HLP). L'ADNc du hFVIII-SQ, dont le domaine B a été supprimé, a ses deux domaines A2 et A3 unis par une séquence d'ADN codant pour un peptide de 14 acides aminés (SQ) du domaine B.
thérapie génique (hémophilie)

valoctocogén roxaparvovec

Vector de virus adeno-asociado recombinante del serotipo 5 (rAAV-5) que codifica para la variante SQ del factor de coagulación VIII humano (F8, FVIII), hFVIII-SQ, bajo el control de un promotor híbrido específico de hígado (HLP). El cDNA de hFVIII-SQ tiene el dominio B delecionado y los dominios A2 y A3 unidos por una secuencia de DNA que codifica un péptido de 14 aminoácidos (SQ) del domino B.
terapia génica (hemofilia)

1819334-78-5

varisacumabum #

varisacumab

immunoglobulin G1-kappa, anti-[*Homo sapiens* VEGFA (vascular endothelial growth factor A, VEGF-A, VEGF)], *Homo sapiens* monoclonal antibody;
gamma1 heavy chain (1-456) [*Homo sapiens* VH (IGHV1-24*01 (89.80%) -(IGHD) -IGHJ6*03) [8.8.19] (1-126) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 K120 (223) (127-224), hinge (225-239), CH2 (240-349), CH3 D12 (365), L14 (367) (350-454), CHS (455-456)) (127-456)], (229-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (98.90%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimer (235-235'':238-238'')-bisdisulfide
angiogenesis inhibitor, antineoplastic

varisacumab

immunoglobuline G1-kappa, anti-[*Homo sapiens* VEGFA (facteur de croissance A de l'endothélium vasculaire, VEGF-A, VEGF)], *Homo sapiens* anticorps monoclonal;
chaîne lourde gamma1 (1-456) [VH *Homo sapiens* (IGHV1-24*01 (89.80%) -(IGHD) -IGHJ6*03) [8.8.19] (1-126) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 K120 (223) (127-224), charnière (225-239), CH2 (240-349), CH3 D12 (365), L14 (367) (350-454), CHS (455-456)) (127-456)], (229-214')-disulfure avec la chaîne légère kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (98.90%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dimère (235-235'':238-238'')-bisdisulfure
inhibiteur de l'angiogénèse, antinéoplasique

varisacumab

inmunoglobulina G1-kappa, anti-[*Homo sapiens* VEGFA (factor de crecimiento A del endotelio vascular, VEGF-A, VEGF)], *Homo sapiens* anticuerpo monoclonal;
cadena pesada gamma1 (1-456) [VH *Homo sapiens* (IGHV1-24*01 (89.80%) -(IGHD) -IGHJ6*03) [8.8.19] (1-126) -*Homo sapiens* IGHG1*01, G1m17,1 (CH1 K120 (223) (127-224), bisagra (225-239), CH2 (240-349), CH3 D12 (365), L14 (367) (350-454), CHS (455-456)) (127-456)], (229-214')-disulfuro con la cadena ligera kappa (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-39*01 (98.90%) -IGKJ4*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01, Km3 A45.1 (153), V101 (191) (108'-214')]; dímero (235-235'':238-238'')-bisdisulfuro
inhibidor de la angiogénesis, antineoplásico

1610010-60-0

Heavy chain / Chaîne lourde / Cadena pesada

```
QVQLVQSGAE VKKPGASVKV SCKASGGTFS SYAISWVRQA PGQGLEWMGG  50
FDPEDGETIY AQKFQGRVTM TEDTSTDTAY MELSSLRSED TAVYYCATGR 100
SMVRGVIIPF NGMDVWGQGT TVTVSSASTK GPSVFPLAPS SKSTSGGTAA 150
LGCLVKDYFP EPVTVSWNSG ALTSGVHTFP AVLQSSGLYS LSSVVTVPSS 200
SLGTQTYICN VNHKPSNTKV DKKVEPKSCD KTHTCPPCPA PELLGGPSVF 250
LFPPKPKDTL MISRTPEVTC VVVDVSHEDP EVKFNWYVDG VEVHNAKTKP 300
REEQYNSTYR VVSVLTVLHQ DWLNGKEYKC KVSNKALPAP IEKTISKAKG 350
QPREPQVYTL PPSRDELTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY 400
KTTPPVLDSD GSFFLYSKLT VDKSRWQQGN VFSCSVMHEA LHNHYTQKSL 450
SLSPGK                                                 456
```

Light chain / Chaîne légère / Cadena ligera

```
DIRMTQSPSS LSASVGDRVT ITCRASQSIS SYLNWYQQKP GKAPKLLIYA 50
ASSLQSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ SYSTPLTFGG 100
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Post-translational modifications
Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
Intra-H (C23-C104) 22-96 153-209 270-330 376-434
22"-96" 153"-209" 270'-330" 376"-434"
Intra-L (C23-C104) 23'-88' 134'-194'
23'"-88'" 134'"-194'"
Inter-H-L (h 5-CL 126) 229-214' 229"-214'"
Inter-H-H (h 11, h 14) 235-235" 238-238"

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
306, 306"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

varodarsenum

varodarsen

all-P-ambo-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioadenylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-methyl-*P*-thiouridylyl-(3'→5')-2'-*O*-methylguanosine

promotion of functional dystrophin synthesis

varodarsen

tout-P-ambo-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-

thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thioguanylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thioadénylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-méthyl-*P*-thiouridylyl-(3'→5')-2'-*O*-méthylguanosine
stimulation de la synthèse de dystrophine fonctionnelle

varodarsén

todo-P-ambo-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tioguanilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tioadenilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiocitidilil-(3'→5')-2'-*O*-metil-*P*-tiouridilil-(3'→5')-2'-*O*-metilguanosina
estimulación de la síntesis de distrofina funcional

$C_{258}H_{344}N_{52}O_{84}P_{24}S_{24}$ 1225408-05-8

(3'-5')-(P-thio)[Um-Um-Um-Gm-Cm-Cm-Gm-Cm-Um-Gm-Cm-Cm-Cm-Am-Am-Um-Gm-Cm-Cm-Am-Um-Cm-Cm-Um-Gm]

Legend: m as suffix = 2'-*O*-methyl

voxelotorum

voxelotor

2-hydroxy-6-({2-[1-(propan-2-yl)-1*H*-pyrazol-5-yl]pyridin-3-yl}methoxy)benzaldehyde
hemoglobin S allosteric modulator

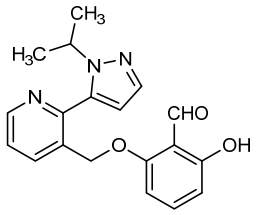
voxélotor

2-hydroxy-6-({2-[1-(propan-2-yl)-1*H*-pyrazol-5-yl]pyridin-3-yl}méthoxy)benzaldéhyde
modulateur allostérique de l'hémoglobine S

voxelotor

2-hidroxi-6-({2-[1-(propan-2-il)-1*H*-pirazol-5-il]piridin-3-il}metoxi)benzaldehido
modulador alostérico de la hemoglobina S

$C_{19}H_{19}N_3O_3$ 1446321-46-5



Names for Radicals and Groups
Some substances for which a proposed international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in a systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international nonproprietary names.

Dénominations applicables aux radicaux et groupes
Certaines substances pour lesquelles une dénomination commune internationale proposée a été établie sont parfois utilisées sous forme de sels ou d'esters. Les radicaux ou groupes correspondants sont alors quelques fois si complexes qu'il est malcommode de les désigner conformément à la nomenclature chimique systématique. Des dénominations communes abrégées ont donc été formées ou choisies pour certains d'entre eux et il est suggéré de les employer avec les dénominations communes internationales proposées.

Denominaciones para Radicales y Grupos
Ciertas sustancias para las cuales hay establecidas una denominación común internacional pueden usarse en forma de sales o de ésteres. Los radicales o grupos correspondientes pueden llegar a tener una composición tan compleja que resulte incómodo referirse a ellos mediante la nomenclatura química sistemática. Las siguientes denominaciones comunes abreviadas han sido ideadas o elegidas para algunos de estos radicales y grupos y se sugiere que se empleen con las denominaciones comunes internacionales propuestas

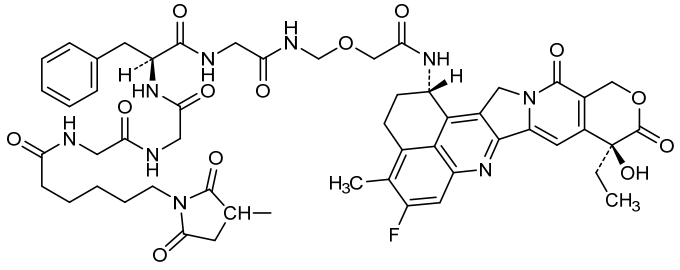
deruxtecanum

deruxtecan (3*RS*)-1-[(10*S*)-10-benzyl-1-{[(1*S*,9*S*)-9-ethyl-5-fluoro-9-hydroxy-4-methyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1*H*,12*H*-benzo[*de*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-1-yl]amino}-1,6,9,12,15,18-hexaoxo-3-oxa-5,8,11,14,17-pentaazatricosan-23-yl]-2,5-dioxopyrrolidin-3-yl

déruxtécan (3*RS*)-1-[(10*S*)-10-benzyl-1-{[(1*S*,9*S*)-9-éthyl-5-fluoro-9-hydroxy-4-méthyl-10,13-dioxo-2,3,9,10,13,15-hexahydro-1*H*,12*H*-benzo[*de*]pyrano[3',4':6,7]indolizino[1,2-*b*]quinolin-1-yl]amino}-1,6,9,12,15,18-hexaoxo-3-oxa-5,8,11,14,17-pentaazatricosan-23-yl]-2,5-dioxopyrrolidin-3-yle

deruxtecán (3*RS*)-1-[(10*S*)-10-bencil-1-{[(1*S*,9*S*)-9-etil-5-fluoro-9-hidroxi-4-metil-10,13-dioxo-2,3,9,10,13,15-hexahidro-1*H*,12*H*-benzo[*de*]pirano[3',4':6,7]indolizino[1,2-*b*]quinolin-1-il]amino}-1,6,9,12,15,18-hexaoxo-3-oxa-5,8,11,14,17-pentaazatricosan-23-il]-2,5-dioxopirrolidin-3-ilo

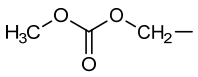
$C_{52}H_{57}FN_9O_{13}$



marboxilum

marboxil	[(methoxycarbonyl)oxy]methyl
marboxil	[(méthoxycarbonyl)oxy]méthyle
marboxilo	[(metoxicarbonil)oxi]metilo

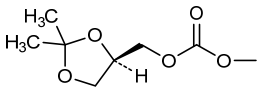
$C_3H_5O_3^{\cdot}$



toniribas

toniribate	*rac*-(2,2-dimethyl-1,3-dioxolan-4-yl)methyl carbonate (ester)
toniribate	carbonate de *rac*-(2,2-diméthyl-1,3-dioxolan-4-yl)méthyle (ester)
toniribato	carbonato de *rac*-(2,2-dimetil-1,3-dioxolan-4-il)metilo (ester)

$C_7H_{11}O_5^{\cdot}$



and enantiomer
et énantiomère
y enantiómero

Electronic structure available on Mednet: http://mednet.who.int/
Structure électronique disponible sur Mednet: http://mednet.who.int/
Estructura electrónica disponible en Mednet: http://mednet.who.int/
* http://www.who.int/medicines/services/inn/publication/en/

AMENDMENTS TO PREVIOUS LISTS
MODIFICATIONS APPORTÉES AUX LISTES ANTÉRIEURES
MODIFICACIONES A LAS LISTAS ANTERIORES

Proposed International Nonproprietary Names (Prop. INN): List 66
Dénominations communes internationales proposées (DCI Prop.): Liste 66
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 66
(WHO Drug Information, Vol. 5, No. 4, 1991)

p. 14	*delete/supprimer/suprimáse* tacrolimus	*insert/insérer/insertese* tacrólimus

Proposed International Nonproprietary Names (Prop. INN): List 69
Dénominations communes internationales proposées (DCI Prop.): Liste 69
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 69
(WHO Drug Information, Vol. 7, No. 2, 1993)

p. 8	*delete/supprimer/suprimáse* sirolimus	*insert/insérer/insertese* sirólimus

Proposed International Nonproprietary Names (Prop. INN): List 81
Dénominations communes internationales proposées (DCI Prop.): Liste 81
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 81
(WHO Drug Information, Vol. 13, No. 2, 1999)

p. 122	*delete/supprimer/suprimáse* pimecrolimús	*insert/insérer/insertese* pimecrólimus

Proposed International Nonproprietary Names (Prop. INN): List 82
Dénominations communes internationales proposées (DCI Prop.): Liste 82
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 82
(WHO Drug Information, Vol. 13, No. 4, 1999)

p. 275	*delete/supprimer/suprimáse* everolimus	*insert/insérer/insertese* everólimus

Proposed International Nonproprietary Names (Prop. INN): List 94
Dénominations communes internationales proposées (DCI Prop.): Liste 94
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 94
(WHO Drug Information, Vol. 19, No. 4, 2005)

p. 351	*delete/supprimer/suprimáse* zotarolimus	*insert/insérer/insertese* zotarólimus
p. 353	*delete/supprimer/suprimáse* temsirolimus	*insert/insérer/insertese* temsirólimus

Proposed International Nonproprietary Names (Prop. INN): List 103
Dénominations communes internationales proposées (DCI Prop.): Liste 103
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 103
(WHO Drug Information, Vol. 24, No. 2, 2010)

p. 175	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	umirolimús	umirólimus

Proposed International Nonproprietary Names (Prop. INN): List 105
Dénominations communes internationales proposées (DCI Prop.): Liste 105
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 105
(WHO Drug Information, Vol. 25, No. 2, 2011)

p. 185	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	olcorolimús	olcorólimus

Proposed International Nonproprietary Names (Prop. INN): List 107
Dénominations communes internationales proposées (DCI Prop.): Liste 107
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 107
(WHO Drug Information, Vol. 25, No. 2, 2011)

p. 161 **antithrombinum gamma #**
antithrombin gamma
antithrombine gamma
antitrombina gamma

replace the structure by the following one
remplacer la structure par la suivante
sustitúyase la estructura por la siguiente

```
HGSPVDICTA KPRDIPMNPM CIYRSPEKKA TEDEGSEQKI PEATNRRVWE 50
LSKANSRFAT TFYQHLADSK NDNDNIFLSP LSISTAFAMT KLGACNDTLQ 100
QLMEVFKFDT ISEKTSDQIH FFFAKLNCRL YRKANKSSKL VSANRLFGDK 150
SLTFNETYQD ISELVYGAKL QPLDFKENAE QSRAAINKWV SNKTEGRITD 200
VIPSEAINEL TVLVLVNTIY FKGLWKSKFS PENTRKELFY KADGESCSAS 250
MMYQEGKFRY RRVAEGTQVL ELPFKGDDIT MVLILPKPEK SLAKVEKELT 300
PEVLQEWLDE LEEMMLVVHM PRFRIEDGFS LKEQLQDMGL VDLFSPEKSK 350
LPGIVAEGRD DLYVSDAFHK AFLEVNEEGS EAAASTAVVI AGRSLNPNRV 400
TFKANRPFLV FIREVPLNTI IFMGRVANPC VK                    432
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro
8-128 21-95 247-430

Glycosylation sites (N) / Sites de glycosylation (N) / Posiciones de glicosilación (N)
Asn-96 Asn-135 Asn-155 Asn-192

α-Sia→3-β-Gal→3-β-Gl-*N*→2-α-Man→6-
β-Man→4-β-Gl-*N*→4-β-Gl-*N*→N
α-Sia→3-β-Gal→3-β-Gl-*N*→2-α-Man→3-

Proposed International Nonproprietary Names (Prop. INN): List 108
Dénominations communes internationales proposées (DCI Prop.): Liste 108
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 108
(WHO Drug Information, Vol. 26, No. 4, 2012)

p. 452	*delete/supprimer/suprimáse*	*insert/insérer/insertese*
	ridaforolimus	ridaforólimus

Proposed International Nonproprietary Names (Prop. INN): List 114
Dénominations communes internationales proposées (DCI Prop.): Liste 114
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 114
(WHO Drug Information, Vol. 29, No. 4, 2015)

p. 523 **enoblituzumabum #**

enoblituzumab — *replace the structure by the following one*
énoblituzumab — *remplacer la structure par la suivante*
enoblituzumab — *sustitúyase la estructura por la siguiente*

Heavy chain / Chaîne lourde / Cadena pesada

```
EVQLVESGGG LVQPGGSLRL SCAASGFTFS SFGMHWVRQA PGKGLEWVAY  50
ISSDSSAIYY ADTVKGRFTI SRDNAKNSLY LQMNSLRDED TAVYYCGRGR 100
ENIYYGSRLD YWGQGTTVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL 150
VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT 200
QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELV GGPSVFLLPP 250
KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPPEEQ 300
YNSTLRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE 350
PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP 400
LVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP 450
GK                                                      452
```

Light chain / Chaîne légère / Cadena ligera

```
DIQLTQSPSF LSASVGDRVT ITCKASQNVD TNVAWYQQKP GKAPKALIYS  50
ASYRYSGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQQ YNNYPFTFGQ 100
GTKLEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV 150
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG 200
LSSPVTKSFN RGEC                                        214
```

Disulfide bridges location / Position des ponts disulfure / Posiciones de los puentes disulfuro

Intra-H (C23-C104)	22-96	149-205	266-326	372-430
	22"-96"	149"-205"	266"-326"	372"-430"
Intra-L (C23-C104)	23'-88'	134'-194'		
	23'"-88'"	134'"-194'"		
Inter-H-L (h 5-CL 126)	225-214'	225"-214'"		
Inter-H-H (h 11, h 14)	231-231"	234-234"		

N-glycosylation sites / Sites de N-glycosylation / Posiciones de N-glicosilación
H CH2 N84.4:
302, 302"
Fucosylated complex bi-antennary CHO-type glycans / glycanes de type CHO bi-antennaires complexes fucosylés / glicanos de tipo CHO biantenarios complejos fucosilados

p. 524 **esaxerenonum**

esaxerenone — *replace the CAS registry number by the following one*
ésaxérénone — *remplacer le numéro dans le registre du CAS par le suivant*
esaxerenona — *sustitúyase el número de registro del CAS por el siguiente*

1632006-28-0

p. 539

delete/supprimer/suprimáse	*insert/insérer/insertese*
lendalizumabum	**olendalizumabum**
lendalizumab	olendalizumab
lendalizumab	olendalizumab
lendalizumab	olendalizumab

p. 540 **leniolisibum**

leniolisib	*replace the chemical name by the following one*
léniolisib	*remplacer le nom chimique par le suivant*
leniolisib	*sustitúyase el nombre químico por el siguiente*

1-[(3*S*)-3-({6-[6-methoxy-5-(trifluoromethyl)pyridin-3-yl]-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4-yl}amino)pyrrolidin-1-yl]propan-1-one

1-[(3*S*)-3-({6-[6-méthoxy-5-(trifluorométhyl)pyridin-3-yl]-5,6,7,8-tétrahydropyrido[4,3-*d*]pyrimidin-4-yl}amino)pyrrolidin-1-yl]propan-1-one

1-[(3*S*)-3-({6-[6-metoxi-5-(trifluorometil)piridin-3-il]-5,6,7,8-tetrahidropirido[4,3-*d*]pirimidin-4-il}amino)pirrolidin-1-il]propan-1-ona

p. 546

delete/supprimer/suprimáse	*insert/insérer/insertese*
nalbuphini sebacas	**dinalbuphini sebacas**
nalbuphine sebacate	dinalbuphine sebacate
sébacate de nalbuphine	sébacate de dinalbuphine
sebacato de nalbufina	sebacato de dinalbufina

p. 555-556

delete/supprimer/suprimáse	*insert/insérer/insertese*
pogalizumabum	**vonlerolizumabum**
pogalizumab	vonlerolizumab
pogalizumab	vonlérolizumab
pogalizumab	vonlerolizumab

p. 559

delete/supprimer/suprimáse	*insert/insérer/insertese*
raxatriginum	**vixotriginum**
raxatrigine	vixotrigine
raxatrigine	vixotrigine
raxatrigina	vixotrigina

p. 564-565

delete/supprimer/suprimáse	*insert/insérer/insertese*
sapelizumabum	**satralizumabum**
sapelizumab	satralizumab
sapélizumab	satralizumab
sapelizumab	satralizumab

Proposed International Nonproprietary Names (Prop. INN): List 115
Dénominations communes internationales proposées (DCI Prop.): Liste 115
Denominaciones Comunes Internacionales Propuestas (DCI Prop.): Lista 115
(WHO Drug Information, Vol. 30, No. 2, 2016)

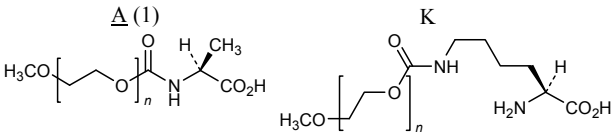
p. 268 **elapegademasum #**

elapegademase — *replace the structure by the following one*
élapégadémase — *remplacer la structure par la suivante*
elapegademasa — *sustitúyase la estructura por la siguiente*

Sequence / Séquence / Secuencia

```
AQTPAFNKPK VELHVHLDGA IKPETILYYG RKRGIALPAD TPEELQNIIG  50
MDKPLSLPEF LAKFDYYMPA IAGSREAVKR IAYEFVEMKA KDGVVYVEVR 100
YSPHLLANSK VEPIPWNQAE GDLTPDEVVS LVNQGLQEGE RDFGVKVRSI 150
LCCMRHQPSW SSEVVELCKK YREQTVVAID LAGDETIEGS SLFPGHVKAY 200
AEAVKSGVHR TVHAGEVGSA NVVKEAVDTL KTERLGHGYH TLEDTTLYNR 250
LRQENMHFEV CPWSSYLTGA WKPDTEHPVV RFKNDQVNYS LNTDDPLIFK 300
STLDTDYQMT KNEMGFTEEE FKRLNINAAK SSFLPEDEKK ELLDLLYKAY 350
GMPSPA                                                  356
```

Potential pegylated residues / Résidus pégylés potentiels / Restos pegilados potenciales



p. 272 **emapalumabum #**

emapalumab — *sustitúyase la descripción por la siguiente*

inmunoglobulina G1-lambda1, anti-[*Homo sapiens* IFNG (interferón gamma, IFN gamma)], *Homo sapiens* anticuerpo monoclonal; cadena pesada gamma1 (1-453) [*Homo sapiens* VH (IGHV3-23*01 -(IGHD) -IGHJ5*02) [8.8.16] (1-123) -IGHG1*03, Gm17,1 (CH1 (124-221), bisagra (222-236), CH2 (237-346), CH3 (347-451), CHS (452-453)) (124-453)], (226-216')-disulfuro con la cadena ligera lambda1 (1'-217') [*Homo sapiens* V-LAMBDA (IGLV6-57*01 (99.00%) -IGLJ3*02) [8.3.10] (1'-111') -IGLC2*01 (112'-217')]; dímero (232-232'':235-235'')-bisdisulfuro

p. 301 **poseltinibum**

poseltinib — *replace the CAS registry number by the following one*
poseltinib — *remplacer le numéro dans le registre du CAS par le suivant*
poseltinib — *sustitúyase el número de registro del CAS por el siguiente*

1353552-97-2

ANNEX 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES[1]

The following procedure shall be followed by the World Health Organization (hereinafter also referred to as "WHO") in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with resolution WHA3.11 of the World Health Assembly, and in the substitution of such names.

Article 1 - Proposals for recommended international nonproprietary names and proposals for substitution of such names shall be submitted to WHO on the form provided therefore. The consideration of such proposals shall be subject to the payment of an administrative fee designed only to cover the corresponding costs of the Secretariat of WHO ("the Secretariat"). The amount of this fee shall be determined by the Secretariat and may, from time to time, be adjusted.

Article 2 - Such proposals shall be submitted by the Secretariat to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, such designated members hereinafter referred to as "the INN Expert Group", for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names for Pharmaceutical Substances", annexed to this procedure[2]. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

Article 3 - Subsequent to the examination provided for in article 2, the Secretariat shall give notice that a proposed international nonproprietary name is being considered.

a) Such notice shall be given by publication in *WHO Drug Information*[3] and by letter to Member States and to national and regional pharmacopoeia commissions or other bodies designated by Member States.

i) Notice shall also be sent to the person who submitted the proposal ("the original applicant") and other persons known to be concerned with a name under consideration.

b) Such notice shall:

i) set forth the name under consideration;

ii) identify the person who submitted the proposal for naming the substance, if so requested by such person;

iii) identify the substance for which a name is being considered;

iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

v) state the authority under which WHO is acting and refer to these rules of procedure.

[1] See Annex 1 in WHO Technical Report Series, No. 581, 1975. The original text was adopted by the Executive Board in resolution EB15.R7 and amended in resolutions EB43.R9 and EB115.R4.

[2] See Annex 2.

[3] Before 1987, lists of international nonproprietary names were published in the *Chronicle of the World Health Organization*.

c) In forwarding the notice, the Secretariat shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by WHO.

Article 4 - Comments on the proposed name may be forwarded by any person to WHO within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

Article 5 - A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information.*

Such objection shall:

i) identify the person objecting;

ii) state his or her interest in the name;

iii) set forth the reasons for his or her objection to the name proposed.

Article 6 - Where there is a formal objection under article 5, WHO may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by WHO of a substitute name or names, a name shall not be selected by WHO as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

Article 7 - Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Secretariat shall give notice in accordance with subsection (a) of article 3 that the name has been selected by WHO as a recommended international nonproprietary name.

Article 8 - In forwarding a recommended international nonproprietary name to Member States under article 7, the Secretariat shall:

a) request that it be recognized as the nonproprietary name for the substance; and

b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

Article 9
a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

i) identify the person making the proposal;

ii) state his or her interest in the proposed substitution; and

iii) set forth the reasons for the proposal; and

iv) describe, and provide documentary evidence regarding the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.

Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).

In addition, the Secretariat shall request comments on the proposal from:

i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and

ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

ii) identify the person who submitted the proposal for substitution (if so requested by such person);

iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

iv) set forth the time within which comments will be received and the person and place to whom they should be directed; and

v) state the authority under which WHO is acting and refer to these rules of procedure.

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing.
Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.

If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).

ANNEX 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES[1]

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. “oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.
For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

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[1] In its Twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, INN in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves the use of a characteristic “stem” indicative of a common property of the members of a group. The reason for, and the implications of, the change are fully discussed.
The guiding principles were updated during the 13th Consultation on nonproprietary names for pharmaceutical substances (Geneva, 27-29 April 1983) (PHARM S/NOM 928 13 May 1983, revised 18 August 1983).

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see General principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.[1] Where a stem is shown without any hyphens it may be used anywhere in the name.

Latin	***English***	
-acum	*-ac*	anti-inflammatory agents, ibufenac derivatives
-adolum	*-adol }*	analgesics
-adol-	*-adol-}*	
-astum	*-ast*	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	*-astine*	antihistaminics
-azepamum	*-azepam*	diazepam derivatives
bol	*bol*	steroids, anabolic
-cain-	*-cain-*	class I antiarrhythmics, procainamide and lidocaine derivatives
-cainum	*-caine*	local anaesthetics
cef-	*cef-*	antibiotics, cefalosporanic acid derivatives
-cillinum	*-cillin*	antibiotics, 6-aminopenicillanic acid derivatives
-conazolum	*-conazole*	systemic antifungal agents, miconazole derivatives
cort	*cort*	corticosteroids, except prednisolone derivatives
-coxibum	*-coxib*	selective cyclo-oxygenase inhibitors
-entanum	*-entan*	endothelin receptor antagonists
gab	*gab*	gabamimetic agents
gado-	*gado-*	diagnostic agents, gadolinium derivatives
-gatranum	*-gatran*	thrombin inhibitors, antithrombotic agents
gest	*gest*	steroids, progestogens
gli	*gli*	antihyperglycaemics
io-	*io-*	iodine-containing contrast media
-metacinum	*-metacin*	anti-inflammatory, indometacin derivatives
-mycinum	*-mycin*	antibiotics, produced by *Streptomyces* strains
-nidazolum	*-nidazole*	antiprotozoal substances, metronidazole derivatives
-ololum	*-olol*	β-adrenoreceptor antagonists
-oxacinum	*-oxacin*	antibacterial agents, nalidixic acid derivatives
-platinum	*-platin*	antineoplastic agents, platinum derivatives
-poetinum	*-poetin*	erythropoietin type blood factors
-pril(at)um	*-pril(at)*	angiotensin-converting enzyme inhibitors
-profenum	*-profen*	anti-inflammatory substances, ibuprofen derivatives
prost	*prost*	prostaglandins
-relinum	*-relin*	pituitary hormone release-stimulating peptides
-sartanum	*-sartan*	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-vaptanum	*-vaptan*	vasopressin receptor antagonists
vin-	*vin- }*	vinca-type alkaloids
-vin-	*-vin-}*	

[1] A more extensive listing of stems is contained in the working document WHO/EMP/RHT/TSN/2013.1 which is regularly updated and can be requested from the INN Programme, WHO, Geneva.

ANNEXE 1

PROCEDURE A SUIVRE EN VUE DU CHOIX DE DENOMINATIONS COMMUNES INTERNATIONALES RECOMMANDEES POUR LES SUBSTANCES PHARMACEUTIQUES[1]

L'Organisation mondiale de la Santé (également désignée ci-après sous l'appellation « OMS ») observe la procédure exposée ci-dessous pour l'attribution de dénominations communes internationales recommandées pour les substances pharmaceutiques, conformément à la résolution WHA3.11 de l'Assemblée mondiale de la Santé, et pour le remplacement de telles dénominations.

Article 1 - Les propositions de dénominations communes internationales recommandées et les propositions de remplacement de telles dénominations sont soumises à l'OMS sur la formule prévue à cet effet. L'examen de telles propositions est soumis au paiement d'une taxe administrative destinée uniquement à couvrir les coûts correspondants assumés par le Secrétariat de l'OMS (« le Secrétariat »). Le montant de cette taxe est déterminé par le Secrétariat et peut être modifié de temps à autre.

Article 2 - Ces propositions sont soumises par le Secrétariat aux experts désignés à cette fin parmi les personnalités inscrites au Tableau d'experts de la Pharmacopée internationale et des Préparations pharmaceutiques, ci-après désignés sous l'appellation « le Groupe d'experts des DCI » ; elles sont examinées par les experts conformément aux « Directives générales pour la formation de dénominations communes internationales pour les substances pharmaceutiques » reproduites ci-après[2]. La dénomination acceptée est la dénomination employée par la personne qui découvre ou qui, la première, fabrique et lance sur le marché une substance pharmaceutique, à moins que des raisons majeures n'obligent à s'écarter de cette règle.

Article 3 - Après l'examen prévu à l'article 2, le Secrétariat notifie qu'un projet de dénomination commune internationale est à l'étude.

a) Cette notification est faite par une insertion dans *WHO Drug Information*[3] et par l'envoi d'une lettre aux Etats Membres et aux commissions nationales et régionales de pharmacopée ou autres organismes désignés par les Etats Membres.

i) Notification est également faite à la personne qui a soumis la proposition (« le demandeur initial ») et à d'autres personnes portant à la dénomination mise à l'étude un intérêt notoire.

b) Cette notification contient les indications suivantes :

i) dénomination mise à l'étude;

ii) nom de l'auteur de la proposition tendant à attribuer une dénomination à la substance, si cette personne le demande ;

iii) définition de la substance dont la dénomination est mise à l'étude ;

iv) délai pendant lequel seront reçues les observations et les objections à l'égard de cette dénomination ; nom et adresse de la personne habilitée à recevoir ces observations et objections ;

v) mention des pouvoirs en vertu desquels agit l'OMS et référence au présent règlement.

[1] Voir annexe 1 dans OMS, Série de Rapports techniques, N° 581, 1975. Le texte original a été adopté par le Conseil exécutif dans sa résolution EB15.R7 et amendé dans ses résolutions EB43.R9 et EB115.R4.

[2] Voir annexe 2.

[3] Avant 1987, les listes de dénominations communes internationales étaient publiées dans la *Chronique de l'Organisation mondiale de la Santé*.

c) En envoyant cette notification, le Secrétariat demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur la dénomination proposée pendant la période au cours de laquelle cette dénomination est mise à l'étude par l'OMS.

Article 4 - Des observations sur la dénomination proposée peuvent être adressées à l'OMS par toute personne, dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l'article 3).

Article 5 - Toute personne intéressée peut formuler une objection formelle contre la dénomination proposée dans les quatre mois qui suivent la date de publication de la dénomination dans *WHO Drug Information* (voir l'article 3).

Cette objection doit s'accompagner des indications suivantes :

i) nom de l'auteur de l'objection ;

ii) intérêt qu'il ou elle porte à la dénomination en cause ;

iii) raisons motivant l'objection contre la dénomination proposée.

Article 6 - Lorsqu'une objection formelle est formulée en vertu de l'article 5, l'OMS peut soit soumettre la dénomination proposée à un nouvel examen, soit intervenir pour tenter d'obtenir le retrait de l'objection. Sans préjudice de l'examen par l'OMS d'une ou de plusieurs appellations de remplacement, l'OMS n'adopte pas d'appellation comme dénomination commune internationale recommandée tant qu'une objection formelle présentée conformément à l'article 5 n'est pas levée.

Article 7 - Lorsqu'il n'est formulé aucune objection en vertu de l'article 5, ou que toutes les objections présentées ont été levées, le Secrétariat fait une notification conformément aux dispositions du paragraphe a) de l'article 3, en indiquant que la dénomination a été choisie par l'OMS en tant que dénomination commune internationale recommandée.

Article 8 - En communiquant aux Etats Membres, conformément à l'article 7, une dénomination commune internationale recommandée, le Secrétariat :
a) demande que cette dénomination soit reconnue comme dénomination commune de la substance considérée ; et
b) demande aux Etats Membres de prendre les mesures nécessaires pour prévenir l'acquisition de droits de propriété sur cette dénomination et interdire le dépôt de cette dénomination comme marque ou appellation commerciale.

Article 9 -
a) Dans le cas exceptionnel où une dénomination commune internationale déjà recommandée donne lieu à des erreurs de médication, de prescription ou de distribution ou en comporte un risque démontrable, en raison d'une similitude avec une autre appellation dans la pratique pharmaceutique et/ou de prescription, et où il apparaît que ces erreurs ou ces risques d'erreur ne peuvent être facilement évités par d'autres interventions que le remplacement éventuel d'une dénomination commune internationale déjà recommandée, ou dans le cas où une dénomination commune internationale déjà recommandée diffère sensiblement de la dénomination commune approuvée dans un nombre important d'Etats Membres, ou dans d'autres circonstances exceptionnelles qui justifient le remplacement d'une dénomination commune internationale recommandée, toute personne intéressée peut formuler une proposition dans ce sens. Cette proposition est présentée sur la formule prévue à cet effet et doit s'accompagner des indications suivantes :

i) nom de l'auteur de la proposition ;

ii) intérêt qu'il ou elle porte au remplacement proposé ;

iii) raisons motivant la proposition ; et

iv) description, faits à l'appui, des autres interventions entreprises pour tenter de régler le problème et exposé des raisons pour lesquelles ces interventions ont échoué.

Les propositions peuvent comprendre une proposition de nouvelle dénomination commune internationale de remplacement, établie conformément aux Directives générales, compte tenu de la substance pharmaceutique pour laquelle la nouvelle dénomination commune internationale de remplacement est proposée.

Le Secrétariat transmet une copie de la proposition pour examen, conformément à la procédure exposée plus loin au paragraphe b), au Groupe d'experts des DCI et au demandeur initial ou à son successeur (s'il s'agit d'une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles).

De plus, le Secrétariat demande aux entités et personnes ci-après de formuler des observations sur la proposition :

i) les Etats Membres et les commissions nationales et régionales de pharmacopée ou d'autres organismes désignés par les Etats Membres (en insérant une note à cet effet dans la lettre mentionnée à l'article 3.a), et

ii) toutes autres personnes portant au remplacement proposé un intérêt notoire.

La demande d'observations contient les indications suivantes :

i) dénomination commune internationale recommandée pour laquelle un remplacement est proposé (et la dénomination de remplacement proposée, si elle est fournie) ;

ii) nom de l'auteur de la proposition de remplacement (si cette personne le demande) ;

iii) définition de la substance faisant l'objet du remplacement proposé et raisons avancées pour le remplacement ;

iv) délai pendant lequel seront reçus les commentaires et nom et adresse de la personne habilitée à recevoir ces commentaires ; et

v) mention des pouvoirs en vertu desquels agit l'OMS et référence au présent règlement.

Des observations sur la proposition de remplacement peuvent être communiquées par toute personne à l'OMS dans les quatre mois qui suivent la date de la demande d'observations.

b) Une fois échu le délai prévu ci-dessus pour la communication d'observations, le Secrétariat transmet les observations reçues au Groupe d'experts des DCI, au demandeur initial ou à son successeur et à l'auteur de la proposition de remplacement. Si, après avoir examiné la proposition de remplacement et les observations reçues, le Groupe d'experts des DCI, l'auteur de la proposition de remplacement et le demandeur initial ou son successeur reconnaissent tous qu'il est nécessaire de remplacer la dénomination commune internationale déjà recommandée, le Secrétariat soumet la proposition de remplacement au Groupe d'experts des DCI pour qu'il y donne suite.

Nonobstant ce qui précède, le demandeur initial ou son successeur n'est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu'il porte un intérêt durable à la dénomination commune internationale recommandée qu'il est proposé de remplacer.

Dans le cas où une proposition de remplacement est soumise au Groupe d'experts des DCI pour qu'il y donne suite, le Groupe choisit une nouvelle dénomination commune internationale conformément aux Directives générales mentionnées à l'article 2 et selon la procédure décrite dans les articles 3 à 8 inclus. La notification faite par le Secrétariat en vertu de l'article 3 et de l'article 7, respectivement, y compris au demandeur initial ou à son successeur (si ce n'est pas la même personne que celle qui a

proposé le remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), doit dans un tel cas indiquer que la nouvelle dénomination remplace une dénomination commune internationale déjà recommandée et que les Etats Membres peuvent souhaiter prendre des mesures transitoires pour les produits existants qui utilisent la dénomination commune internationale déjà recommandée sur leur étiquette conformément à la législation nationale.

Si, après examen de la proposition de remplacement et des observations communiquées conformément à la procédure exposée plus haut, le Groupe d'experts des DCI, le demandeur initial ou son successeur et l'auteur de la proposition de remplacement ne s'accordent pas sur le fait qu'il y a des raisons impératives de remplacer une dénomination commune internationale déjà recommandée, cette dernière est conservée (étant entendu toujours que le demandeur initial ou son successeur n'est pas habilité à refuser son accord à une proposition de remplacement au cas où il ne peut être démontré qu'il porte un intérêt durable à la dénomination commune internationale recommandée qu'il est proposé de remplacer). Dans un tel cas, le Secrétariat informe l'auteur de la proposition de remplacement, ainsi que le demandeur initial ou son successeur (s'il s'agit d'une personne différente de celle qui a formulé la proposition de remplacement et pour autant que le demandeur initial ou son successeur soit connu ou puisse être retrouvé moyennant des efforts diligents, notamment des contacts avec les associations industrielles), les Etats Membres, les commissions nationales et régionales de pharmacopée, les autres organismes désignés par les Etats Membres et toutes autres personnes portant un intérêt notoire au remplacement proposé que, malgré une proposition de remplacement, il a été décidé de conserver la dénomination commune internationale déjà recommandée (avec une brève description de la ou des raisons pour lesquelles la proposition de remplacement n'a pas été jugée suffisamment impérative).

ANNEXE 2

DIRECTIVES GENERALES POUR LA FORMATION DE DENOMINATIONS COMMUNES INTERNATIONALES APPLICABLES AUX SUBSTANCES PHARMACEUTIQUES[1]

1. Les dénominations communes internationales (DCI) devront se distinguer les unes des autres par leur consonance et leur orthographe. Elles ne devront pas être d'une longueur excessive, ni prêter à confusion avec des appellations déjà couramment employées.

2. La DCI de chaque substance devra, si possible, indiquer sa parenté pharmacologique. Les dénominations susceptibles d'évoquer pour les malades des considérations anatomiques, physiologiques, pathologiques ou thérapeutiques devront être évitées dans la mesure du possible.

Outre ces deux principes fondamentaux, on respectera les principes secondaires suivants :

3. Lorsqu'on formera la DCI de la première substance d'un nouveau groupe pharmacologique, on tiendra compte de la possibilité de former ultérieurement d'autres DCI appropriées pour les substances apparentées du même groupe.

4. Pour former des DCI des acides, on utilisera de préférence un seul mot. Leurs sels devront être désignés par un terme qui ne modifie pas le nom de l'acide d'origine : par exemple «oxacilline» et «oxacilline sodique», «ibufénac» et «ibufénac sodique».

5. Les DCI pour les substances utilisées sous forme de sels devront en général s'appliquer à la base active (ou à l'acide actif). Les dénominations pour différents sels ou esters d'une même substance active ne différeront que par le nom de l'acide inactif (ou de la base inactive).

[1] Dans son vingtième rapport (OMS, Série de Rapports techniques, N° 581, 1975), le Comité OMS d'experts des Dénominations communes pour les Substances pharmaceutiques a examiné les directives générales pour la formation des dénominations communes internationales et la procédure à suivre en vue de leur choix, compte tenu de l'évolution du secteur pharmaceutique au cours des dernières années. La modification la plus importante a été l'extension aux substances de synthèse de la pratique normalement suivie pour désigner les substances tirées ou dérivées de produits naturels. Cette pratique consiste à employer des syllabes communes ou groupes de syllabes communes (segments-clés) qui sont caractéristiques et indiquent une propriété commune aux membres du groupe des substances pour lequel ces segments-clés ont été retenus. Les raisons et les conséquences de cette modification ont fait l'objet de discussions approfondies.
Les directives ont été mises à jour lors de la treizième consultation sur les dénominations communes pour les substances pharmaceutiques (Genève, 27-29 avril 1983) (PHARM S/NOM 928, 13 mai 1983, révision en date du 18 août 1983).

En ce qui concerne les substances à base d'ammonium quaternaire, la dénomination s'appliquera de façon appropriée au cation et à l'anion en tant qu'éléments distincts d'une substance quaternaire. On évitera de choisir une désignation évoquant un sel aminé.

6. On évitera d'ajouter une lettre ou un chiffre isolé ; en outre, on renoncera de préférence au trait d'union.

7. Pour simplifier la traduction et la prononciation des DCI, la lettre « f » sera utilisée à la place de « ph », « t » à la place de « th », « e » à la place de « ae » ou « oe », et « i » à la place de « y » ; l'usage des lettres « h » et « k » sera aussi évité.

8. On retiendra de préférence, pour autant qu'elles respectent les principes énoncés ici, les dénominations proposées par les personnes qui ont découvert ou qui, les premières, ont fabriqué et lancé sur le marché les préparations pharmaceutiques considérées, ou les dénominations déjà officiellement adoptées par un pays.

9. La parenté entre substances d'un même groupe (voir Directive générale 2) sera si possible indiquée dans les DCI par l'emploi de segments-clés communs. La liste ci-après contient des exemples de segments-clés pour des groupes de substances, surtout pour des groupes récents. Il y a beaucoup d'autres segments-clés en utilisation active.[1] Les segments-clés indiqués sans trait d'union pourront être insérés n'importe où dans une dénomination.

Latin	**Français**	
-acum	*-ac*	substances anti-inflammatoires du groupe de l'ibufénac
-adolum	*-adol* }	analgésiques
-adol-	*-adol-* }	
-astum	*-ast*	antiasthmatiques, antiallergiques n'agissant pas principalement en tant qu'antihistaminiques
-astinum	*-astine*	antihistaminiques
-azepamum	*-azépam*	substances du groupe du diazépam
bol	*bol*	stéroïdes anabolisants
-cain-	*-caïn-*	antiarythmiques de classe I, dérivés du procaïnamide et de la lidocaïne
-cainum	*-caïne*	anesthésiques locaux
cef-	*céf-*	antibiotiques, dérivés de l'acide céphalosporanique
-cillinum	*-cilline*	antibiotiques, dérivés de l'acide 6-aminopénicillanique
-conazolum	*-conazole*	agents antifongiques systémiques du groupe du miconazole
cort	*cort*	corticostéroïdes, autres que les dérivés de la prednisolone
-coxibum	*-coxib*	inhibiteurs sélectifs de la cyclo-oxygénase
-entanum	*-entan*	antagonistes du récepteur de l'endothéline
gab	*gab*	gabamimétiques
gado-	*gado-*	agents diagnostiques, dérivés du gadolinium
-gatranum	*-gatran*	antithrombines, antithrombotiques
gest	*gest*	stéroïdes progestogènes
gli	*gli*	antihyperglycémiants
io-	*io-*	produits de contraste iodés
-metacinum	*-métacine*	substances anti-inflammatoires du groupe de l'indométacine
-mycinum	*-mycine*	antibiotiques produits par des souches de *Streptomyces*
-nidazolum	*-nidazole*	substances antiprotozoaires du groupe du métronidazole
-ololum	*-olol*	antagonistes des récepteurs β-adrénergiques
-oxacinum	*-oxacine*	substances antibactériennes du groupe de l'acide nalidixique
-platinum	*-platine*	antinéoplasiques, dérivés du platine
-poetinum	*-poétine*	facteurs sanguins de type érythropoïétine
-pril(at)um	*-pril(ate)*	inhibiteurs de l'enzyme de conversion de l'angiotensine
-profenum	*-profène*	substances anti-inflammatoires du groupe de l'ibuprofène
prost	*prost*	prostaglandines

[1] Une liste plus complète de segments-clés est contenue dans le document de travail WHO/EMP/RHT/TSN/2013.1 qui est régulièrement mis à jour et qui peut être demandé auprès du programme des DCI, OMS, Genève.

-relinum	*-réline*		peptides stimulant la libération d'hormones hypophysaires
-sartanum	*-sartan*		antagonistes d'un récepteur de l'angiotensine II, antihypertenseurs (non peptidiques)
-vaptanum	*-vaptan*		antagonistes du récepteur de la vasopressine
vin-	*vin-*	}	alcaloïdes du type vinca
-vin-	*-vin-*	}	

ANEXO 1

PROCEDIMIENTO DE SELECCIÓN DE DENOMINACIONES COMUNES INTERNACIONALES RECOMENDADAS PARA SUSTANCIAS FARMACÉUTICAS[1]

La Organización Mundial de la Salud (OMS) seguirá el procedimiento que se expone a continuación tanto para seleccionar denominaciones comunes internacionales recomendadas para las sustancias farmacéuticas, de conformidad con lo dispuesto en la resolución WHA3.11, como para sustituir esas denominaciones.

Artículo 1 - Las propuestas de denominaciones comunes internacionales recomendadas y las propuestas de sustitución de esas denominaciones se presentarán a la OMS en los formularios que se proporcionen a estos efectos. El estudio de estas propuestas estará sujeto al pago de una tasa destinada a sufragar los costos de administración que ello suponga para la Secretaría de la OMS («la Secretaría»). La Secretaría establecerá la cuantía de esa tasa y podrá ajustarla periódicamente.

Artículo 2 - Estas propuestas serán sometidas por la Secretaría a los miembros del Cuadro de Expertos en Farmacopea Internacional y Preparaciones Farmacéuticas encargados de su estudio, en adelante designados como «el Grupo de Expertos en DCI», para que las examinen de conformidad con los «Principios generales de orientación para formar denominaciones comunes internacionales para sustancias farmacéuticas», anexos a este procedimiento.[2] A menos que haya poderosas razones en contra, la denominación aceptada será la empleada por la persona que haya descubierto o fabricado y comercializado por primera vez esa sustancia farmacéutica.

Artículo 3 - Tras el examen al que se refiere el artículo 2, la Secretaría notificará que está en estudio un proyecto de denominación internacional.

a) Esa notificación se hará mediante una publicación en *Información Farmacéutica OMS*[3] y el envío de una carta a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros.

> *i*) La notificación será enviada también a la persona que haya presentado la propuesta («el solicitante inicial») y a otras personas que tengan un interés especial en una denominación objeto de estudio.

b) En esa notificación se incluirán los siguientes datos:

> *i*) la denominación sometida a estudio;
>
> *ii*) la identidad de la persona que ha presentado la propuesta de denominación de la sustancia, si lo pide esa persona;
>
> *iii*) la identidad de la sustancia cuya denominación está en estudio;

[1] Véase el anexo 1 en OMS, Serie de Informes Técnicos, Nº 581, 1975. El texto vigente fue adoptado por el Consejo Ejecutivo en su resolución EB15.R7 y modificado en las resoluciónes EB43.R9 y EB115.R4..

[2] Véase el anexo 2.

[3] Hasta 1987 las listas de DCI se publicaban en la *Crónica de la Organización Mundial de la Salud*.

iv) el plazo fijado para recibir observaciones y objeciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

c) Al enviar esa notificación, la Secretaría solicitará de los Estados Miembros la adopción de todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación propuesta, durante el periodo en que la OMS la tenga en estudio.

Artículo 4 - Toda persona puede formular a la OMS observaciones sobre la denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3.

Artículo 5 - Toda persona interesada puede presentar una objeción formal a una denominación propuesta dentro de los cuatro meses siguientes a su publicación en *Información Farmacéutica OMS*, conforme a lo dispuesto en el artículo 3.
Esa objeción deberá acompañarse de los siguientes datos:

i) la identidad de la persona que formula la objeción;

ii) las causas que motivan su interés por la denominación; y

iii) las causas que motivan su objeción a la denominación propuesta.

Artículo 6 - Cuando se haya presentado una objeción formal en la forma prevista en el artículo 5, la OMS podrá reconsiderar el nombre propuesto o utilizar sus buenos oficios para intentar lograr que se retire la objeción. La OMS no seleccionará como denominación común internacional una denominación a la que se haya hecho una objeción formal, presentada según lo previsto en el artículo 5, que no haya sido retirada, todo ello sin perjuicio de que la Organización examine otra denominación o denominaciones sustitutivas.

Artículo 7 - Cuando no se haya formulado ninguna objeción en la forma prevista en el artículo 5, o cuando todas las objeciones presentadas hayan sido retiradas, la Secretaría notificará, conforme a lo dispuesto en el párrafo *a*) del artículo 3, que la denominación ha sido seleccionada por la OMS como denominación común internacional recomendada.

Artículo 8 - Al comunicar a los Estados Miembros una denominación común internacional, conforme a lo previsto en el artículo 7, la Secretaría:

a) solicitará que esta denominación sea reconocida como denominación común para la sustancia de que se trate; y

b) solicitará a los Estados Miembros que adopten todas las medidas necesarias para impedir la adquisición de derechos de patente sobre la denominación, y prohíban que sea registrada como marca de fábrica o como nombre comercial.

Artículo 9
a) En el caso excepcional de que, debido a su semejanza con otra denominación utilizada en las prácticas farmacéuticas y/o de prescripción, una denominación común internacional recomendada anteriormente ocasione errores de medicación, prescripción o distribución, o suponga un riesgo manifiesto de que esto ocurra, y parezca que tales errores o potenciales errores no sean fácilmente subsanables con otras medidas que no sean la posible sustitución de esa denominación común internacional recomendada anteriormente; en el caso de que una denominación común internacional recomendada anteriormente difiera considerablemente de la denominación común aprobada en un número importante de Estados Miembros, o en otras circunstancias excepcionales que justifiquen el cambio de una denominación común internacional recomendada, cualquier persona interesada puede presentar propuestas en este sentido. Esas propuestas se presentarán en los formularios que se proporcionen a estos efectos e incluirán los siguientes datos:

i) la identidad de la persona que presenta la propuesta;

ii) las causas que motivan su interés en la sustitución propuesta;

iii) las causas que motivan la propuesta; y

iv) una descripción, acompañada de pruebas documentales, de las otras medidas que se hayan adoptado con el fin de resolver la situación y de los motivos por los cuales dichas medidas no han sido suficientes.

Entre esas propuestas podrá figurar una relativa a una nueva denominación común internacional sustitutiva, formulada con arreglo a los Principios generales y que tenga en cuenta la sustancia farmacéutica para la que se proponga la nueva denominación común internacional sustitutiva.

La Secretaría enviará al Grupo de Expertos en DCI y al solicitante inicial o a su sucesor (en el caso de que sea una persona diferente de la que ha presentado la propuesta de sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales) una copia de la propuesta, para que sea examinada de conformidad con el procedimiento descrito en el párrafo *b*) *infra*.
Además, la Secretaría solicitará observaciones sobre la propuesta:

i) a los Estados Miembros y a las comisiones nacionales y regionales de las farmacopeas u otros organismos designados por los Estados Miembros (ello se hará incluyendo una notificación a tal efecto en la carta a la que se refiere el párrafo *a*) del artículo 3), y

ii) a cualquier persona que tenga un interés especial en la sustitución propuesta.

Al solicitar que se formulen estas observaciones se facilitarán los siguientes datos:

i) la denominación común internacional recomendada que se propone sustituir (y la denominación sustitutiva propuesta, si se ha facilitado);

ii) la identidad de la persona que ha presentado la propuesta de sustitución (si lo pide esa persona);

iii) la identidad de la sustancia a la que se refiere la sustitución propuesta y las razones para presentar la propuesta de sustitución;

iv) el plazo fijado para recibir observaciones, así como el nombre y la dirección de la persona a quien deban dirigirse; y

v) los poderes conferidos para el caso a la OMS y una referencia al presente procedimiento.

Toda persona puede formular a la OMS observaciones sobre la sustitución propuesta dentro de los cuatro meses siguientes a la fecha en que se realizó la solicitud de observaciones.

b) Una vez agotado el mencionado plazo para la formulación de observaciones, la Secretaría enviará todos los comentarios recibidos al Grupo de Expertos en DCI, al solicitante inicial o a su sucesor, y a la persona que haya presentado la propuesta de sustitución. Si después de examinar la propuesta de sustitución y las observaciones recibidas, el Grupo de Expertos en DCI, la persona que haya presentado la propuesta de sustitución y el solicitante inicial, o su sucesor, están de acuerdo en la necesidad de sustituir la denominación común internacional recomendada anteriormente, la Secretaría remitirá la propuesta de sustitución al Grupo de Expertos en DCI para que la tramite.
No obstante lo anterior, el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone.

En caso de que la propuesta de sustitución sea presentada al Grupo de Expertos en DCI para que la tramite, este grupo seleccionará una nueva denominación común internacional de conformidad con los Principios generales a los que se refiere el artículo 2 y al procedimiento establecido en los artículos 3 a 8 inclusive. En ese caso, en las notificaciones que la Secretaría ha de enviar con arreglo a los artículos 3 y 7, respectivamente, incluida la notificación al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), se indicará que la nueva denominación sustituye a una denominación común internacional recomendada anteriormente y que los Estados Miembros podrán, si lo estiman oportuno, adoptar disposiciones transitorias aplicables a los productos existentes en cuya etiqueta se utilice, con arreglo a la legislación nacional, la denominación común internacional recomendada anteriormente que se haya sustituido.

En caso de que, después de haber estudiado la propuesta de sustitución y los comentarios recibidos de conformidad con el procedimiento descrito anteriormente, el Grupo de Expertos en DCI, el solicitante inicial o su sucesor y la persona que haya presentado la propuesta de sustitución no lleguen a un acuerdo sobre la existencia de razones poderosas para sustituir una denominación común internacional recomendada anteriormente, esta denominación se mantendrá (siempre en el entendimiento de que el solicitante inicial o su sucesor no tendrán derecho a impedir el acuerdo sobre una propuesta de sustitución en el caso de que hayan dejado de tener un interés demostrable en la denominación común internacional cuya sustitución se propone). En ese caso, la Secretaría comunicará a la persona que haya propuesto la sustitución, así como al solicitante inicial o a su sucesor (en el caso de que no sea la misma persona que propuso la sustitución y siempre que el solicitante inicial o su sucesor sean conocidos o puedan ser encontrados mediante esfuerzos diligentes, como el contacto con las asociaciones industriales), a los Estados Miembros, a las comisiones nacionales y regionales de las farmacopeas o a otros organismos designados por los Estados Miembros y a cualquier otra persona que tenga interés en la sustitución propuesta, que, pese a la presentación de una propuesta de sustitución, se ha decidido mantener la denominación común internacional recomendada anteriormente (con una descripción de la o las razones por las que se ha considerado que la propuesta de sustitución no estaba respaldada por razones suficientemente poderosas).

ANEXO 2

PRINCIPIOS GENERALES DE ORIENTACIÓN PARA FORMAR DENOMINACIONES COMUNES INTERNACIONALES PARA SUSTANCIAS FARMACÉUTICAS[1]

1. Las denominaciones comunes internacionales (DCI) deberán diferenciarse tanto fonética como ortográficamente. No deberán ser incómodamente largas, ni dar lugar a confusión con denominaciones de uso común.

2. La DCI de una sustancia que pertenezca a un grupo de sustancias farmacológicamente emparentadas deberá mostrar apropiadamente este parentesco. Deberán evitarse las denominaciones que puedan tener connotaciones anatómicas, fisiológicas, patológicas o terapéuticas para el paciente.

Estos principios primarios se pondrán en práctica utilizando los siguientes principios secundarios:

3. Al idear la DCI de la primera sustancia de un nuevo grupo farmacológico, deberá tenerse en cuenta la posibilidad de poder formar DCI convenientes para las sustancias emparentadas que se agreguen al nuevo grupo.

4. Al idear DCI para ácidos, se preferirán las de una sola palabra; sus sales deberán denominarse sin modificar el nombre del ácido: p. ej. «oxacilina» y «oxacilina sódica», «ibufenaco» y «ibufenaco sódico».

[1] En su 20º informe (OMS, Serie de Informes Técnicos, Nº 581, 1975), el Comité de Expertos de la OMS en Denominaciones Comunes para las Sustancias Farmacéuticas revisó los Principios generales para formar denominaciones comunes internacionales (DCI), y su procedimiento de selección, a la luz de las novedades registradas en los últimos años en materia de compuestos farmacéuticos. El cambio más importante había consistido en hacer extensivo a la denominación de sustancias químicas sintéticas el método utilizado hasta entonces para las sustancias originadas en productos naturales o derivadas de éstos. Dicho método conlleva la utilización de una «partícula» característica que indica una propiedad común a los miembros de un grupo. En el citado informe se examinan en detalle las razones y consecuencias de este cambio.
Los Principios generales de orientación se actualizaron durante la 13ª consulta sobre denominaciones comunes para sustancias farmacéuticas (Ginebra, 27 a 29 de abril de 1983) (PHARM S/NOM 928, 13 de mayo de 1983, revisado el 18 de agosto de 1983).

5. Las DCI para las sustancias que se usan en forma de sal deberán en general aplicarse a la base activa o al ácido activo. Las denominaciones para diferentes sales o esteres de la misma sustancia activa solamente deberán diferir en el nombre del ácido o de la base inactivos.
En los compuestos de amonio cuaternario, el catión y el anión deberán denominarse adecuadamente por separado, como componentes independientes de una sustancia cuaternaria y no como sales de una amina.

6. Deberá evitarse el empleo de letras o números aislados; también es indeseable el empleo de guiones.

7. Para facilitar la traducción y la pronunciación, se emplearán de preferencia las letras «f» en lugar de «ph», «t» en lugar de «th», «e» en lugar de «ae» u «oe», e «i» en lugar de «y»; se deberá evitar el empleo de las letras «h» y «k».

8. Siempre que las denominaciones propuestas estén de acuerdo con estos principios, recibirán una consideración preferente las denominaciones propuestas por la persona que haya descubierto las sustancias, o que fabrique y comercialice por primera vez una sustancia farmacéutica, así como las denominaciones ya adoptadas oficialmente en cualquier país.

9. El parentesco entre sustancias del mismo grupo se pondrá de manifiesto en las DCI (véase el Principio 2) utilizando una partícula común. En la lista que figura a continuación se indican ejemplos de partículas para grupos de sustancias, en particular para grupos nuevos. Existen muchas otras partículas que se usan habitualmente.[1] Cuando una partícula aparece sin guión alguno, puede utilizarse en cualquier lugar de la palabra.

Latin	**Español**	
-acum	*-aco*	antiinflamatorios derivados del ibufenaco
-adolum	*-adol*)	analgésicos
-adol-	*-adol-*)	
-astum	*-ast*	antiasmáticos, sustancias antialérgicas cuya acción principal no es la antihistamínica
-astinum	*-astina*	antihistamínicos
-azepamum	*-azepam*	derivados del diazepam
bol	*bol*	esteroides anabolizantes
-cain-	*-caína-*	antiarrítmicos de clase I, derivados de procainamida y lidocaína
-cainum	*-caína-*	anestésicos locales
cef-	*cef-*	antibióticos, derivados del ácido cefalosporánico
-cillinum	*- cilina*	antibióticos derivados del ácido 6-aminopenicilánico
-conazolum	*-conazol*	antifúngicos sistémicos derivados del miconazol
cort	*cort*	corticosteroides, excepto derivados de prednisolona
-coxibum	*-coxib*	inhibidores selectivos de ciclooxigenasa
-entanum	*-entán*	antagonistas del receptor de endotelina
gab	*gab*	gabamiméticos
gado-	*gado-*	agentes para diagnóstico derivados de gadolinio
-gartranum	*-gatrán*	inhibidores de la trombina antitrombóticos
gest	*gest*	esteroides progestágenos
gli	*gli*	hipoglucemiantes, antihiperglucémicos
io-	*io-*	medios de contraste iodados
-metacinum	*-metacina*	antiinflamatorios derivados de indometacina
-mycinum	*-micina*	antibióticos producidos por cepas de *Streptomyces*
-nidazolum	*-nidazol*	antiprotozoarios derivados de metronidazol
-ololum	*-olol*	antagonistas de receptores β-adrenérgicos
-oxacinum	*-oxacino*	antibacterianos derivados del ácido nalidíxico
-platinum	*-platino*	antineoplásicos derivados del platino

[1] En el documento de trabajo WHO/EMP/RHT/TSN/2013.1, que se actualiza periódicamente y puede solicitarse al Programa sobre Denominaciones Comunes Internacionales, OMS, Ginebra, figura una lista más amplia de partículas.

-poetinum	*-poetina*	factores sanguíneos similares a la eritropoyetina
-pril(at)um	*-pril(at)*	inhibidores de la enzima conversora de la angiotensina
-profenum	*-profeno*	antiinflamatorios derivados del ibuprofeno
prost	*prost*	prostaglandinas
-relinum	*-relina*	péptidos estimulantes de la liberación de hormonas hipofisarias
-sartanum	*-sartán*	antihipertensivos (no peptídicos) antagonistas del receptor de angiotensina II
-vaptanum	*-vaptán*	antagonistas del receptor de vasopresina
vin-	*vin-)*	alcaloides de la vinca
-vin-	*-vin-)*	

WHO/EMP/RHT/TSN/2014.1

International Nonproprietary Names (INN) for biological and biotechnological substances

(a review)

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(a review)

International Nonproprietary Names (INN) Programme

Technologies Standards and Norms (TSN)
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)

International Nonproprietary Names (INN) for biological and biotechnological substances

(a review)

FORMER DOCUMENT NUMBER: INN Working Document 05.179

Printed by the WHO Document Production Services, Geneva, Switzerland

CONTENTS

0. INTRODUCTION

More than 50 years ago, WHO established the International Nonproprietary Name (INN) Expert Group / WHO Expert Committee on Specifications for Pharmaceutical Preparations, to assign nonproprietary names to medicinal substances, so that each substance would be recognized globally by a unique name. These INNs do not give proprietary rights, unlike a trade mark, and can be used freely as they are public property.

INNs have been assigned to biological products since the early days of the INN Programme. As well as many names for individual substances, animal insulin preparations were given an INN in Recommended list 3 in 1959. In the period up to 1980, names were assigned to antibiotics, synthetic peptides, hormones and other proteins. In names of compounds related by structure and / or function, specific letter groups, called stems, are included to aid recognition by health professionals. The *-actid*e for synthetic polypeptides with a corticotrophin-like action is an example.

In 1982, the name *insulin human* was proposed for the recombinant protein identical to natural human insulin, and since then names have been assigned to a growing number of recombinant products. Within the INN Programme, names have not been assigned to natural human blood products or vaccines. For those groups of biological products, the WHO Expert Committee on Biological Standardization (ECBS) has been adopting the scientific names of the biological products within the definitions of respective requirements.

Since the time when *insulin human* became the first recommended INN (rINN) for a recombinant product, the range of biological / biotechnological products has increased in size and complexity. For example, new stems have been introduced for tissue plasminogen activators (*-plase*) among other groups. Analogues of recombinant glycosylated proteins produced in different cell systems have been classified using Greek letters as indicators in the sequence of product introduction: erythropoietin (*epoetin alfa*, *beta* and so on) and glycoprotein hormones (*follitropin*) are examples. In the 1990s, a systematic scheme for naming monoclonal antibodies was implemented, based on the stem *-mab*, which indicates the origin (mouse, human, etc) of the antibody and its intended use: tumour, immunomodulator and so on.

As a result of the scientific and technical developments currently taking place, new products of biotechnology and other biological products are being introduced and more products can be expected for the treatment or prevention of disease. Examples of such new products include recombinant blood products, transgenic products (human proteins expressed in animals or plants), products for gene therapy and novel vaccines.

As this area is becoming more and more complex and challenging, the INN Expert Group has requested the WHO-INN Secretariat to prepare a working document intended to summarize and review the past and present INN situation in this field.

This document, first published on the website of the INN Programme in 2006, therefore presents an inventory of the policy decisions taken by the INN Expert Group during all these years of change, and of the names assigned to biological and biotechnological substances. Considering the potential for further developments in the field of biologicals, this review is intended to be a *living document* which will be regularly updated to include new policies, and future INNs assigned.

Comments and suggestions from all interested parties are most welcome and will be presented to the INN Expert Group for their consideration and for possible incorporation in future updates of this review.

You are reading the current updated version, also available as pdf-copy at:

http://www.who.int/medicines/services/inn/publication/en/index.html.

1. PHARMACOLOGICAL CLASSIFICATION OF BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES [(1)]

Alimentary tract and metabolism

insulins (see item 4.16).

Anti-infectives

antimicrobial, bactericidal permeability increasing polypeptides (see item 4.1).

Antineoplastics

peptide vaccines / recombinant vaccines (see item 4.23)

toxins (see item 4.29).

Blood and agents acting on the haemopoietic system

antithrombins (see item 4.3)

blood coagulation cascade inhibitors (see item 4.4)

blood coagulation factors (see item 4.5)

erythropoietin type blood factors (see item 4.8)

heparin derivatives including low molecular mass heparins (see item 4.14)

hirudin derivatives (see item 4.15)

thrombomodulins (see item 4.28).

Immunomodulators and immunostimulants

colony stimulating factors (see item 4.6)

interferons (see item 4.17)

interleukin receptor antagonists (see item 4.18)

interleukin type substances (see item 4.19)

monoclonal antibodies (see item 4.20)

receptor molecules, native or modified (see item 4.26).

Hormones, hormone antagonists, hormone-release stimulating peptides or hormone-release inhibiting peptides (excluding insulins)

gonadotropin-releasing-hormone (GnRH) inhibitors, peptides (see item 4.10)

growth hormone (GH) derivatives (see item 4.12)

growth hormone antagonists (see item 4.13)

oxytocin derivatives (see item 4.21)

pituitary / placental glycoprotein hormones (see item 4.24)

pituitary hormone-release stimulating peptides (see item 4.25)

synthetic polypeptides with a corticotropin-like action (see item 4.27)

vasoconstrictors, vasopressin derivatives (see item 4.30).

Various

antisense oligonucleotides (see item 4.2)

enzymes (see item 4.7)

gene therapy products (see item 4.9)

growth factors (see item 4.11)

peptides and glycopeptides (for special groups of peptides see *-actide* (see item 4.27), *-pressin* (see item 4.30), *-relin* (see item 4.25), *-tocin* (see item 4.21)) (see item 4.22).

2. CURRENT STATUS OF EXISTING STEMS OR SYSTEMS FOR BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES[(1) (2) (3) (4) (5) (6) (7)]

2.1. Groups with respective stems

Name of the group	**Stem**
antisense oligonucleotides	*-rsen*
blood coagulation cascade inhibitors	*-cogin*
blood coagulation factors	*-cog*
colony stimulating factors	*-stim*
enzymes	*-ase*
erythropoietin type blood factors	*-poetin*
growth factors	*-ermin*
growth hormone derivatives	*som-*
heparin derivatives including low molecular mass heparins	*-parin*
hirudin derivatives	*-irudin*
gonadotropin-releasing-hormone (GnRH) inhibitors, peptides	*-relix*
interleukin receptor antagonists	*-kinra*
interleukin type substances	*-kin*
monoclonal antibodies	*-mab*
oxytocin derivatives	*-tocin*
peptides and glycopeptides (for special groups of peptides see *-actide*, *-pressin, -relin, -tocin*)	*-tide*
pituitary hormone-release stimulating peptides	*-relin*
receptor molecules, native or modified (a preceding infix should designate the target)	*-cept*
synthetic polypeptides with a corticotropin-like action	*-actide*
vasoconstrictors, vasopressin derivatives	*-pressin*

2.2. Groups with respective pre-stems

Name of the group	Pre-stem
aptamers, classical and mirror ones	*-apt-*
antimicrobial, bactericidal permeability increasing polypeptides	*-ganan*
neurotrophins	*-neurin*
small interfering RNA	*-siran-*

2.3. Groups with INN schemes

Name of the group
antithrombins
gene therapy products
insulins
interferons
pituitary / placental glycoprotein hormones

2.4. Groups without respective stems / pre-stems and without INN schemes

Name of the group
growth hormone antagonists
thrombomodulins
toxins

3. GENERAL POLICIES FOR BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES

3.1. General policies for blood products [4]

- INNs have not been assigned to natural human blood products.
- Many natural blood products have well-established names, so the recombinant version should have a distinctive name reflecting as much as possible the established name used in the field.
- It is essential to add "activated" to the name of the blood product when this is presented for therapeutic use in its activated form.

3.2. General policies for fusion proteins[1] [4]

- INNs have been assigned to some fusion proteins. If a stem exists for one or the other part of the fusion protein, this stem should be brought into the name. This allows the constant part of a fusion protein to be recognized in the name.
- At present it is considered unnecessary to indicate that the product is a fusion product within the name, but this position may need to be reviewed in the future.

3.3. General policies for gene therapy products [2]

In 2005, the two-word nomenclature scheme for gene therapy products was formally adopted by the members of the INN Expert Group designated to deal with the selection of nonproprietary names. The 2012 updated scheme is shown in Table 1.

[1] The list of INN for composite proteins published is given in Annex 1, including some fusion proteins.

Table 1 Two-word scheme for gene therapy products (updated in 2012)

	prefix	infix	suffix
word 1 (gene component)	random to contribute to euphonious and distinctive name e.g. *al-*; *bet-*; *val-*	to identify the gene using, when available, existing infixes for biological products or using similar infix as for the protein for which the gene codes. e.g.-*cima-*: cytosine deaminase *-ermin-*: growth factor *-kin-*: interleukin *-lim-*: immunomodulator *-lip-*: human lipoprotein lipase *-mul-*: multiple gene *-stim-*: colony stimulating factor *-tima-*: thymidine kinase *-tusu-*: tumour suppression	*-(a vowel)gene* e.g. *-(o)gene*
word 2 (vector component)	random to contribute to euphonious and distinctive name	e.g. *-adeno-*: adenovirus *-cana-*: canarypox virus *-foli-*: fowlpox virus *-herpa-*: herpes virus *-lenti-*: lentivirus *-morbilli-*: paramyxoviridae morbillivirus *-parvo-*: adeno-associated virus (parvoviridae dependovirus) *-retro-*: other retrovirus *-vaci-*: vaccinia virus	*-vec* (non-replicating viral vector) *-repvec* (replicating viral vector)
			-plasmid (plasmid vector)

In the case of non-plasmid naked DNA products, there is no need for a second word in the name.

3.4. General policies for glycosylated compounds [8]

For glycoproteins / glycopeptides

- For groups identified with a stem, e.g. for erythropoetins: *-poetin*, differences in the amino acid chain are indicated by using a

random prefix and differences in the glycosylation pattern are indicated by another designator expressed by a Greek letter[2] spelt in full and added as a second word to the name (e.g. *epoetin alfa (66)*, *darbepoetin alfa (85)*; see item 4.8).

- For blood coagulation factors obtained by recombinant biotechnology, the differences in the glycosylation pattern are indicated by a Greek letter spelt in full and added as a second word to the name (e.g. *eptacog alfa (activated) (77)*, *octocog alfa (73)*); when the amino acid sequence differs from the natural product this is indicated by using a random prefix (e.g. *beroctocog alfa (98)*; see item 4.5).

- Similarly, for enzymes identified with a stem *-ase* obtained by recombinant biotechnology and differing in the amino acid chain, these differences are indicated by using a random prefix and differences in the glycosylation pattern are indicated by a Greek letter spelt in full and added as a second word to the name (e.g. *alglucosidase alfa (91)*, *bucelipase alfa (95)*; see item 4.7).

- The Greek letters should be used in the Greek alphabetical order (see Annex 2).

3.5. General policies for immunoglobulins fractionated from plasma [(9) (10)]

Not to select an INN for immunoglobulins fractionated from plasma is the current policy.

The "systematic" or descriptive name is essential since the prescriber must know all the information conveyed by it and there is no benefit in assigning an INN from which it will not be readily apparent.

3.6. General policies for monoclonal antibodies [(1) (3) (11)3]

- INN for monoclonal antibodies (mAbs) are composed of a prefix, a substem A, a substem B and a suffix.
- The common stem for mAbs is *-mab,* placed as a suffix.

[2] The transliteration of Greek letters in English, French and Spanish is given in Annex 2.
[3] It contains the revised naming scheme for monoclonal antibodies; the previous naming scheme for monoclonal antibodies is given in Annex 3.

- The stem *-mab* is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.
- Substem B indicates the species on which the immunoglobulin sequence of the mAb is based (shown in Table 2).

Table 2 Substem B for the species

a	rat
axo (pre-sub-stem)	rat-mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
-xizu-	chimeric-humanized
zu	humanized

The distinction between chimeric and humanized antibodies is as follows:

Chimeric: A chimeric antibody is one for which both chain types are chimeric as a result of antibody engineering. A chimeric chain is a chain that contains a foreign variable domain (originating from one species other than human, or synthetic or engineered from any species including human) linked to a constant region of human origin. The variable domain of a chimeric chain has a V region amino acid sequence which, analysed as a whole, is closer to non-human species than to human.

Humanized: A humanized antibody is one for which both chain types are humanized as a result of antibody engineering. A humanized chain is typically a chain in which the complementarity determining regions (CDR) of the variable domains are foreign (originating from one species other than human, or synthetic) whereas the remainder of the chain is of human origin. Humanization assessment is based on the resulting amino acid sequence, and not on the methodology per se, which allows protocols other than grafting to be used. The variable domain of a humanized chain has a V region amino acid sequence which, analysed as a whole, is closer to human than to other species.

The *-xizu-* infix is used for an antibody having both chimeric and humanized chains.
The *-axo-* infix is used for an antibody having both rat and mouse chains.

- Substem A indicates the target (molecule, cell, organ) class (shown in Table 3).

Table 3 Substem A for target class

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-gr(o)-	skeletal muscle mass related growth factors and receptors
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)-	neural
-s(o)-	bone
-tox(a)-	toxin
-t(u)-	tumour
-v(i)-	viral

In principle, a single letter, e.g. *-b-* for bacterial is used as substem A. Whenever substem B starts with a consonant (e.g. *x* or *z),* to avoid problems in pronunciation, an additional vowel indicated in the table, e.g. *-ba-* is inserted.

Prefix

The prefix should be random, i.e. the only requirement is to contribute to a euphonious and distinctive name.

Second word

If the monoclonal antibody is conjugated to another protein or to a chemical (e.g. chelator), identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For instance, for mAbs conjugated to a toxin, the suffix *-tox* is used in the second word.

If the monoclonal antibody is radiolabelled, the radioisotope is listed first in the INN, e.g. *technetium (^{99m}Tc) nofetumomab merpentan (81).*

The prefix *peg-* can be used for pegylated mAbs, but this should be avoided if it leads to over-long INN. In most cases, it is best to adopt two-word INN for pegylated mAbs, with the first word describing the mAb and the second being *pegol* or a related designation.

3.7. General policies for non-glycosylated compounds [8]

For proteins / peptides:

- Identification of the group with a stem, e.g. for hirudin analogues:-*irudin*, and indication of differences in the amino acid chain by using a random prefix (e.g. *bivalirudin (72)*).
- Identification of the group with a word, e.g. insulin, and indication of differences in the composition of the amino acid chain as a second element of the name (e.g. *insulin argine (58)*).

3.8. General policies for skin substitutes [4]

The products within this system are made of cells within a matrix, and skin substitutes can be considered to be engineered tissue and thus fall outside the scope of the INN system.

3.9. General policies for transgenic products [4]

- If an INN already exists, the same name should be used for the transgenic product, qualified in some way to identify that this product is transgenic.
- A similar system to that used for glycosylated recombinant products is suggested to differentiate new or additional sources of the same substance, and the source of the substance should be included in the definition of the INN.

3.10. General policies for vaccines [4] [5] [6] [7]

- At present, vaccines are not included within the INN system, but names are assigned through recommendations of the Expert Committee on Biological Standardization and through the pharmacopoeial monograph.
- During the INN Consultation in 1993, it was agreed that the prerequisite for an INN application for a recombinant vaccine[4] would be fulfilled if the manufacturer was able to provide all information outlined in the guidelines entitled Definition of INNs for Substances Prepared by Biotechnology (WHO / Pharm S / Nom 1348[12]).
- During the INN Consultation in 1998, following discussion on recombinant viruses, the experts agreed not to attempt to name live viruses.
- Another approach in vaccine technology is the development of peptide vaccines[5] (epitopes involved in immune response formation): since these peptides are chemically well-defined, they fall within the INN naming system.

3.11. General policies for cell therapy products

During the 55th INN Consultation in 2012, the INN Expert Group decided in principle to name some cell therapy products. A possible INN naming scheme for cell therapy products is currently under development.

[4] The definition of recombinant vaccines is given in item 4.23.
[5] The definition of peptide vaccines is given in item 4.23.

4. SUMMARY OF INN ASSIGNED TO BIOLOGICAL AND BIOTECHNOLOGICAL SUBSTANCES[(1) (3) (7) (8) (13) (14) (15) (16) (17) (18) (19) (20) (21)]

4.1. Antimicrobial, bactericidal permeability increasing polypeptides

The pre-stem for antimicrobial, bactericidal permeability increasing polypeptides is *-ganan*.

iseganan (85)[6], *omiganan (89)*, *pexiganan (78).*

4.2. Antisense oligonucleotides

The common stem for antisense oligonucleotides is *-rsen*.

aganirsen (103), *alicaforsen (97)*, *anivamersen (105)*, *apatorsen (110)*, *aprinocarsen (97)*, *beclanorsen (101)*, *cenersen (97)*, *custirsen (99)*, *drisapersen (106)*, *eteplirsen (103)*, *gataparsen (103)*, *mipomersen (100)*, *mongersen (111)*, *oblimersen (97)*, *trabedersen (98).*

-virsen **(antivirals)**: *afovirsen (97)*, *fomivirsen (97)*, *miravirsen (101)*, *radavirsen (106)*, *trecovirsen (97).*

4.3. Antithrombins

antithrombin III (60), *antithrombin alfa (93)* (Rec. Glycoprotein (432aa) from transgenic goats), *antithrombin gamma (107)*.

[6] The numbers in parentheses indicate the Proposed list number.

4.4. Blood coagulation cascade inhibitors

The common stem for blood coagulation cascade inhibitors is *-cogin*.

drotrecogin alfa (activated) (86), *pegnivacogin (106)*, *taneptacogin alfa (90)*, *tifacogin (78)*.

4.5. Blood coagulation factors

The common stem for blood coagulation factors is *-cog*.

The sub-stems *-eptacog*, *-octocog*, *-nonacog/-trenonacog* and *-tridecacog* have been selected up to date for recombinant blood coagulation factors.

A prefix will be necessary if the amino acid sequence does not match that of the naturally occurring material.

In accordance with the general policy, *alfa, beta,* etc, will be added for the glycoproteins (see item 3.4 - general policies for glycosylated compounds).

When the additional statement "activated" is needed, e.g. for the blood coagulation factor VIIa, it should be spelt out in full and added in parentheses after the name.

blood coagulation factor VII: *-eptacog*

eptacog alfa (activated) (77), *eptacog alfa pegol (activated) (101)*, *oreptacog alfa (activated) (109)*, *vatreptacog alfa (activated) (98)*

blood factor VIII: *-octocog*

beroctocog alfa (98), *damoctocog alfa pegol (109)*, *efmoroctocog alfa (111)*, *lonoctocog alfa (111)*, *moroctocog alfa (72)*, *octocog alfa (73)*, *rurioctocog alfa pegol (111)*, *simoctocog alfa (104)*, *turoctocog alfa (108)*, *turoctocog alfa pegol (108)*

blood factor IX: *-nonacog* (with Ala at the position 148 (Ala-alloform))

albutrepenonacog alfa (109), *nonacog alfa (77)*, *nonacog beta pegol (104)*, *nonacog gamma (108)*

-*trenonacog* (with Thr at the position 148 *(*Thr-alloform))

eftrenonacog alfa (109), *trenonacog alfa (107)*

blood coagulation factor XIII: -*tridecacog*

catridecacog (99)

recombinant von Willebrand factor (vWF): -*vonicog*

vonicog alfa (102).

4.6. Colony stimulating factors

The common stem for colony stimulating factors is -*stim*.

ancestim (79) (cell growth factor), *garnocestim (86)* (immunomodulator), *pegacaristim (80)* (megakaryocyte growth factor), *romiplostim (97)* (thrombopoietin receptor (MPL) agonist)

combination of two different types of colony stimulating factors: -*distim*

leridistim (80), *milodistim (75)*

granulocyte macrophage colony stimulating factor (GM-CSF) type substances: -*gramostim*

ecogramostim (62), *molgramostim (64)*, *regramostim (65)*, *sargramostim (66)*

granulocyte colony stimulating factor (G-CSF) type substances: -*grastim*

balugrastim (107), *eflapegrastim (111)*, *empegfilgrastim (107)*, *filgrastim (64)*, *lenograstim (64)*, *lipegfilgrastim (107)*, *nartograstim (66)*, *pegbovigrastim (109)*, *pegfilgrastim (86)*, *pegnartograstim (80)*, *pegteograstim (109)*

macrophage stimulating factors (M-CSF) type substances: -*mostim*

cilmostim (71), *lanimostim (91)*, *mirimostim (65)*

interleukin-3 analogues and derivatives: *-plestim*

daniplestim (76), *muplestim (74)*.

4.7. Enzymes

The common stem for enzymes, in general, is *-ase*.

Sub-stems are referring to the activity of the substances.

proteinase:

with -ase suffix:
crisantaspase (111), *brinase (22)*, *calaspargase pegol (105)*, *kallidinogenase (22)*, *ocrase (28)*, *pegaspargase (64)*, *promelase (47)*, *serrapeptase (31)*, *sfericase (40)*, *streptokinase (6)*, *urokinase (48)*, *urokinase alfa (77)*

without *-ase* suffix:
batroxobin (29), *bromelains (18)*, *chymopapain (26)*, *chymotrypsin (10)*, *defibrotide (44)*, *fibrinolysin (human) (10)*, *sutilains (18)*

lipase*: -lipase*

bucelipase alfa (95), *burlulipase (107)*, *rizolipase (22)*, *sebelipase alfa (107)*

enzymes with superoxide dismutase activity: *-dismase*

- *ledismase (70)*, *sudismase (58)*

- isomerase (belongs to this group but in which the preferred stem has not been used)

  orgotein (31), *pegorgotein (72)*

plasminogen activator combined with another enzyme: *-diplase*

amediplase (79)

tissue-type-plasminogen activators: *-teplase*

alteplase (73), *desmoteplase (80)*, *duteplase (62)*, *lanoteplase (76)*, *monteplase (72)*, *nateplase (73)*, *pamiteplase (78)*, *reteplase (69)*, *silteplase (65)*, *tenecteplase (79)*

anistreplase (59) (belongs to this group but in which the preferred stem has not been used)

urokinase-type-plasminogen activators: *-uplase*

nasaruplase (76), *nasaruplase beta (86)*, *saruplase (76)*

others:

agalsidase alfa (84): human alpha-galactosidase isoenzyme A, isolated from human cell line, clone RAG 001, glycoform α

agalsidase beta (84): α-galactosidase (human clone λAG^{18} isoenzyme A subunit protein moiety reduced), glycoform β

alfimeprase (85): [3-L-serine]fibrolase-(3-203)-peptide (fibrolase : fibrinolytic enzyme isolated from *Agkistrodon contrix contrix* venom)

alglucerase (68): glucosylceramidase (human placenta isoenzyme protein moiety reduced)

alglucosidase alfa (91): human lysosomal prepro-α-glucosidase-(57-952)-peptide 199-arginine-223-histidine variant

asfotase alfa (104): tissue-nonspecific alkaline phosphatase- IgG_1 fusion protein; human tissue-nonspecific isozyme alkaline phosphatase (AP-TNAP, EC=3.1.3.1) fusion protein with leucyl-lysyl-human immunoglobulin G1 Fc region {(6-15)-H-CH2-CH3 of IGHG1*03} fusion protein with aspartyl-isoleucyl-deca(aspartic acid), dimer (493-493':496-496')-bisdisulfide

cerliponase alfa (111): immature human tripeptidyl-peptidase 1 (cell growth-inhibiting gene 1 protein, lysosomal pepstatin-insensitive protease, TPP-1, EC 3.4.14.9), 544 residues protein, produced in Chinese hamster ovary (CHO) cells, glycoform alfa

condoliase (106): endolyase, chondroitin ABC (C-ABC). glycosaminoglycan lyase chondroitin ABC endolyase 1 (chondroitinase ABC) *Proteus vulgaris*

dornase alfa (70): deoxyribonuclease (human clone 18-1 protein moiety)

elosulfase alfa (108): human *N*-acetylgalactosamine-6-sulfatase (chondroitinsulfatase, galactose-6-sulfate sulfatase, EC=3.1.6.4) dimer (139-139')-disulfide glycosylated (produced by CHO cells)

epafipase (85): 2-acetyl-1-alkyl-*sn*-glycero-3-phosphocholine deacetylase-(6-400)-peptide(human)

eufauserase (84): broad spectrum serine-protease enzyme, extracted from the Antartic krill (*Euphausia superba*)

galsulfase (92): *N*-acetylgalactosamine 4-sulfatase (human CSL4S-342 cell)

glucarpidase (92): recombinant glutamate carboxypeptidase (carboxypeptidase G2)

hyalosidase (50): hyaluronoglucosaminidase *or* E.C. 3.2.1.35

hyaluronidase (1): enzymes of various origins which depolymerize hyaluronic acid

idursulfase (90): α-L-iduronate sulfate sulfatase

idursulfase beta (106): iduronate 2-sulfatase (α-L-iduronate sulfate sulfatase), human proenzyme produced in CHO cells (glycoform beta)

imiglucerase (72): 495-L-histidineglucosylceramidase (human placenta isoenzyme protein moiety)

laronidase (86): 8-L-histidine-α-L-iduronidase (human)

olipudase alfa (111): recombinant DNA derived des-(1-13)-human sphingomyelin phosphodiesterase (acid sphingomyelinase, EC-3.1.4.12), produced in Chinese hamster ovary (CHO) cells, glycoform alfa

pegademase (63): adenosine deaminase, reaction product with succinic anhydride, esters with polyethylene glycol monomethyl ether
The source of the product should be indicated

pegadricase (105): pegylated Urate Oxidase from *Candida utilis*, [198-threonine(S>T)]uricase (EC 1.7.3.3, urate oxidase) *Pichia jadinii* (Yeast) (*Candida utilis*) tetramer, 6-amino group of an average of 3 lysine residues, mostly in position 16, 19, and 85 of each monomer, are amidified with α-(3-carboxypropanoyl)-ω-methoxypoly(oxyethylene)

pegargiminase (111): [111-glutamic acid,209-serine]arginine deiminase (ADI, arginine dihydrolase, AD) from *Mycoplasma hominis*, an average of five amino groups are amidified with 4-[ω-methoxypoly(oxyethylene)]-4-oxobutanoyl, produced in *Escherichia coli*

pegcrisantaspase (111): recombinant L-asparaginase derived from *Erwinia chrysanthemi* pegylated with 5 kDa methoxy polyethylene glycol (m-PEG-NHS), produced in *Escherichia coli*:
L-asparaginase (EC 3.5.1.1, L-asparagine amidohydrolase) *Erwinia chrysanthemi* tetramer α4, an average of 10 (*a*) out of 18 amino groups of each monomer are amidified with 5-{[α-methylpoly(oxyethylene)]amino}-5-oxopentanoyl

pegloticase (98): tetramer α_4 of des-(1-5)-[6-threonine,45-threonine, 290-lysine, 300-serine]uricase (EC 1.7.3.3, urate oxidase) from *Sus scrofa* (porcine), non acetylated, of which some of the lysine 6-amine residues are engaged in a carbamate linkage with a monomethylic ether of polyoxyethylene (macrogol)

pegvaliase (111): pegylated, recombinant DNA derived *Anabaena variabilis* phenylalanine ammonia lyase mutein (S 503, S 565), produced in *Escherichia coli*:
[503,565-diserine (C>S)]phenylalanine ammonia-lyase (EC 4.3.1.24) *Anabaena variabilis* in which an average of 5 lysyl residues are *N*6-{6-[ω-methoxypoly(oxyethylene)]hexanoyl} substituted

penicillinase (111): an enzyme obtained by fermentation from cultures of *Bacillus Cereus*

ranpirnase (81): ribonuclease (*Rana pipiens*)

rasburicase (82): urate oxydase (tetramer of the *N*-acetylpolypeptide of 301 amino acids

reveglucosidase alfa (111): des-(2-7)-human insulin-like growth factor II fusion protein with glycyl-L-alanyl- L-prolyl-human lysosomal alpha-glucosidase (acid maltase, aglucosidase alfa) produced in Chinese hamster ovary (CHO) cells, glycoform alfa

senrebotase (107): L-methionylglycyl-L-seryl-des-(445-glycine,446-L-tyrosine)-[2-L-glutamic acid,432,442,444,447-tetra-L-aspartic acid]botulinum neurotoxin A precursor 27-L-alanine variant light chain (433-41')-disulfide with [14-L-arginine,15-L-lysine]human nociceptin fusion protein with L-alanyl-L-leucyl-L-alanyltris(tetraglycyl-L-seryl)-[3-L-valine,4-L-leucine,5-L-glutamine-418-L-leucine,419-L-aspartic acid]botulinum neurotoxin A heavy chain-(1-419)-peptide

streptodornase (6): enzyme obtained from cultures of various strains of *Streptococcus hemolyticus* and capable of hydrolysing desoxyribonucleoproteins

taliglucerase alfa (101): L-glutamyl-L-phenylalanyl-[495(*497*)-L-histidine(R>H)]human glucosylceramidase (beta-glucocerebrosidase) peptide with L-aspartyl-L-leucyl-L-leucyl-L-valyl-L-aspartyl-L-threonyl-L-methionine,glycosylated peptide *1-506*

tilactase (50): *β-D*-galactosidase *or* EC 3.2123

velaglucerase alfa (98): human glucosylceramidase (EC 3.2.1.45 or beta-glucocerebrosidase), glycoform α.

vonapanitase (111): recombinant DNA derived type I pancreatic elastase, produced in *Pichia pastoris*: [26-tryptophan(Arg>Trp),202-leucine(Val>Leu),225-arginine(Gln>Arg)]mature human CELA1 (chymotrypsin-like elastase family member 1, pancreatic elastase 1, elastase 1, EC 3.4.21.36)non-glycosylated

vorhyaluronidase alfa (111): human hyaluronidase PH-20 (hyaluronoglucosaminidase PH-20, sperm adhesion molecule 1, EC 3.2.1.35) precursor-(36-482)-peptide (mature-(1-447)-peptide), produced in Chinese hamster ovary (CHO) DG44dhfr- cells, glycoform alfa.

4.8. Erythropoietin type blood factors

The common stem for erythropoietin type blood factors is *-poetin*.

In the case of erythropoietins, it was decided to select *epoetin* together with a Greek letter to differentiate between compounds of the same amino acid sequence as human erythropoietin which vary in the glycosylation pattern (see item 3.4 - general policies for glycosylated compounds).

Substances with different amino acid sequences will be named using the *-poetin* stem and a random prefix.

darbepoetin alfa (85), *epoetin alfa (66)*, *epoetin beta (62)*, *epoetin gamma (67)*, *epoetin delta (85)*, *epoetin epsilon (72)*, *epoetin zeta (95)*, *epoetin theta (95)*, *epoetin kappa (97)*, *epoetin omega (73)*.

4.9. Gene therapy products

alferminogene tadenovec (95), *alipogene tiparvovec (99)*, *amolimogene bepiplasmid (98)*, *beperminogene perplasmid (95)*, *contusugene ladenovec (97)*, *golnerminogene pradenovec (101)*, *pexastimogene devacirepvec (108)*, *riferminogene pecaplasmid (100)*, *rilimogene galvacirepvec (107)*, *rilimogene glafolivec (107)*, *sitimagene ceradenovec (97)*, *taberminogene vadenovec (100)*, *talimogene laherparepvec (104)*, *tipapkinogene sovacivec (102)*, *velimogene aliplasmid (97)*, *vocimagene amiretrorepvec (107).*

4.10. Gonadotropin-releasing-hormone (GnRH) inhibitors, peptides

The common stem for gonadotropin-releasing-hormone (GnRH) inhibitors, peptides is *-relix*.

abarelix (78), *cetrorelix (66)*, *degarelix (86)*, *detirelix (56)*, *ganirelix (65)*, *iturelix (79)*, *ozarelix (94)*, *prazarelix (81)*, *ramorelix (69)*, *teverelix (78).*

4.11. Growth factors

The common stem for growth factors is *-ermin*.

Sub-stems allow distinction between the various types of growth factors.

INNs for tumour necrosis factors (TNF) are also classified under the stem *-ermin*.

vascular endothelial growth factors: *-bermin*

telbermin (85)

epidermal growth factors: *-dermin*

murodermin (63), *nepidermin (97)*

fibroblast growth factors: *-fermin*

ersofermin (66), *palifermin (88)*, *repifermin (82)*, *sprifermin (105)*, *trafermin (74)*, *velafermin (94)*

leukaemia-*inhibiting* factors: *-filermin*

emfilermin (82)

tumour necrosis factors: *-nermin*

ardenermin (88), *dulanermin (99)*, *plusonermin (73)*, *sonermin (68)*, *tasonermin (78)*

platelet-derived growth factors: *-plermin*

becaplermin (74)

insulin-like growth factors: *-sermin*

mecasermin (66), *mecasermin rinfabate (92)*

transforming growth factors: *-termin*

cetermin (74), *liatermin (81)*

bone morphogenetic proteins: *-otermin*

avotermin (77), *dibotermin alfa (89)*, *eptotermin alfa (92)*, *nebotermin (109)*, *radotermin (92)*

others:

cimaglermin alfa (110) (recombinant DNA derived glial growth factor 2 (GGF2))

dapiclermin (93) (modified ciliary neurotrophic factor (CNTF)).

4.12. Growth hormone (GH) derivatives

The common stem for growth hormone derivatives is *som-*.

human growth hormone derivatives:

somatrem (54), *somatropin (74)*, *somatropin pegol (103)*

For substances other than human, suffixes are added to indicate the species specificity of the structure.

bovine-type substances: *-bove*

somagrebove (63), *somavubove (63)*, *sometribove (74)*, *somidobove (58)*

porcine-type substances: *-por*

somalapor (62), *somenopor (62)*, *somfasepor (66)*, *sometripor (75)*

salmon-type substances: *-salm*

somatosalm (69)

others (growth hormone related peptides):

somatorelin (57) (pituitary hormone-release stimulating peptides, see item 4.25), *somatostatin (46)* (growth hormone release inhibitor).

4.13. Growth hormone antagonists

pegvisomant (82).

4.14. Heparin derivatives including low molecular mass heparins

The common stem for heparin derivatives including low molecular mass heparins is *-parin*.

ardeparin sodium (68), *adomiparin sodium (104)*, *bemiparin sodium (75)*, *certoparin sodium (70)*, *dalteparin sodium (77)*, *deligoparin sodium (89)*, *enoxaparin sodium (77)*, *heparin sodium (54)*, *livaraparin calcium (86)*, *minolteparin sodium (74)*, *nadroparin calcium (78)*, *parnaparin sodium (77)*, *reviparin sodium (78)*, *semuloparin sodium (99)*, *sevuparin sodium (106)*, *tafoxiparin sodium (102)*, *tinzaparin sodium (77).*

4.15. Hirudin derivatives

The common stem for hirudin derivatives is *-irudin*.

bivalirudin (72), *desirudin (76)*, *lepirudin (76)*, *pegmusirudin (77).*

4.16. Insulins

Up to now, the insulin derivatives have been named using the two-word approach. The compounds named represent a structure with an additional amino acid, such as *insulin argine (58)*, or represent modifications of the amino acid sequence, i.e. *insulin aspart (76)*.

biphasic insulin injection (16), *compound insulin zinc suspension (06)*, *dalanated insulin (104)*, *globin zinc insulin injection (06)*, *insulin argine (58)*, *insulin aspart (76)*, *insulin defalan (37)*, *insulin degludec (101)*, *insulin detemir (80)*, *insulin glargine (76)*, *insulin glulisine (84)*, *insulin human (48)*, *insulin lispro (72)*, *insulin peglispro (107)*, *insulin tregopil (103)*, *insulin zinc suspension (amorphous) (04)*, *insulin zinc suspension (crystalline) (04)*, *isophane insulin (04)*, *neutral insulin injection (15)*, *protamine zinc insulin injection (06)*

argine: B30-yl-L-arginyl-L-arginine

aspart: [B28-L-aspartic acid]

dalanated: des-B30-alanine

defalan: des-B1-phenylalanine

degludec: $N^{6,\ B29}$-[*N*-(15-carboxypentadecanoyl)-L-γ-glutamyl]-des-30B-L-threonine

detemir: $N^{6,B29}$-tetradecanoyl-des-B30-L-threonine

glargine: [A21-glycine], B30-yl-L-arginyl-L-arginine

glulisine: [B3-lysine, B29-glutamic acid]

lispro: [B28-L-lysine, B29-L-proline]

tregopil: $N^{6,\ B29}$-(4,7,10,13-tetraoxatetradecanoyl).

4.17. Interferons

Interferon was published as an INN in 1962 with a general definition based on the origin and activity, e.g. "a protein formed by the interaction of animal cells with viruses capable of conferring on animal cells resistance to virus infection".

The name was revised in the 1980s when human interferon and its variations *alfa*, *beta* and *gamma* were produced by recombinant biotechnology. The INN Expert Group would have preferred to replace the old INN interferon by alfaferon, betaferon and gammaferon; however, this approach could not be adopted as these names had already been registered as trade marks. The system adopted was thus to take interferon alfa, interferon beta and interferon gamma, and to provide, when necessary, for further distinction by additional numbers, or in the case of mixtures, by additional codes. Additional Arabic numbers can be used to distinguish subspecies which differ significantly in primary amino acid sequence, but are still considered to belong to one of the primary groups e.g. Interferon alfa-1, interferon alfa- 2. Small (lower case) letters are used to subdivide such groups further on the basis of less significant differences like one, two or three amino acid differences or post translational modifications, including glycosylation e.g. Interferon alfa-2a, Interferon alfa-2b, Interferon beta-1a, Interferon beta-1b.

albinterferon alfa-2b (99), *cepeginterferon alfa-2b (105)*, *interferon alfa (73)*, *interferon alfacon-1 (77)*, *interferon beta (73)*, *interferon gamma (73)*, *peginterferon alfa-2a (84)*, *peginterferon alfa-2b (84)*, *peginterferon beta-1a (108)*, *peginterferon lambda-1a (105)*, *ropeginterferon alfa-2b (109)*.

4.18. Interleukin receptor antagonists

The common stem for interleukin receptor antagonists is *-kinra*.

interleukin-1 (IL-1) receptor antagonists: *-nakinra*

anakinra (72)

interleukin-4 (IL-4) receptor antagonists: *-trakinra*

pitrakinra (87).

4.19. Interleukin type substances

The common stem for interleukin type substances is *-kin*.

In accordance with general policy for naming glycosylated proteins (see item 3.4), it was agreed to publish the INNs for glycosylated interleukins with alfa, beta.

interleukin-1 (IL-1) analogues and derivatives: *-nakin*

interleukin-1α analogues and derivatives: *-onakin*

pifonakin (77)

interleukin-1β analogues and derivatives: *-benakin*

mobenakin (72)

interleukin-2 (IL-2) analogues and derivatives: *-leukin*

adargileukin alfa (89), *aldesleukin (63)*, *celmoleukin (65)*, *denileukin diftitox (78)*, *pegaldesleukin (74)*, *teceleukin (67)*, *tucotuzumab celmoleukin (95)*

interleukin-3 (IL-3) analogues and derivatives: *-plestim* (belongs to this group but in which the preferred stem has not been used)

daniplestim (76), *muplestim (74)*

interleukin-4 (IL-4) analogues and derivatives: *-trakin*

binetrakin (82)

interleukin-6 (IL-6) analogues and derivatives: *-exakin*

atexakin alfa (72)

interleukin-8 (IL-8) analogues and derivatives: *-octakin*

canoctakin (110), *emoctakin (74)*

interleukin-10 (IL-10) analogues and derivatives: *-decakin*

ilodecakin (81)

interleukin-11 (IL-11) analogues and derivatives: *-elvekin*

oprelvekin (76)

interleukin-12 (IL-12) analogues and derivatives: *-dodekin*

edodekin alfa (79)

interleukin-13 (IL-13) analogues and derivatives: *-tredekin*

cintredekin besudotox (92)

interleukin-18 (IL-18) analogues and derivatives: *-octadekin*

iboctadekin (92)

interleukin-21 (IL-21) analogues and derivatives: *-enicokin*

denenicokin (99)

neurotrophins (interleukin-78, brain derived neurotropic factor): *-neurin* (pre-stem, belongs to this group but in which the preferred stem has not been used)

abrineurin (84).

4.20. Monoclonal antibodies

The common stem for monoclonal antibodies is *-mab*.

INNs for monoclonal antibodies alphabetically by origin:

-*axomab* (pre-sub-stem, rat-murine hybrid)

catumaxomab (93), *ertumaxomab (93)*

-*omab* (mouse origin)

abagovomab (95), *afelimomab (80)*, *altumomab (80)*, *anatumomab mafenatox (86)*, *arcitumomab (74)*, *bectumomab (81)*, *begelomab (111)*, *besilesomab (92)*, *biciromab (66)*, *blinatumomab (100)*, *capromab (80)*, *detumomab (80)*, *dorlimomab aritox (66)*, *edobacomab (80)*, *edrecolomab (74)*, *elsilimomab (89)*, *enlimomab (80)*, *enlimomab pegol (77)*, *epitumomab (97)*, *epitumomab cituxetan (89)*, *faralimomab (81)*, *gavilimomab (84)*, *ibritumomab tiuxetan (86)*, *igovomab (86)*, *imciromab (66)*, *inolimomab (80)*, *lemalesomab (86)*, *maslimomab (66)*, *minretumomab (80)*, *mitumomab (82)*, *moxetumomab pasudotox (102)*, *nacolomab tafenatox (80)*, *naptumomab estafenatox (96)*, *nerelimomab (81)*, *odulimomab (81)*, *oregovomab (86)*, *racotumomab (100)*, *satumomab (81)*, *solitomab (106)*, *sulesomab (86)*, *taplitumomab paptox (84)*, *technetium (^{99m}Tc) fanolesomab (86)*, *technetium (^{99m}Tc) nofetumomab merpentan (81)*, *technetium (^{99m}Tc) pintumomab (86)*, *telimomab aritox (66)*, *tenatumomab (99)*, *tositumomab (80)*, *vepalimomab (80)*, *zolimomab aritox (80)*

-*umab* (human origin)

abrilumab (111), *actoxumab (111)*, *adalimumab (85)*, *adecatumumab (90)*, *aducanumab (110)*, *alirocumab (107)*, *anetumab ravtansine (109)*, *anifrolumab (109)*, *atinumab (104)*, *atorolimumab (80)*, *belimumab (89)*, *bertilimumab (88)*, *bezlotoxumab (107)*, *bimagrumab (111)*, *briakinumab (101)*, *brodalumab (105)*, *canakinumab (97)*, *carlumab (104)*, *cixutumumab (100)*, *conatumumab (99)*, *daratumumab (101)*, *denosumab (94)*, *diridavumab (111)*, *drozitumab (103)*, *dupilumab (108)*, *dusigitumab (108)*, *efungumab (95)*, *eldelumab (109)*, *enfortumab vedotin (109)*, *enoticumab (107)*, *evolocumab (108)*, *exbivirumab (91)*, *fasinumab (107)*, *fezakinumab (101)*, *figitumumab (100)*, *firivumab (111)*, *flanvotumab (106)*, *fletikumab (110)*, *foralumab (103)*, *foravirumab (100)*, *fresolimumab (101)*, *fulranumab (104)*, *ganitumab (103)*, *gantenerumab (108)*, *glembatumumab (102)*, *golimumab (91)*, *guselkumab (109)*, *icrucumab (104)*, *imalumab (111)*, *inclacumab (106)*, *intetumumab (101)*, *ipilimumab (94)*, *iratumumab (94)*, *lenzilumab (111)*, *lerdelimumab (86)*, *lexatumumab (95)*, *libivirumab (91)*, *lirilumab (107)*, *lucatumumab (98)*, *mapatumumab (93)*, *mavrilimumab (102)*, *metelimumab (88)*, *morolimumab (79)*, *namilumab (104)*, *narnatumab (105)*, *nebacumab (66)*, *necitumumab (100)*, *nesvacumab (108)*, *nivolumab (111)*, *ofatumumab (93)*, *olaratumab (103)*, *orticumab (107)*, *oxelumab (105)*, *panitumumab (96)*, *panobacumab (100)*, *patritumab (106)*,

placulumab (107), *pritumumab (89)*, *radretumab (104)*, *rafivirumab (100)*, *ramucirumab (110)*, *raxibacumab (92)*, *regavirumab (80)*, *rilotumumab (101)*, *robatumumab (100)*, *roledumab (103)*, *sarilumab (106)*, *secukinumab (102)*, *seribantumab (108)*, *sevirumab (66)*, *sifalimumab (104)*, *sirukumab (105)*, *stamulumab (95)*, *tabalumab (105)*, *tarextumab (109)*, *teprotumumab (108)*, *tosatoxumab (109)*, *tovetumab (109)*, *tralokinumab (102)*, *tremelimumab (97)*, *tuvirumab (66)*, *ulocuplumab (110)*, *urelumab (104)*, *ustekinumab (99)*, *vantictumab (109)*, *varlilumab (111)*, *vesencumab (104)*, *votumumab (80)*, *zalutumumab (93)*, *zanolimumab (92)*, *ziralimumab (84)*

-*ximab* (chimeric origin)

abciximab (80), *amatuximab (104)*, *basiliximab (81)*, *bavituximab (95)*, *brentuximab vedotin (103)*, *cetuximab (82)*, *clenoliximab (77)*, *coltuximab ravtansine (109)*, *dinutuximab (109)*, *ecromeximab (87)*, *ensituximab (103)*, *futuximab (107)*, *galiximab (89)*, *girentuximab (101)*, *indatuximab ravtansine (105)*, *infliximab (77)*, *iodine (^{124}I) girentuximab (101)*, *keliximab (81)*, *lumiliximab (90)*, *margetuximab (109)*, *modotuximab (110)*, *pagibaximab (93)*, *priliximab (80)*, *pritoxaximab (108)*, *rituximab (77)*, *setoxaximab (108)*, *siltuximab (100)*, *teneliximab (87)*, *ublituximab (104)*, *vapaliximab (87)*, *volociximab (93)*

-*xizumab* (chimeric-humanized origin)

ontuxizumab (109), *otelixizumab (99)*, *pasotuxizumab (111)*

-*zumab* (humanized origin)

abituzumab (109), *alacizumab pegol (98)*, *alemtuzumab (83)*, *anrukinzumab (98)*, *apolizumab (87)*, *aselizumab (88)*, *bapineuzumab (93)*, *benralizumab (102)*, *bevacizumab (86)*, *bimekizumab (110)*, *bivatuzumab (86)*, *blosozumab (105)*, *bococizumab (110)*, *brontictuzumab (111)*, *cantuzumab mertansine (105)*, *cantuzumab ravtansine (105)*, *caplacizumab (106)*, *cedelizumab (81)*, *certolizumab pegol (97)*, *citatuzumab bogatox (99)*, *clazakizumab (107)*, *codrituzumab (109)*, *concizumab(108)*, *crenezumab (105)*, *dacetuzumab (98)*, *daclizumab (78)*, *dalotuzumab (107)*, *dapirolizumab pegol (110)*, *demcizumab (107)*, *denintuzumab mafodotin (111)*, *duligotuzumab (110)*, *eculizumab (87)*, *efalizumab (85)*, *elotuzumab (100)*, *emactuzumab (111)*, *emibetuzumab (111)*, *enavatuzumab (104)*, *enokizumab (104)*, *epratuzumab (82)*, *erlizumab (84)*, *etaracizumab (99)*, *etrolizumab (104)*, *farletuzumab (100)*, *felvizumab (77)*, *ficlatuzumab (105)*, *fontolizumab (87)*, *gemtuzumab (83)*, *gevokizumab (104)*, *ibalizumab (97)*, *idarucizumab (109)*, *imgatuzumab (107)*, *inotuzumab ozogamicin (92)*, *itolizumab (103)*, *ixekizumab (105)*, *labetuzumab (85)*, *lampalizumab (107)*, *lebrikizumab (101)*, *lifastuzumab vedotin (110)*, *ligelizumab (107)*, *lintuzumab (86)*, *lodelcizumab (108)*, *lorvotuzumab mertansine (103)*,

lulizumab pegol (111), *lumretuzumab (111)*, *matuzumab (88)*, *mepolizumab (81)*, *milatuzumab (98)*, *mogamulizumab (104)*, *motavizumab (95)*, *natalizumab (79)*, *nimotuzumab (94)*, *obinutuzumab (109)*, *ocaratuzumab (107)*, *ocrelizumab (95)*, *olokizumab (103)*, *omalizumab (84)*, *onartuzumab (104)*, *oportuzumab monatox (100)*, *otlertuzumab (110)*, *ozanezumab (108)*, *ozoralizumab (105)*, *palivizumab (79)*, *parsatuzumab (107)*, *pascolizumab (87)*, *pateclizumab (105)*, *pembrolizumab (110)*, *perakizumab (108)*, *pertuzumab (89)*, *pexelizumab (86)*, *pidilizumab (108)*, *pinatuzumab vedotin (108)*, *polatuzumab vedotin (110)*, *ponezumab (104)*, *quilizumab (106)*, *ralpancizumab (110)*, *ranibizumab (90)*, *reslizumab (85)*, *romosozumab (106)*, *rontalizumab (101)*, *rovelizumab (81)*, *ruplizumab (83)*, *samalizumab (105)*, *sibrotuzumab (86)*, *simtuzumab (107)*, *siplizumab (87)*, *sofituzumab vedotin (110)*, *solanezumab (107)*, *sontuzumab (94)*, *suvizumab (102)*, *tadocizumab (94)*, *talizumab (89)*, *tanezumab (99)*, *tefibazumab (92)*, *teplizumab (97)*, *tigatuzumab (98)*, *tildrakizumab (108)*, *tocilizumab (90)*, *toralizumab (87)*, *trastuzumab (78)*, *trastuzumab emtansine (103)*, *tregalizumab (104)*, *tucotuzumab celmoleukin (95)*, *urtoxazumab (90)*, *vanucizumab (111)*, *vatelizumab (105)*, *vedolizumab (100)*, *veltuzumab (98)*, *visilizumab (84)*, *vorsetuzumab (107)*, *vorsetuzumab mafodotin (107)*, *yttrium (^{90}Y) clivatuzumab tetraxetan (102)*, *yttrium ^{90}Y tacatuzumab tetraxetan (93)*

***Others*:** *muromonab-CD3 (59)* (the first monoclonal antibody to which an INN was assigned belongs to this group but it was named before the stem was established).

4.21. Oxytocin derivatives

The common stem for oxytocin derivatives is *-tocin*.

argiprestocin (13), *aspartocin (11)*, *carbetocin (45)*, *cargutocin (35)*, *demoxytocin (22)*, *merotocin (111)*, *nacartocin (51)*, *oxytocin (13)*.

4.22. Peptides and glycopeptides

for special groups of peptides see *-actide* (see item 4.27), *-pressin* (see item 4.30), *-relin* (see item 4.25), *-tocin* (see item 4.21)

The common stem for peptides and glycopeptides is *-tide*.

analgesic: *leconotide (86)*, *ziconotide (78)*

angiogenesis inhibitor: *cilengitide (81)*

angiotensin converting-enzyme inhibitor: *teprotide (36)*

antianaemic: *peginesatide (108)*

antiarrhythmic: *danegaptide (101)*, *rotigaptide (94)*

anti-inflammatory: *icrocaptide (89)*

antidepressant: *nemifitide (87)*

antidiabetic: *albenatide (111)*, *amlintide (76)*, *davalintide (101)*, *exenatide (89)*, *langlenatide (111)*, *lixisenatide (99)*, *pramlintide (74)*, *seglitide (57)*

antidiarrhoeal: *lagatide (75)*

antineoplastic: *paclitaxel trevatide (109)*

antithrombotic: *eptifibatide (78)* (*-fiba-* is a pre-substem for platelet aggregation inhibitor (GPIIb/IIIa receptor antagonist))

antiviral: *enfuvirtide (85)*, *tifuvirtide (91)*

natriuretic peptides: *anaritide (57)*, *carperitide (65)*, *cenderitide (105)*, *neseritide (80)*, *ularitide (69)*

autoimmune disorders: *dalazatide (111)*, *dirucotide (100)*

β1-adrenergic receptor analogue: *mibenratide* (111)

calcium sensing receptor agonist: *velcalcetide (109)*

cicatrisation promoter: *aclerastide (110)*, *ensereptide (107)*

diagnostic: *betiatide (58)*, *bibapcitide (78)*, *ceruletide (34)*, *depreotide (80)*, *flotegatide (^{18}F) (108)*, *fluciclatide (^{18}F) (103)*, *maraciclatide (103)*, *mertiatide (60)*, *pendetide (70)*, *technetium (^{99m}Tc) apcitide (86)*, *technetium (^{99m}Tc) etarfolatide (107)*, *teriparatide (50)*

expectorant (in cystic fibrosis): *lancovutide (99)*

gastro-intestinal bleeding / antineoplastic: *edotreotide (84)*, *ilatreotide (68)*, *lanreotide (64)*, *octreotide (52)*,

pentetreotide (66), *vapreotide (62)*

gastro-intestinal functions normalizing agent: *linaclotide (97)*, *plecanatide (104)*

glucagon-like peptide (GLP) analogues: *-glutide*

albiglutide (97), *dulaglutide (103)*, *elsiglutide (104)*, *liraglutide (87)*, *semaglutide (101)*, *taspoglutide (99)*, *teduglutide (90)*

growth stimulant-veterinary: *nosiheptide (35)*

gut motility increasing: *ociltide (52)*

hormone analogue: *abaloparatide (109)*, *semparatide (80)*, *teriparatide (50)* *(see diagnostic)*

immunological agents - antineoplastics: *almurtide (74)*, *delmitide (92)*, *edratide (89)*, *goralatide (72)*, *mifamurtide (95)*, *murabutide (49)*, *pentigetide (60)*, *pimelautide (53)*, *prezatide copper acetate (67)*, *rolipoltide (94)*, *romurtide (61)*, *tabilautide (60)*, *temurtide (60)*, *tigapotide (95)*

immunological agents for active immunization: *-motide* (see item 4.23)

abecomotide (109), *alicdamotide (109)*, *amilomotide (105)*, *asudemotide (107)*, *disomotide (94)*, *elpamotide (103)*, *latromotide (107)*, *ovemotide (94)*, *pradimotide (107)*, *tanurmotide (109)*, *tecemotide (108)*, *tertomotide (98)*, *tiplimotide (82)*, *trempamotide (107)*, *zastumotide (110)*

inhibition of growth hormone release: *pasireotide (90)*

kallicrein inhibitor: *ecallantide (93)*

melanocortin receptor agonist: *afamelanotide (99)*, *bremelanotide (95)*, *modimelanotide*

neuromodulator / neuroprotective agent: *davunetide (100)*, *ebiratide (56)*, *obinepitide (96)*, *vanutide cridificar (100)*

peptic ulcer: *sulglicotide (29)*, *triletide (50)*

pulmonary surfactant: *lusupultide (80)*, *sinapultide (78)*

sedative: *emideltide (70)*

thrombin receptor as an agonist, promoter of bone and skin wound healing: *rusalatide (96)*

transforming growth factor beta-1 inhibitor: *disitertide (99)*

treatment of Parkinson's disease: *doreptide (59)*, *pareptide (38)*

zonulin antagonist (in celiac disease): *larazotide (99)*

other: *defibrotide (44)* (nucleotide, the preferred stem has been used but not in accordance with its definition see item 4.7).

4.23. Peptide vaccines / recombinant vaccines

Definition of peptide vaccines: vaccine in which antigens are produced from synthetic peptides and transported through the bloodstream by an adjuvant, in order to stimulate an immune response.

Definition of recombinant vaccines: vaccine produced from a cloned gene.

Description of recombinant vaccines: there are certain antigens on viruses and bacteria which are better at stimulating an antibody response by the animal than others. The genes for these antigens can be isolated, and made to produce large quantities of the antigens they code for. A recombinant vaccine contains these antigens, not the whole organism. Compare with "modified live vaccine" and "killed vaccine".

peptide vaccines (see item 4.22): *-motide*

abecomotide (109), *alicdamotide (109)*, *amilomotide (105)*, *asudemotide (107)*, *disomotide (94)*, *elpamotide (103)*, *latromotide (107)*, *ovemotide (94)*, *pradimotide (107)*, *tanurmotide (109)*, *tecemotide (108)*, *tertomotide (98)*, *tiplimotide (82)*, *trempamotide (107)*, *zastumotide (110).*

recombinant vaccine:

verpasep caltespen (95) (heat-shock protein HSP 65 (*Mycobacterium bovis* strain BCG) fusion protein with transcription factor E7 (human papilloma virus 16)).

The suffix *-tespen* is the indicator of heat shock protein.

4.24. Pituitary / placental glycoprotein hormones

The names selected by the International Union of Pure and Applied Chemistry–International Union of Biochemistry (IUPAC-IUB) have, to date, been chosen for compounds with an amino acid sequence identical to that of the naturally occurring human hormones. Addition of a Greek letter as the second part of the name will allow differentiation of different glycosylation patterns for compounds produced by biotechnology (see item 3.4 - general policies for glycosylated compounds).

follicle stimulating hormones: ending in *(-)follitropin*

corifollitropin alfa (80), *follitropin alfa (71)*, *follitropin beta (75)*, *follitropin gamma (106)*, *urofollitropin (57)*, *varfollitropin alfa (101)*

gonadotropin: ending in *-gonadotropin*

choriogonadotropin alfa (76), *chorionic gonadotrophin (01)*: chorionic gonadotropins, obtained from human serum and urine during pregnancy and has both lutropin and follitropin activity

serum gonadotrophin (01): used for the follicle stimulating hormone (FSH, follitropin) from serum of pregnant mares

luteinizing hormones: ending in *(-)lutropin*

lutropin alfa (71).

4.25. Pituitary hormone-release stimulating peptides

The common stem for pituitary hormone-release stimulating peptides is *-relin.*

LHRH-release-stimulating peptides:

avorelin (74), *buserelin (36)*, *deslorelin (61)*, *fertirelin (42)*, *gonadorelin (32)*, *goserelin (55)*, *histrelin (53)*, *leuprorelin (47)*, *lutrelin (51)*, *nafarelin (50)*, *peforelin (93)*, *triptorelin (58)*, *zoptarelin doxorubicin (107)*

growth hormone release-stimulating peptides: *-morelin*

anamorelin (97), *capromorelin (83)*, *dumorelin (59)*, *examorelin (72)*, *ipamorelin (78)*, *lenomorelin (106)*, *macimorelin (100)*, *pralmorelin (77)*, *rismorelin (74)*, *sermorelin (56)*, *somatorelin (57)*, *tabimorelin (86)*, *tesamorelin (96)*, *ulimorelin (103)*

thyrotropin releasing hormone analogues: *-tirelin*

azetirelin (60), *montirelin (58)*, *orotirelin (58)*, *posatirelin (60)*, *protirelin (31)*, *taltirelin (75)*

thyrotropin alfa (78) (thyrotropin releasing hormone (TRH) analog, belongs to this group but in which the preferred stem has not been used)

other: *corticorelin (66)* (diagnostic agent).

4.26. Receptor molecules, native or modified

The stem for receptor molecules, native or modified is *-cept*.

A preceding infix should designate the target.

B-cell activating factor receptors: *-ba-*
briobacept (98)

vascular endothelial growth factor receptors: *-ber-*
aflibercept (96), *conbercept (105)*

complement receptors: *-co-*
mirococept (91)

subgroup of interferon receptors: *-far-*
bifarcept (86)

frizzled family receptors: *-fri-*
ipafricept (109)

lymphocyte function-associated antigen 3 receptors: *-lefa-*
alefacept (84)

interleukin-1 receptors: *-na-*
rilonacept (95)

tumour necrosis factor (TNF) receptors: *-ner-*
baminercept (99), *etanercept (81)*, *lenercept (72)*, *onercept (86)*, *pegsunercept (95)*

cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptors: *-ta-*
abatacept (91), *belatacept (93)*

transmembrane activator and calcium modulator and cyclophilin ligand interactor: *-taci-*
atacicept (95)

transforming growth factor receptors: *-ter-*
dalantercept (105), *luspatercept (110)*, *ramatercept (108)*, *sotatercept (104)*

antiviral receptors: *-vir-*
alvircept sudotox (69).

4.27. Synthetic polypeptides with a corticotropin-like action

The common stem for synthetic polypeptides with a corticotropin-like action is *-actide*.

alsactide (45), *codactide (24)*, *giractide (29)*, *norleusactide (18)*, *seractide (31)*, *tetracosactide (18)*, *tosactide (24)*, *tricosactide (44)*, *tridecactide (97).*

4.28. Thrombomodulins

sothrombomodulin alfa (101), *thrombomodulin alfa (94).*

4.29. Toxins

toxin ML-1 (mistletoe lectin I) *(Viscum album)*: *aviscumine (86)*.

4.30. Vasoconstrictors, vasopressin derivatives

The common stem for vasoconstrictors, vasopressin derivatives is *-pressin*.

argipressin (13), *desmopressin (33)*, *felypressin (13)*, *lypressin (13)*, *ornipressin (22)*, *selepressin (105)*, *terlipressin (46)*, *vasopressin injection (16)*.

4.31. Various[7]

- *abicipar pegol (108)*: pegylated composite protein for clinical applications (CPCA), with alternative scaffold domain to antigen receptors based on ankyrin repeats, anti-[*Homo sapiens* VEGFA (vascular endothelial growth factor A, VEGF-A, VEGF)];
  glycyl-seryl-ankyrin repeats (3-35, 36-68, 69-101, 102-123)-lysyldialanyl-bis(triglycyl-seryl) linker (127-134)-cysteinyl (1-135), conjugated via a maleimide group linker (thioether bond to C135) to a single linear methoxy polyethylene glycol 20 (mPEG20)

- *alisporivir (100)*: [8-(*N*-methyl-D-alanine),9-(*N*-ethyl-L-valine)]cyclosporine

- *agatolimod (98)*: DNA, d(*P*-thio)(T-C-G-T-C-G-T-T-T-T-G-T-C-G-T-T-T-T-G-T-C-G-T-T)

- *andexanet alfa (110):* des-(6-39)-human blood-coagulation factor X light chain (98-108')-disulfide with [185'-alanine (S>A)]human activated factor Xa heavy chain, produced in Chinese hamster ovary (CHO) cells (glycoform alfa)

[7] The descriptions following the INN names may not be the complete definitions as shown in the publications of INN Lists.

- *angiotensin II (65)*: 5-L-isoleucineangiotensin II (the source of the material should be indicated)

- *angiotensinamide (12)*: N-{1-{N-{N-{N-[N-(N^2-asparaginylarginyl)valyl]tyrosyl}valyl}histidyl}prolyl}-3-phenylalanine

- *asvasiran (111):* small interfering RNA (siRNA) inhibitor of human Respiratory Syncytial Virus replication;
  duplex of guanylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-uridylyl-(3'→5')-uridylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-cytidylyl-(3'→5')-adenylyl-(3'→5')-adenylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-uridylyl-(3'→5')-cytidylyl-(3'→5')-adenylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-thymidylyl-(3'→5')-thymidine and thymidylyl-(5'→3')-thymidylyl-(5'→3')-cytidylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-uridylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-uridylyl-(5'→3')-cytidine

- *bamosiran (106)*: siRNA inhibitor of β2-adrenergic receptor production

- *bevasiranib (108)*: siRNA inhibitor of Vascular Endothelial Growth Factor (VEGF) production

- *blisibimod (107*): B-cell activating factor (BAFF)-binding peptide fragment/human IgG1 Fc fusion protein

- *calcitonin (80)*: a polypeptide hormone that lowers the calcium concentration in blood (the species specificity should be indicated in brackets behind the name)

- *conestat alfa (107)*: human plasma protease C1 inhibitor (C1 esterase inhibitor) (*N*,*O*-glycosylated recombinant protein expressed in the mammary gland of transgenic rabbits), glycoform α

- *dianexin (109)*: recombinant DNA derived annexin A5 dimer covalently linked by a 14 residues peptide linker, produced in *Escherichia coli* (nonglycosylated): L-methionyl-human annexin A5 fusion protein with glycyl-L-seryl-L-leucyl-L-α-glutamyl-L-valyl-L-leucyl-L-phenylalanyl-L-glutaminylglycyl-L-prolyl-L-serylglycyl-L-lysyl-L-leucyl-human annexin A5

- *delcasertib (105)*: human immunodeficiency virus 1 protein Tat-(46-57)-peptide (1→1')-disulfide with L-cysteinyl-[mouse protein kinase C delta type-(8-17)-peptide]

- *edifoligide (89)*: oligonucleotide

- *egaptivon pegol (111)*: a pegylated aptamer which binds von Willebrand factor; 5'-*O*-{[6-(carboxyamino)hexyl]hydroxyphosphoryl}-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyadenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyl-*P*-thioguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-2'-deoxyguanylyl-(3'→5')-thymidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxycytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→3')-thymidine, carbamate ester with monomethyl ether of polyethylene gycol (20 kDa)

- *emapticap pegol (108)*: β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanosine 6-{2-(*N*-[ω-methylpoly(oxyethan-1,2-diyl)]-2-{[ω-methylpoly(oxyethan-1,2-diyl)]oxy}acetamido)acetamido}hexyl hydrogen 5'-phosphate

- *epelestat (92)*: human recombinant neutrophil elastase inhibitor, bovine pancreatic trypsin inhibitor (BPTI) homologue

- *hemoglobin glutamer (80)*: the species specificity should be indicated in brackets behind the name, "(bovine)"; the average mass of the polymer is given as e.g. haemoglobin glutamer-250 for 250kD

- *hemoglobin crosfumaril (76)*: hemoglobin A_0 (human $\alpha_2\beta_2$ tetrameric subunit), α-chain 99,99'-diamide with fumaric acid

- *hemoglobin crosfumaril (bovine) (108)*: $S^{3}.^{\beta 92}$,$S^{3}.^{\beta' 92}$-bis(2-amino-2-oxoethyl)-$N^{6.\alpha 99}$,$N^{6.\alpha' 99}$-(but-2-enedioyl)bovine hemoglobulin ($\alpha_2\beta_2$ tetramer)

- *hemoglobin raffimer (89)*

- *imetelstat (101)*: oligonucleotide telomerase inhibitor; 3'-amino-3'-deoxy-*P*-thiothymidylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'→5')-3'-amino-3'-deoxy-*P*-thiothymidylyl-(3'→5')-3'-amino-3'-deoxy-*P*-thiothymidylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioguanylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thiocytidylyl-(3'→5')-3'-amino-2',3'-dideoxy-*P*-thioadenylyl-(3'→5')-3'-amino-2',3'-dideoxyadenosine 5'-{*O*-[2-hydroxy-3-(hexadecanoylamino)propyl] hydrogen phosphorothioate}

- *enadenotucirev (111)*: chimeric oncolytic adenovirus Ad3/Ad11p containing two deletions in the viral genome in the E3 region (2444 bp) and in the E4 region (24bp) and 197 non-homologous nucleotides in the E2B region

- *entolimod (108)*: L-methionyl-L-arginylglycyl-L-seryl-hexa(L-histidyl)glycyl-(*Enterobacteria phage T7* major capsid protein 10A-(1-11)-peptidyl)-L-arginyl-L-aspartyl-L-leucyl-L-tyrosyl-tetra(L-aspartyl)-L-lysyl-L-aspartyl-L-prolyl-(*Salmonella dublin* flagellin-(1-176)-peptidyl)-L-seryl-L-prolylglycyl-L-isoleucyl-L-seryl-pentaglycyl-L-isoleucyl-L-leucyl-L-aspartyl-L-seryl-L-methionylglycyl-(*Salmonella dublin* flagellin-(402-505)-peptide)

- *iodinated (^{125}I) human serum albumin (24)*: human serum albumin iodinated with radioactive iodine (^{125}I)

- *iodinated (^{131}I) human serum albumin (24)*: human serum albumin iodinated with radioactive iodine (^{131}I)

- *iroplact (74)*: *N*-L-methionyl blood platelet factor 4 (human subunit)

- *ismomultin alfa (91)*: 47-261-Glycoprotein gp 39 (human clone CDM8-gp39 reduced)

- *lexaptepid pegol (108)*: β-L-guanylyl-(3'→5')-β-L-cytidylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-cytidylyl-(3'→5')-β-L-cytidylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-uridylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-adenylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-cytidylyl-(3'→5')-β-L-guanylyl-(3'→5')-β-L-cytidine 6-{2-(*N*-[ω-methylpoly(oxyethan-1,2-diyl)]-2-{[ω-methylpoly(oxyethan-1,2-diyl)]oxy}acetamido)acetamido}hexyl hydrogen 5'-phosphate

- *litenimod (96)*: (3'-5')d(*P*-thio)(T-A-A-A-C-G-T-T-A-T-A-A-C-G-T-T-A-T-G-A-C-G-T-C-A-T)

- *macrosalb (^{131}I) (33)*: macroaggregated iodinated (^{131}I) human albumin

- *macrosalb (^{99m}Tc)(33)*: technetium (^{99m}Tc) labelled macroaggregated human serum albumin

- *metenkefalin (97)*: L-tyrosylglycylglycyl-L-phenylalanyl-L-methionine β-endorphin human-(1-5)-peptide

- *metreleptin (82)*: *N*-methionylleptin (human)

- *mirostipen (85)*: [23-methionine] human myeloid progenitor inhibitory factor 1-(23-99)-peptide

- *nagrestipen (76)*: 26-L-alaninelymphokine MIP 1α (human clone pAT464 macrophage inflammatory)

- *ocriplasmin (101)*: truncated human plasmin:
  human plasmin heavy chain A-(543-561)-peptide (548-666;558-566)-bisdisulfide with human plasmin light chain B

- *olaptesed pegol (109)*: β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-uridylyl-(3′→5′)-β-L-adenylyl-(3′→5′)-β-L-cytidylyl-(3′→5′)-β-L-guanylyl-(3′→5′)-β-L-cytidine 6-{2-(*N*-[ω-methylpoly(oxyethan-1,2-diyl)]-2-{[ω-methylpoly(oxyethan-1,2-diyl)]oxy}acetamido)acetamido}hexyl hydrogen 5’-phosphate

- *opebacan (83)*: 132-L-alanine-1-193-bactericidal / permeability-increasing protein (human)

- *orgotein (31)*: a group of soluble metalloproteins isolated from liver, red blood cells, and other mammalian tissues

- *ovandrotone albumin (52)*: 3-[(3,17-dioxoandrost-4-en-7α-yl)thio]propionic acid, serum albumin conjugate

- *parathyroid hormone (90)*: non glycosylated human parathyroid hormone, the origin should be indicated between brackets after the INN, for example (r. *E. coli*) for recombinant produced by *Escherichia coli*

- *patisiran (109)*: small interfering RNA (siRNA);
  RNA duplex of guanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-adenylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-adenylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-adenylyl-(3'→5')-guanylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-adenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-thymidylyl-(3'→5')-thymidine with thymidylyl-(5'→3')-thymidylyl-(5'→3')-

cytidylyl-(5'→3')-adenylyl-(5'→3')-2'-*O*-methyluridylyl-(5'→3')-uridylyl-(5'→3')-guanylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-uridylyl-(5'→3')-cytidylyl-(5'→3')-adenylyl-(5'→3')-2'-*O*-methyluridylyl-(5'→3')-adenylyl-(5'→3')-adenylyl-(5'→3')-guanylyl-(5'→3')-guanylyl-(5'→3')-uridylyl-(5'→3')-adenosine

- *pegaptanib (88)*: 5'-ester of (2'-deoxy-2'-fluoro)C-Gm-Gm-A-A-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-Am-Gm-(2'-deoxy-2'-fluoro)U-Gm-Am-Am-(2'-deoxy-2'-fluoro)U-Gm-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)U-Am-(2'-deoxy-2'-fluoro)C-Am-(2'-deoxy-2'-fluoro)U-(2'-deoxy-2'-fluoro)C-(2'-deoxy-2'-fluoro)C-Gm-(3'→3')-dT with α,α'-[[(1*S*)-1-[[5-(phosphonooxy)pentyl]carbamoyl]pentane-1,5-diyl]bis(iminocarbonyl)]bis[ω-methoxypoly(oxyethane-1,2-diyl)]

- *pegdinetanib (103)*: 94 residues protein derived from human fibronectin 10th type III domain, pegylated: glycyl[1438-L-arginine(D>R),1439-L-histidine(A>H),1441-L-histidine(A>H),1442-L-phenylalanine(V>F),1443-L-proline(T>P),1444-L-threonine(V>T),1467-L-leucine(G>L),1468-L-glutamine(S>Q),1469-L-proline(K>P),1470-L-proline(S>P),1492-L-aspartic acid(G>D),1493-glycine(R>G),1494-L-arginine(G>R),1495-L-asparagine(D>N),1496-glycine(S>G),1497-L-arginine(P>R),1498-L-leucine(A>L),1499-L-leucine(S>L),1501-L-isoleucine(K>I),1515-*S*-[(3*RS*)-1-(1-{[α-methylpoly(oxyethylene)]carbamoyl}-3-[({[α-methylpoly(oxyethylene)]carbamoyl}oxy)methyl]-8,13-dioxo-1,4-dioxa-9,12-diazapentadecan-15-yl)-2,5-dioxopyrrolidin-3-yl]-L-cysteine(S>C)]human fibronectin-(1424-1516)-peptide

- *revusiran (111)*: [(2*S*,4*R*)-1-{30-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-14,14-bis[16-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-5,11-dioxo-2,16-dioxa-6,10-diazahexadecyl]-12,19,25-trioxo-16,30-dioxa-13,20,24-triazatriacontanoyl}-4-hydroxypyrrolidin-2-yl]methyl hydrogen 2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluoroguanylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluoroadenylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyluridylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-deoxy-2'-fluoroadenylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluorouridylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-*O*-methylcytidylyl-(3'→5')-2'-deoxy-2'-fluorocytidylyl-(3'→5')-2'-*O*-methyladenylyl-(3'→5')-2'-deoxy-2'-fluoroadenylyl-(3'→5')-2'-*O*-methylguanylyl-(3'→5')-2'-deoxy-2'-fluoroadenylate duplex with 2'-*O*-methyl-*P*-thiocytidylyl-(5'→3')-2'-deoxy-2'-fluoro-*P*-thiouridylyl-(5'→3')-2'-*O*-methyladenylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl-(5'→3')-2'-*O*-methylcytidylyl-(5'→3')-2'-deoxy-

2'-fluorocytidylyl-(5'→3')-2'-*O*-methyluridylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-*O*-methyladenylyl-(5'→3')-2'-deoxy-2'-fluoroadenylyl-(5'→3')-2'-*O*-methylguanylyl-(5'→3')-2'-*O*-methyluridylyl-(5'→3')-2'-*O*-methyladenylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl-(5'→3')-2'-*O*-methyladenylyl-(5'→3')-2'-deoxy-2'-fluorouridylyl-(5'→3')-2'-deoxy-2'-fluorouridylyl-(5'→3')-2'-deoxy-2'-fluoroguanylyl-(5'→3')-2'-*O*-methylguanylyl-(5'→3')-2'-deoxy-2'-fluorouridylyl-(5'→3')-2'-*O*-methyluridylyl-(5'→3')-2'-deoxy-2'-fluorocytidylyl-(5'→3')-2'-*O*-methyluridine

- *rintatolimod (102)*: poly[5']-inosinylyl-(3'→) duplex with poly[dodecakis[3']-cytidylyl-(5'→)3')-uridylyl-(5'→)

- *secretin (01)*: hormone of the duodenal mucosa which activates the pancreatic secretion and lowers the blood-sugar level

- *secretin human (106*): human peptide hormone secretin

- *serelaxin (105)*: human relaxin 2 (relaxin H2)

- *talactoferrin alfa (93)*: recombinant human lactoferrin

- *tadekinig alfa (90)*: interleukin-18 binding protein (human gene IL 18BP isoform a precursor)

- *thrombin alfa (97)*: human thrombin (recombinant, glycoform α)

- *tiprelestat (103)*: human elafin (elastase-specific inhibitor, skin-derived antileukoproteinase, peptidase inhibitor 3)

- *topsalysin (111)*: recombinant DNA derived proaerolysin, pore-forming protein, from *Aeromonas hydrophila,* with the furin site substituted with a prostate specific antigen (PSA) cleavage site, fusion protein with 6 histidines, produced in *Escherichia coli* (nonglycosylated): [427-L-histidine(K>H),428-L-serine(V>S),429-L-serine(R>S),430-L-lysine(R>K),431-L-leucine(A>L),432-L-glutamine(R>Q)]proaerolysin *Aeromonas hydrophila* fusion protein with hexa-L-histidine

- *torapsel (91)*: 42-89-glycoprotein (human clone PMT21:PL85 P-selectin glycoprotein ligand 1) fusion protein with immunoglobulin (human constant region)

- *trebananib (106):* immunoglobulin G1 Fc fragment fused with two synthetic polypeptides that bind the *Homo sapiens* ANGPT2 (angiopoietin 2); methionyl (1) -gamma1 heavy chain fragment (2-228) [*Homo sapiens* IGHG1*01 hinge (EPKSC 1-5>del) (2-11), CH2 (12-121), CH3 (122-228)] fused, at the C-terminal end, with a synthetic polypeptide that comprises two 14-mer amino acid repeats that bind angiopoietin 2 (229-287) [linker (229-235) -14-mer (236-249) – linker (250-271) -14-mer (272-285) -leucyl-glutamate]; (7-7':10-10')-bisdisulfide dimer

- *tremacamra (78)*: 1-453-glycoprotein ICAM-I (human reduced)

- *troplasminogen alfa (99)*: thrombin-activable plasminogen; endo-[(558a(*559*)-558h(*365*))-human coagulation factor XI-(363-370)-peptide]-des-(559-562)-[606(*610*)-lysine,623(*627*)-lysine]human plasminogen, glycoform α

- *votucalis (96)*: methionyl[145-leucine]FS-HBP2 (*Rhipicephalus appendiculatus* (Brown ear tick) Female-Specific Histamine-Binding Protein 2).

5. CURRENT CHALLENGES

The challenges currently faced include the following:

- The INN Expert Group, when selecting names for recombinant proteins, has to deal not with substances with well-defined structures but with products of highly complex composition or even with mixtures of such products.
- It is not only modified proteins that might differ from their naturally occurring counterparts, products derived by expression of the natural gene in foreign host cells may also differ structurally, biologically or immunologically from the natural protein.
- Glycoproteins particularly may occur in forms that differ in the structure of one or more of their carbohydrate units, a phenomenon known as microheterogeneity and resulting in a heterogeneous population of molecules. Such differences may affect both the size and the charge of individual glycoproteins.
- A variety of novel biotechnology-derived products are under development, all of which will require specific policies on how to deal with such products.
- Clearly, the INN nomenclature of biological medicinal products is an area of increasing complexity.

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** These documents are available on the INN Programme Website at: http://www.who.int/medicines/services/inn/en/.*

ANNEX 1

The list of INN for composite proteins published[8]

classified by groups

alb- (human serum albumin)

alb- & -cog

albutrepenonacog alfa (109)

human coagulation factor IX (EC 3.4.21.22, Christmas factor, plasma thromboplastin component) 148-threonine variant fusion protein with prolyl(human coagulation factor IX 148-threonine variant-(137-153)-peptide) fusion protein with human serum albumin, produced in CHO cells (alfa glycoform)

alb- & -interferon

albinterferon alfa-2b (99)

human serum albumin (585 residues) fusion protein with human interferon α-2b (165 residues)

alb- & -tide

albenatide (111)

S$^{3.34}$-{1-[(23*S*)-23-{[exendin-4 *Heloderma suspectum* precursor-(48-86)-peptidyl (exenatidyl)]amino}-3,12,24-trioxo-7,10-dioxa-4,13,18,25-tetraazapentacosyl]-2,5-dioxopyrrolidin-3-yl}human serum albumin.
Peptide is synthetic, and human serum albumin is produced in *Saccharomyces cerevisiae*.

[8] It should be noted that this list may not be comprehensive (eg. pegylated substances are not included) and the descriptions under the names are the ones published.

albiglutide (97)

([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)([8-glycine]human glucagon-like peptide 1-(7-36)-peptidyl)(human serum albumin (585 residues))

Others:

-al-& -grastim

balugrastim (107)

human serum albumin (585 residues) fusion protein with des-(1-alanine,37-valine,38-serine,39-glutamic acid)-human granulocyte colony-stimulating factor (pluripoietin)

-ase

reveglucosidase alfa (111)

des-(2-7)-human insulin-like growth factor II fusion protein with glycyl-L-alanyl-L-prolyl-human lysosomal alpha-glucosidase (acid maltase, aglucosidase alfa) produced in Chinese hamster ovary (CHO) cells, glycoform alfa

senrebotase (107)

L-methionylglycyl-L-seryl-des-(445-glycine,446-L-tyrosine)-[2-L-glutamic acid,432,442,444,447-tetra-L-aspartic acid]botulinum neurotoxin A precursor 27-L-alanine variant light chain (433-41')-disulfide with [14-L-arginine,15-L-lysine]human nociceptin fusion protein with L-alanyl-L-leucyl-L-alanyltris(tetraglycyl-L-seryl)-[3-L-valine,4-L-leucine,5-L-glutamine-418-L-leucine,419-L-aspartic acid]botulinum neurotoxin A heavy chain-(1-419)-peptide

-cept

abatacept (91)

1-25-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human heavy chain fragment), bimolecular (146→146')-disulfide

aflibercept (96)

des-432-lysine-[human vascular endothelial growth factor receptor 1-(103-204)-peptide (containing Ig like C2 type 2 domain) fusion protein with human vascular endothelial growth factor receptor 2-(206-308)-peptide (containing Ig like C2 type 3 domain fragment) fusion protein with human immunoglobulin G1-(227 *C*-terminal residues)-peptide (Fc fragment)], (211-211':214-214')-bisdisulfide dimer

alefacept (84)

1-92-antigen LFA-3 (human) fusion protein with human immunoglobulin G1 (hinge-C_H2-C_H3 γ1-chain), dimer

atacicept (95)

[86-serine,101-glutamic acid,196-serine,197-serine,222-aspartic acid,224-leucine][human tumor necrosis factor receptor superfamily member 13B-(30-110)-peptide (TACI fragment containing TNFR-Cys 1 and TNFR-Cys 2) fusion protein with human immunogobulin G1-(232 *C*-terminal residues)-peptide (γ1-chain Fc fragment), (92-92':95-95')-bisdisulfide dimer

baminercept (99)

human tumor necrosis factor receptor superfamily member 3 (lymphotoxin-β receptor, TNF C receptor)-(2-195)-peptide (fragment of extracellular domain) fusion protein with human immunoglobulin heavy constant γ1 chain Fc fragment [227 residues, hinge (195-205) des-(1-4),C5>V, CH2 (206-315), CH3 (316-421) des-K^{107}]

belatacept (93)

[Tyr^{29},Glu^{104},Gln^{125},Ser^{130},Ser^{136},Ser^{139},Ser^{148}](antigen CTLA-4 human-3-126]-peptide (fragment containing the human extracellular domain) fusion protein with immunoglobulin G1-[233 amino acids from the C-terminal of the heavy chain]-peptide (fragment containing the human monoclonal Fc domain), bimolecular (120→120')-disulfide

briobacept (98)

aspartyl[1-valine,20-asparagine,27-proline](human tumor necrosis factor receptor superfamily member 13C (BAFF receptor, BlyS receptor 3 or CD268 antigen)-(1-71)-peptidyl (part of the extracellular domain))valyl(human immunoglobulin G1 Fc fragment, *Homo sapiens* IGHG1-(104-329)-peptide) (79-79':82-82')-bisdisulfide dimer

conbercept (105)

fusion protein for immune applications (FPIA) comprising *Homo sapiens* FLT1 (fms-related tyrosine kinase 1, vascular endothelial growth factor receptor 1, VEGFR1, vascular permeability factor receptor, tyrosine-protein kinase FRT) fragment, fused with *Homo sapiens* KDR (kinase insert domain receptor, vascular endothelial growth factor receptor 2, VEGFR2, protein-tyrosine kinase receptor FLK1, CD309) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
FLT1, 132-232 precursor fragment (1-101)-KDR, 227-421 precursor fragment (102-296) -glycyl-prolyl-glycyl (297-299) -gamma1 chain H-CH2-CH3 fragment (300-526) [*Homo sapiens* IGHG1*03 hinge 6-15 P13>L (307) (300-309), CH2 (310-419), CH3-CH-S (420-526)]; (305-305':308-308')-bisdisulfide dimer

dalantercept (105)

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVRL1 (activin A receptor type II-like 1, activin receptor-like kinase 1, ALK1, ALK-1, serine/threonine-protein kinase receptor R3, SKR3, transforming growth factor-beta superfamily receptor type I, TGF-B superfamily receptor type I, TSR-I, HHT2, ORW2) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
ACVR2L1, 22-120 precursor fragment (1-99) -threonyl-triglycyl (100-103) -gamma1 chain H-CH2-CH3 fragment (104-328) [*Homo sapiens* IGHG1*03 hinge 8-15 (104-111), CH2 L1.3>A (115), G1>A (118), A115>V (211) (112-221), CH3 S85.3>P (284) (222-328)]; (107-107':110-110')-bisdisulfide dimer

etanercept (81)

1-235-tumor necrosis factor receptor (human) fusion protein with 236-467-immunoglobulin G1 (human γ1-chain Fc fragment), dimer

ipafricept (109)

fusion protein for immune applications (FPIA) comprising *Homo sapiens* FZD8 (frizzled family receptor 8, Frizzled-8) extracellular domain, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
Homo sapiens FZD8 precursor fragment 28-158 (1-131) -*Homo sapiens* IGHG1*01 H-CH2-CH3 fragment (hinge 1-15 C5>S (136) (132-146), CH2 (147-256), CH3 (257-361), CHS (362-363)) (132-363); dimer (142-142':145-145')-bisdisulfide

lenercept (72)

1-182-tumor necrosis factor receptor (human reduced), (182→104')-protein with 104-330-immunoglobulin G1 (human clone pTJ5 Cγ 1 reduced)

luspatercept (110)

fusion protein for immune applications (FPIA) comprising the *Homo sapiens* ACVR2B (activin receptor type 2B, activin A receptor type IIB, activin receptor type IIB, ACTR-IIB, ActR-IIB) extracellular domain, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
Homo sapiens ACVR2B precursor fragment 25-131 L79>D (55) (1-107) -linker triglycyl (108-110) -gamma1 chain H-CH2-CH3 fragment [*Homo sapiens* IGHG1*03 (hinge 8-15 (111-118), CH2 (119-228), CH3 (229-333), CHS (334-335))] (111-335); dimer (114-114':117-117')-bisdisulfide

ramatercept (108)

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVR2B (activin A receptor type IIB, ActR-IIB) fragment, fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
Homo sapiens ACVR2B precursor fragment 20-134 (1-115) –triglycyl (116-118) -*Homo sapiens* IGHG1*03 H-CH2-CH3 fragment (hinge 8-15 (119-126), CH2 A115>V (226) (127-236), CH3 (237-341), CHS (342-343)) (119-343); dimer (122-122':125-125')-bisdisulfide

rilonacept (95)

[653-glycine][human interleukin-1 receptor accessory protein-(1-339)-peptide (extracellular domain fragment) fusion protein with human type 1 interleukin-1 receptor-(5-316)-peptide (extracellular domain fragment) fusion protein with

human immunoglobulin G1-(229 *C*-terminal residues)-peptide (Fc fragment)], (659-659':662-662')-bisdisulfide dimer

sotatercept (104)

fusion protein for immune applications (FPIA) comprising *Homo sapiens* ACVR2A (activin receptor type 2A, activin receptor type IIA) fragment fused with *Homo sapiens* immunoglobulin G1 Fc fragment;
Homo sapiens ACVR2A, 21-135 precursor fragment (1-115) -threonyl-triglycyl linker (116-119) -gamma1 chain H-CH2-CH3 fragment (120-344) [*Homo sapiens* IGHG1*03 hinge (120-127), CH2, A115>V (227) (128-237), CH3 (238-344)]; (123-123':126-126')-bisdisulfide dimer

-cept & -tox[9] (-tox is for toxins (active or inactived proteins))

alvircept sudotox (69)

N^2-L-methionyl-1-178-antigen CD4 (human clone pT4B protein moiety reduced)(178→248')-protein with 248-L-histidine-249- L-methionine-250- L-alanine-251- L-glutamic acid-248-613-exotoxin A(*Pseudomonas aeruginosa* reduced)

-kin & -tox

cintredekin besudotox (92)

toxin hIL13-PE38QQR (plasmid phuIL13-Tx)

denileukin diftitox (78)

N-L-methionyl-387-L-histidine-388-L-alanine-1-388-toxin (*Corynebacterium diphtheriae* strain C7) (388→2')-protein with 2-133-interleukin 2 (human clone pTlL2-21a)

[9] The names and the descriptions of toxins are published in Annex 4-1 of "International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others: comprehensive list (WHO/EMP/RHT/TSN/2014.2)".

-mab & -dotin[10]

brentuximab vedotin (103)

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* TNFRSF8 (tumor necrosis factor receptor superfamily member 8, KI-1, CD30)], chimeric monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-446) [Mus musculus VH (IGHV1-84*02 -(IGHD)-IGHJ3*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*01 CH3 K130>del (118-446)], (220-218')-disulfide (if not conjugated) with kappa light chain (1'-218') [Mus musculus V-KAPPA (IGKV3-4*01 -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')];(226-226")-disulfide dimer; conjugated, on an average of 3 to 5 cysteinyl, to monomethylauristatin E (MMAE), via a maleimidecaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate (mc-val-cit-PABC) linker

vedotin

1-(6-{[(2S)-1-({(2S)-5-carbamoylamino-1-[(4-{[(2S)-{[(2S)-1-{[(3R,4S,5S)-1-{(2S)-2-[(1R,2R)-3-{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]amino}-1-methoxy-2-methyl-3-oxopropyl]pyrrolidin-1-yl}-3-methoxy-5-methyl-1-oxoheptan-4-yl](methyl)amino}-3-methyl-1-oxobutan-2-yl]amino}-3-methyl-1-oxobutan-2-yl]methylcarbamoyloxy}phenyl)amino]-1-oxopentan-2-yl}amino)-3-methyl-1-oxobutan-2-yl]amino}-6-oxohexyl)-2,5-dioxopyrrolidin-3-yl

enfortumab vedotin (109)

immunoglobulin G1-kappa, anti-[*Homo sapiens* PVRL4 (poliovirus receptor-related 4, nectin-4, nectin 4, PPR4, LNIR], *Homo sapiens* monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-447) [*Homo sapiens* VH (IGHV3-48*02 (98.00%) -(IGHD)-IGHJ6*01) [8.8.10] (1-117) -IGHG1*03 (CH1 (118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-214')-disulfide with kappa light chain (1'-214') [*Homo sapiens* V-KAPPA (IGKV1-12*01 (96.80%) -IGKJ4*01) [6.3.9] (1'-107') -IGKC*01 (108'-214')]; dimer (226-226":229-229")-bisdisulfide; conjugated, on an average of 3 to 4 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidecaproyl-valyl-citrullinyl-*p*-aminobenzylcarbamate (mc-val-cit-PABC) linker

vedotin (for *vedotin*, please refer to *brentuximab vedotin (103)*)

[10] The names ending in *–dotin* and the descriptions are published in Annex 4-2 of "International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others: comprehensive list (WHO/EMP/RHT/TSN/2014.2)".

lifastuzumab vedotin (110)

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* SLC34A2 (solute carrier family 34 sodium phosphate member 2, sodium/phosphate cotransporter 2B, NaPi2b, NaPi3b)], humanized monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-450) [humanized VH (*Homo sapiens* IGHV3-23*04 (85.70%) -(IGHD)-IGHJ5*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03 (CH1 R120>K (217) (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (78.00%) -IGKJ1*01) [11.3.9] (1'-112')-*Homo sapiens* IGKC*01 (113'-219')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 3 to 4 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproylvalyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker

vedotin (for *vedotin*, please refer to *brentuximab vedotin (103)*)

pinatuzumab vedotin (108)

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* CD22 (sialic acid binding Ig-like lectin 2, SIGLEC2, SIGLEC-2, Blymphocyte cell adhesion molecule, BL-CAM, Leu-14)], humanized monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-450) [humanized VH (*Homo sapiens* IGHV3-66*01 (79.60%) -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03 (CH1 R120>K (217) (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-219')-disulfide (if not conjugated) with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (80.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 3 to 4 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidecaproyl-valylcitrullinyl-*p*-aminobenzylcarbamate (mc-val-cit-PABC) linker

vedotin (for *vedotin*, please refer to *brentuximab vedotin (103)*)

polatuzumab vedotin (110)

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* CD79B (immunoglobulin-associated CD79 beta)], humanized monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-447) [humanized VH (*Homo sapiens* IGHV3-23*04 (76.50%)-(IGHD)-IGHJ4*01) [8.8.10] (1-117) -*Homo sapiens* IGHG1*03 (CH1

R120>K (214)(118-215), hinge (216-230), CH2 (231-340), CH3 (341-445), CHS (446-447)) (118-447)], (220-218')-disulfide with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (85.90%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; dimer (226-226":229-229")-bisdisulfide; conjugated, on an average of 3 to 4 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproyl-valyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker

vedotin (for *vedotin*, please refer to *brentuximab vedotin (103)*)

sofituzumab vedotin (110)

immunoglobulin G1-kappa auristatin E conjugate, anti-[*Homo sapiens* MUC16 (mucin 16, MUC-16, cancer antigen 125, CA125)], humanized monoclonal antibody conjugated to auristatin E;
gamma1 heavy chain (1-446) [humanized VH (*Homo sapiens* IGHV3-48*03 (79.80%) -(IGHD)-IGHJ4*01) [9.8.9] (1-116) -*Homo sapiens* IGHG1*03 (CH1 R120>K (213) (117-214), hinge (215-229), CH2 (230-339), CH3 (340-444), CHS (445-446)) (117-446)], (219-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-5*01 (87.90%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; dimer (225-225":228-228")-bisdisulfide; conjugated, on an average of 3 to 4 cysteinyl, to monomethylauristatin E (MMAE), via a cleavable maleimidocaproylvalyl-citrullinyl-*p*-aminobenzyloxycarbonyl (mc-val-cit-PABC) type linker

vedotin (for *vedotin*, please refer to *brentuximab vedotin (103)*)

denintuzumab mafodotin (111)

immunoglobulin G1-kappa auristatin F conjugate, anti-[*Homo sapiens* CD19 (B lymphocyte surface antigen B4, Leu-12)], humanized monoclonal antibody;
gamma1 heavy chain (1-450) [humanized VH (*Homo sapiens* IGHV4-31*02 (84.80%) -(IGHD)-IGHJ4*01) [10.7.12] (1-120) -*Homo sapiens* IGHG1*01 (CH1 (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-213')-disulfide with kappa light chain (1'-213') [humanized V-KAPPA (*Homo sapiens* IGKV3-11*01 (85.30%) -IGKJ2*02) [5.3.9] (1'-106') -*Homo sapiens* IGKC*01 (107'-213')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 4 cysteinyl, to monomethylauristatin F (MMAF), via a noncleavable maleimidocaproyl (mc) linker

mafodotin

N-{(2R,3R)-3-[(2S)-1-[(3R,4S,5S)-4-({*N*-[6-(2,5-dioxo-2,5-dihydro-1*H*-pyrrol-1-yl)hexanoyl]-*N*-methyl-L-valyl-L-valyl}methylamino)-

3-methoxy-5-methylheptanoyl]pyrrolidin-2-yl]-3-methoxy-2-methylpropanoyl}-L-phenylalanine

vorsetuzumab mafodotin (107)

immunoglobulin G1-kappa auristatin F conjugate, anti-[*Homo sapiens* CD70 (tumor necrosis factor superfamily member 7, TNFSF7, CD27LG, CD27L)], humanized monoclonal antibody conjugated to auristatin F; gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV1-2*02 (86.70%) -(IGHD)-IGHJ6*01) [8.8.11] (1-118) -*Homo sapiens* IGHG1*01 (119-448)], (221-218')-disulfide (if not conjugated) with kappa light chain (1'-218') [humanized V-KAPPA (*Homo sapiens* IGKV4-1*01 (79.20%) -IGKJ1*01) [10.3.9] (1'-111') -*Homo sapiens* IGKC*01 (112'-218')]; (227-227":230-230")-bisdisulfide dimer; conjugated, on an average of 3 to 5 cysteinyl, to monomethylauristatin F (MMAF), via a non-cleavable maleimidocaproyl (mc) linker

mafodotin (for *mafodotin*, please refer to *denintuzumab mafodotin (111)*)

-mab & -kin

tucotuzumab celmoleukin (95)

immunoglobulin G1, anti-(tumor associated calcium signal transducer 1 (KS 1/4 antigen)) (human-mouse monoclonal huKS-IL2 heavy chain) fusion protein with interleukin 2 (human), disulfide with human-mouse monoclonal huKS-IL2 light chain, dimer

-mab & -tansine[11]

anetumab ravtansine (109)

immunoglobulin G1-lambda2, anti-[*Homo sapiens* MSLN (mesothelin, pre-pro-megakaryocyte-potentiating factor, megakaryocyte potentiating factor, MPF, CAK1)], *Homo sapiens* monoclonal antibody conjugated to maytansinoid DM4; gamma1 heavy chain (1-450) [*Homo sapiens* VH (IGHV5-51*01 (94.90%) -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -IGHG1*01 (CH1 (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-216')-

[11] The names ending in *–tansine* and the descriptions are published in Annex 4-2 of "International Nonproprietary Names (INN) for pharmaceutical substances. Names for radicals, groups & others: comprehensive list (WHO/EMP/RHT/TSN/2014.2)".

disulfide with lambda light chain (1'-217') [*Homo sapiens* V-LAMBDA (IGLV2-14*01 (95.60%) -IGLJ2*01) [9.3.11] (1'-111') -IGLC2*01 A43>G (155) (112'-217')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 3 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]

ravtansine

4-[(5-{[(1*S*)-1-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-oxopropan-2-yl](methyl)amino}-2-methyl-5-oxopentan-2-yl)disulfanyl]butanoyl

cantuzumab ravtansine (105)(66)

immunoglobulin G1-kappa, anti-[*Homo sapiens* MUC1 sialylated carbohydrate, tumour-associated (CA242, cancer antigen 242)], humanized monoclonal antibody conjugated to maytansinoid DM4;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109),D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228":231-231")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]

ravtansine (for *ravtansine*, please refer to *anetumab ravtansine (109)*)

coltuximab ravtansine (109)

immunoglobulin G1-kappa, anti-[*Homo sapiens* CD19 (B lymphocyte surface antigen B4, Leu-12)], chimeric monoclonal antibody conjugated to maytansinoid DM4;
gamma1 heavy chain (1-450) [Mus musculus VH (IGHV1-69*02 -(IGHD)-IGHJ4*01) [8.8.13] (1-120) -*Homo sapiens* IGHG1*01 (CH1 (121-218), hinge (219-233), CH2 (234-343), CH3 (344-448), CHS (449-450)) (121-450)], (223-211')-disulfide with kappa light chain (1'-211') [Mus musculus V-KAPPA (IGKV4-70*01 -IGKJ1*01) [5.3.7] (1'-104') -*Homo sapiens* IGKC*01 (105'-211')]; dimer (229-229":232-232")-bisdisulfide; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-

oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]

ravtansine (for *ravtansine*, please refer to *anetumab ravtansine (109)*)

indatuximab ravtansine (105)(67)

immunoglobulin G4-kappa, anti-[*Homo sapiens* SDC1 (syndecan-1, CD138)], chimeric monoclonal antibody conjugated to maytansinoid DM4;
gamma4 heavy chain (1-449) [Mus musculus VH (IGHV1-9*01 - (IGHD)-IGHJ4*01) [8.8.15] (1-122) -*Homo sapiens* IGHG4*01 (123-449)], (136-214')-disulfide with kappa light chain (1'-214') [Mus musculus V-KAPPA (IGKV10-94*01 -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (228-228":231-231")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM4 [$N^{2'}$-deacetyl-$N^{2'}$-(4-mercapto-4-methyl-1-oxopentyl)-maytansine] via the reducible SPDB linker [*N*-succinimidyl 4-(2-pyridyldithio)butanoate]

ravtansine (for *ravtansine*, please refer to *anetumab ravtansine (109))*

cantuzumab mertansine (105)(66)

immunoglobulin G1-kappa, anti-[*Homo sapiens* MUC1 sialylated carbohydrate, tumour-associated (CA242, cancer antigen 242)], humanized monoclonal antibody conjugated to maytansinoid DM1;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV7-4-1*02 (76.50%) -(IGHD)-IGHJ2*01 R120>Q (111), L123>T (114)) [8.8.12] (1-119) -*Homo sapiens* IGHG1*01 (120-449)], (222-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-28*01 (82.00%) -IGKJ3*01 V124>L (109), D125>E (110), I126>L (111)) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (228-228":231-231")-bisdisulfide dimer; conjugated, on an average of 4 lysyl, to maytansinoid DM1 [$N^{2'}$-deacetyl-$N^{2'}$-(3-mercapto-1-oxopropyl)-maytansine] via the reductible SPP linker [*N*-succinimidyl 4-(2-pyridyldithio)pentanoate]

mertansine

x(4*RS*)-4[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-2-oxoethyl]methylamino}-3-oxopropyl)disulfanyl]pentanoyl}

lorvotuzumab mertansine (103)(65)

immunoglobulin G1-kappa, anti-[*Homo sapiens* NCAM1 (neural cell adhesion molecule 1, CD56, NCAM-1)], humanized monoclonal antibody conjugated to maytansinoid DM1;
gamma1 heavy chain (1-448) [humanized VH (*Homo sapiens* IGHV3-30*03 (91.80%) -(IGHD)-IGHJ4*01) [8.8.11] (1-118) –*Homo sapiens* IGHG1*01 (119-448)], (221-219')-disulfide with kappa light chain (1'-219') [humanized V-KAPPA (*Homo sapiens* IGKV2-30*02 (92.00%) -IGKJ1*01) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219')]; (227-227":230-230")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM1 via a thiopentanoate linker

mertansine (for *mertansine*, please refer to *cantuzumab mertansine (105)(66)*)

trastuzumab emtansine (103)(65)

immunoglobulin G1-kappa, anti-[*Homo sapiens* ERBB2 (epidermal growth factor receptor 2, HER-2, p185c-erbB2, NEU, EGFR2)], humanized monoclonal antibody conjugated to maytansinoid DM1;
gamma1 heavy chain (1-449) [humanized VH (*Homo sapiens* IGHV3-66*01 (81.60%) -(IGHD)-IGHJ6*01 T123>L) [8.8.13] (1-120) -*Homo sapiens* IGHG1*03 (121-449) CH1 R120>K], (223-214')-disulfide with kappa light chain (1'-214') [humanized V-KAPPA (*Homo sapiens* IGKV1-39*01 (86.30%) -IGKJ1*01) [6.3.9] (1'-107') -*Homo sapiens* IGKC*01 (108'-214')]; (229-229":232-232")-bisdisulfide dimer; conjugated, on an average of 3 to 4 lysyl, to maytansinoid DM1 via a succinimidyl-4-(*N*-maleimidomethyl) cyclohexane-1-carboxylate (SMCC) linker

emtansine

4-({3-[(3-{[(1*S*)-2-{[(1*S*,2*R*,3*S*,5*S*,6*S*,16*E*,18*E*,20*R*,21*S*)-11-chloro-21-hydroxy-12,20-dimethoxy-2,5,9,16-tetramethyl-8,23-dioxo-4,24-dioxa-9,22-diazatetracyclo[19.3.1.$1^{10,14}$.$0^{3,5}$]hexacosa-10,12,14(26),16,18-pentaen-6-yl]oxy}-1-methyl-2-oxoethyl]methylamino}-3-oxopropyl)sulfanyl]-2,5-dioxopyrrolidin-1-yl}methyl)cyclohexylcarbonyle

-mab & -tox

anatumomab mafenatox (86)

immunoglobulin G 1, anti-(human tumor-associated glycoprotein 72) (human-mouse clone pMB125 Fab fragment γ1-chain) fusion protein with enterotoxin A

(227-alanine) (*Staphylococcus aureus*) complex with mouse clone pMB125 κ-chain)

citatuzumab bogatox (99)

immunoglobulin Fab fusion protein, anti-[*Homo sapiens* tumor-associated calcium signal transducer 1 (TACSTD1, gastrointestinal tumor-associated protein 2, GA733-2, epithelial glycoprotein 2, EGP-2, epithelial cell adhesion molecule Ep-CAM, KSA, KS1/4 antigen, M4S, tumor antigen 17-1A, CD326)], humanized Fab fused with *Bougainvillea spectabilis Willd* rRNA N-glycosidase [type I ribosome inactivating protein (RIP), bouganin], VB6-845; gamma1 heavy chain fragment (1-225) [hexahistidyl (1-6) -humanized VH from 4D5MOC-B (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGHJ4*01, V124>L) [8.8.9] (7-122) -*Homo sapiens* IGHG1*01 CH1-hinge fragment EPKSC (123-225)], (225-219')-disulfide with kappa fusion chain (1'-481') [humanized V-KAPPA from clone 4D5MOC-B (*Homo sapiens* FR/*Mus musculus* CDR, *Homo sapiens* IGKJ1*01, I126>L) [11.3.9] (1'-112') -*Homo sapiens* IGKC*01 (113'-219') -12-mer furin linker (proteolytic cleavage spacer from Pseudomonas exotoxin A) (220'-231') -*Bougainvillea spectabilis Willd* bouganin fragment (27-276 from precursor, V354'>A, D358'>A, Y364'>N, I383'>A) (232'-481')]

dorlimomab aritox (66)

ricin A chain-antibody ST 1 F(ab')2 fragment immunotoxin

moxetumomab pasudotox (102)

immunoglobulin Fv fragment fused to *Pseudomonas* toxin, anti-[*Homo sapiens* CD22 (sialic acid-binding Ig-like lectin 2, Siglec-2, SIGLEC2, Leu-14, B-lymphocyte cell adhesion molecule, BL-CAM)], *Mus musculus* monoclonal antibody disulfide stabilized Fv fragment with the variable heavy VH domain fused with the truncated form PE38 of *Pseudomonas aeruginosa* exotoxin A (VH-PE38), disulfide linked with the variable kappa domain (V-KAPPA)];
VH-PE38 (1-476) comprising the VH domain (1-123) [methionyl -*Mus musculus* VH [(IGHV5-12-1*01 -(IGHD)-IGHJ3*01) [8.8.16] (2-123)] fused with a 7-mer linker (124-130) and with the *Pseudomonas aeruginosa* exotoxin A (ETA) PE38 fragment (131-476) [277-638 precursor fragment with del 389-405>N (131-476), containing domain II (131-243) with furin proteolytic cleavage site (152-164), domain Ib (244-267), domain III (268-476)], (45-101')-disulfide with V-KAPPA (1'-108') [methionyl -*Mus musculus* V-KAPPA [(IGHKV10-96*01 -IGKJ1*01) [6.3.9] (2'-108')]

nacolomab tafenatox (80)

immunoglobulin G1, anti-(human colorectal tumor antigen C242) Fab fragment (mouse monoclonal r-C242Fab-SEA clone pkP941 γ1-chain) fusion protein with enterotoxin A (*Staphylococcus aureus*), disulfide with mouse monoclonal r-C242Fab-SEA clone pkP941 κ-chain

naptumomab estafenatox (96)

immunoglobulin fragment, anti-[trophoblast glycoprotein (TPBG, 5T4)] monoclonal 5T4 gamma1 heavy chain fragment fusion protein [*Mus musculus* VH (5T4V14: H41>P, S44>G, I69>T, V113>G)-IGHG1_CH1)] - [Glycyl-Glycyl-Prolyl] - superantigen SEA/E-120 (synthetic), non-disulfide linked with monoclonal 5T4 kappa light chain [*Mus musculus* V-KAPPA (5T4V18: F10>S, T45>K, I63>S, F73>L, T77>S, L78>V, L83>A)-IGKC]

oportuzumab monatox (100)

immunoglobulin scFv fusion protein, anti-[*Homo sapiens* tumor-associated calcium signal transducer 1 (TACSTD1, gastrointestinal tumor-associated protein 2, GA733-2, epithelial glycoprotein 2, EGP- 2, epithelial cell adhesion molecule Ep-CAM, KSA, KS1/4 antigen, M4S1, tumor antigen 17-1A, CD326)] humanized monoclonal antibody scFv fused with *Pseudomonas aeruginosa* exotoxin A; hexahistidyl -humanized scFv [V-KAPPA (*Homo sapiens* IGKV1- 39*01 (78%)-IGKJ1*01, I126>L) [11.3.9] (7-118) -26-mer linker -VH (*Homo sapiens* IGHV7-4-1*02 -(IGHD)-IGHJ4*01, V124>L) [8.8.9] (145-260)] -20-mer linker -*Pseudomonas aeruginosa* exotoxin A (ETA) [277-633 precursor fragment, containing domain II (281-393) with furin proteolytic cleavage site (302-313), domain Ib (394-433), domain III (434-637)] (281-637) -hexahistidyl-lysyl-aspartyl-glutamylleucyl

taplitumomab paptox (84)

immunoglobulin G1, anti-(human antigen CD19) (mouse monoclonal B43 γ1-chain), disulfide with mouse monoclonal B43 κ-chain, dimer, disulfide with protein PAP (pokeweed antiviral)

telimomab aritox (66)

ricin A chain-antibody T 101 Fab fragment immunotoxin

zolimomab aritox (80)

immunoglobulin G1, anti-(human CD5 (antigen) heavy chain) (mouse monoclonal H65-RTA γ1-chain), disulfide with mouse monoclonal H65-RTA light chain, dimer, disulfide with ricin (castor bean A-chain)

-tide

cenderitide (105)

natriuretic peptide receptor type B (NPR-B) agonist;
human C-type natriuretic peptide-(32-53)-peptide (CNP-22) fusion protein with eastern green mamba (*Dendroaspis angusticeps*) natriuretic peptide-(24-38)-peptide

elsiglutide (104)

[2-glycine(A>G),3-glutamic acid(D>E),8-serine(D>S),10-leucine(M>L),11-serine(N>S),16-alanine(N>A),24-alanine(N>A),28-alanine(Q>A)]human glucagon-like peptide 2 (GLP-2) fusion protein with hexalysinamide

langlenatide (109)

exenatide derivative and human IgG4 Fc dimer linked together with polyethylene glycol derivative:
$N^{6.27}$,$N.^{1'}$-[ω-(oxypropane-1,3-diyl)-α-(propane-1,3-diyl)poly(oxyethylene)] [1-(imidazol-4-ylacetic acid)]exendin-4 Heloderma suspectum (Gila monster), human immunoglobulin G4 Fc fragment-(9'-229')-peptide dimer (3'-3'')-disulfide

vanutide cridificar (100)

inactivated diphtheria toxin (carrier) covalently linked to human beta-amyloid protein 42 short fragments: pentadecakis[$N^{6\text{-Lys}}$-(sulfanylacetyl)]-[52-glutamic acid(G>E)]diphtheria toxin *Corynebacterium diphtheriae* thioether with human beta-amyloid protein 42-(1-7)-peptidylcysteine

-motide

amilomotide (105)

virus like particle of bacteriophage Q-beta coat protein that is coupled to multiple copies of human beta-amyloid1-6 peptide fragment;
reaction products of bacteriophage Q-beta coat protein with human beta-amyloid protein-(1-6)-peptidylglycylglycyl-L-cysteine and 3-(2,5-dioxo-2,5-dihydro-1*H*-pyrrole-1-yl)-*N*-{6-[(2,5-dioxopyrrolidin-1-yl)oxy]-6-oxohexyl}propanamide

tecemotide (108)

human mucin-1 (carcinoma-associated mucin, episialin, CD227)-(107-131)-peptide (sequence 40 times repeated) fusion protein with 6-*N*-hexadecanoyl-L-lysylglycine

zastumotide (110)

19,137,308,342,395-penta[*S*-(2-amino-2-oxoethyl)]-{[2-aspartic acid(K^2>D),3-proline(L^3>P)]glycerophosphoryl diester phosphodiesterase (*Haemophilus influenzae* strain 86-028NP EC 3.1.4.46)-(1-127)-peptide fusion protein with [2-aspartic acid(P^2>D)]human melanoma-associated antigen 3 (MAGE-3 antigen, antigen MZ2-D, cancer/testis antigen 1.3 or CT1.3) fusion protein with diglycylheptahistidine}

CPCA with Fc

This item includes INN assigned to composite proteins for clinical applications (CPCA) (or peptides) fused with immunoglobulin Fc with the aim of increasing their half-life.

Before the *ef*-suffix was implemented:

asfotase alfa (104)

tissue-nonspecific alkaline phosphatase- IgG_1 fusion protein;human tissue-nonspecific isozyme alkaline phosphatase (AP-TNAP, EC=3.1.3.1) fusion protein with leucyl-lysyl-human immunoglobulin G1 Fc region {(6-15)-H-CH2-CH3 of IGHG1*03} fusion protein with aspartyl-isoleucyl-deca(aspartic acid), dimer (493-493':496-496')-bisdisulfide

blisibimod (107)

B-cell activating factor (BAFF)-binding peptide fragment/human IgG1 Fc fusion protein

dulaglutide (103)

glucagon-like peptide-1-immunoglobulin G4 fusion protein, [2-glycyl,16-L-glutamyl,30-glycyl][human glucagon-like peptide 1-(7-37)-peptide] {(8-A>G,22-G>E,36-R>G)-GLP-1(7-37)} fusion protein with tris(tetraglycyl-L-seryl)-L-alanine (linker) fusion protein with des-276-lysine-[57-L-proline,63-L-alanine,64-L-alanine]human immunoglobulin G4 Fc region {(10-S>P)-H-(4-F>A,5-L>A)-CH2-(107-K>-)-CH3 of IGHG4*01}, dimer (55-55':58-58')-bisdisulfide

romiplostim (97)

L-methionyl[human immunogloblin heavy constant gamma 1-(227 *C*-terminal residues)-peptide (Fc fragment)] fusion protein with 41 amino acids peptide, (7-7':10,10')-bisdisulfide dimer

torapsel (91)

42-89-glycoprotein (human clone PMT21:PL85 P-selectin glycoprotein ligand fusion protein with immunoglobulin (human constant region)

trebananib (106)

immunoglobulin G1 Fc fragment fused with two synthetic polypeptides that bind the *Homo sapiens* ANGPT2 (angiopoietin 2);
methionyl (1) -gamma1 heavy chain fragment (2-228) [*Homo sapiens* IGHG1*01 hinge (EPKSC 1-5>del) (2-11), CH2 (12-121), CH3 (122-228)] fused, at the C-terminal end, with a synthetic polypeptide that comprises two 14-mer amino acid repeats that bind angiopoietin 2 (229-287) [linker (229-235) -14-mer (236-249) – linker (250-271) -14-mer (272-285) -leucyl-glutamate]; (7-7':10-10')-bisdisulfide dimer

ef-

eflapegrastim (111)

human granulocyte colony-stimulating factor and human IgG4 Fc dimer linked together with polyethylene glycol derivative, produced in *Escherichia coli*:
*N*α.1,*N*1.9'-[ω-(oxypropane-1,3-diyl)-α-(propane-1,3-diyl)poly(oxyethylene)] des-(1-L-alanine,37-39)-[18-L-serine(C>S)]human granulocyte colony-stimulating factor (G-CSF, pluripoietin) (1-174)-peptide and des-(1-8)-human immunoglobulin G4 Fc fragment (IGHG4*01 H-CH2-CH3) (1'-221')-peptide dimer (11'-11")-disulfide

efmoroctocog alfa (111)

recombinant DNA derived (1-742)-(1637-2332)-human blood coagulation factor VIII fusion protein with immunoglobulin G1 Fc domain fragment, produced in HEK293H cells, glycoform alfa:
des-(743-1636)-human blood coagulation factor VIII (antihemophilic factor, procoagulant component) fusion protein with human immunoglobulin G1 Fc fragment (IGHG1*01 H-CH2-CH3)-(6-231)-peptide (1444-6':1447-9')-bisdisulfide with human immunoglobulin G1 Fc fragment (IGHG1*01 H-CH2-CH3)-(6-231)-peptide

eftrenonacog alfa (109)

recombinant DNA derived human blood coagulation factor IX fusion protein with one Fc fragment of the human immunoglobulin G1 Fc fragment dimer, produced in HEK293H cells (glycoform alfa):
human blood coagulation factor IX (EC 3.4.21.22, Christmas factor, plasma thromboplastin component) variant 148-T, fusion protein with human immunoglobulin G1 Fc fragment (IGHG1*01 H-CH2-CH3)-(6-231)-peptide (421-6':424-9')-bisdisulfide with human immunoglobulin G1 Fc fragment (IGHG1*01 H-CH2-CH3)-(6-231)-peptide

Others

dianexin (109)

recombinant DNA derived annexin A5 dimer covalently linked by a 14 residues peptide linker, produced in *Escherichia coli* (nonglycosylated):
L-methionyl-human annexin A5 fusion protein with glycyl-L-seryl-L-leucyl-L-α-glutamyl-L-valyl-L-leucyl-L-phenylalanyl-L-glutaminylglycyl-L-prolyl-L-serylglycyl-L-lysyl-L-leucyl-human annexin A5

mipsagargin (110)

sarcoplasmic/endoplasmic reticulum Ca^{2+} dependent ATPase (SERCA) inhibitor conjugated to a peptide targeting prostate-specific membrane antigen (PSMA): N^4-(12-{[(3*S*,3a*R*,4*S*,6*S*,6a*R*,7*S*,8*S*,9b*S*)-6-(acetyloxy)-3,3a-dihydroxy-3,6,9-trimethyl-8-{[(2*Z*)-2-methylbut-2-enoyl]oxy}-7-(octanoyloxy)-2-oxo-2,3,3a,4,5,6,6a,7,8,9b-decahydroazuleno[4,5-*b*]furan-4-yl]oxy}-12-oxododecyl)-L-asparaginyl-L-γ-glutamyl-L-γ-glutamyl-L-γ-glutamyl-L-glutamic acid

topsalysin (111)

recombinant DNA derived proaerolysin, pore-forming protein, from *Aeromonas hydrophila,* with the furin site substituted with a prostate specific antigen (PSA) cleavage site, fusion protein with 6 histidines, produced in *Escherichia coli* (nonglycosylated):
[427-L-histidine(K>H),428-L-serine(V>S),429-L-serine(R>S),430-L-lysine(R>K),431-L-leucine(A>L),432-L-glutamine(R>Q)]proaerolysin *Aeromonas hydrophila* fusion protein with hexa-L-histidine

transferrin aldifitox (95)

a conjugate of the precursor of human serotransferrin (siderophillin) with a primary amine group used to form an amidine with (4-iminobutane-1,4-diyl)sulfanediyl[(3RS)-2,5-dioxopyrrolidine-1,3-diyl]-1,3-phenylenecarbonyl and forming an *N*-benzoyl derivative of a primary amine group of diphtheria [550-L-phenylalanine]toxin from *Corynebacterium diphtheriae*-(26-560)-peptide

verpasep caltespen (95)

60 kDa chaperonin 2 (heat shock protein 65 from *Mycobacterium bovis* strain BCG) fusion protein with L-histidylprotein E7 from human papillomavirus type 16.

zoptarelin doxorubicin (107)

[6-D-lysine]human gonadoliberin-1 (LHRH) and doxorubicin covalently linked together with glutaric acid:
5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-N^6-[5-(2-{(2*S*,4*S*)-4-[(3-amino-2,3,6-trideoxy-α-L-*lyxo*-hexopyranosyl)oxy]-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl}-2-oxoethoxy)-5-oxopentanoyl]-D-lysine-L-leucyl-L-arginyl-L-prolylglycinamide

ANNEX 2

Transliteration of Greek letters in English, French and Spanish

Upper case	Lower case	English	French	Spanish	
Α	α	alfa (and **not** alpha)	alfa (and **not** alpha)	alfa	
Β	β	beta	bêta	beta	
Γ	γ	gamma	gamma	gamma	
Δ	δ	delta	delta	delta	
Ε	ε	epsilon	epsilon	épsilon	
Ζ	ζ	zeta	zêta	**ds**eta	*
Η	η	eta	êta	eta	
Θ	θ	theta	thêta	**z**eta	*
Ι	ι	iota	iota	iota	
Κ	κ	kappa	kappa	kappa	
Λ	λ	lambda	lambda	lambda	
Μ	μ	mu	mu	mi	
Ν	ν	nu	nu	ni	
Ξ	ξ	xi	xi	xi	
Ο	ο	omicron	omicron	ómicron	
Π	π	pi	pi	pi	
Ρ	ρ	rho	rhô	ro	
Σ	σ	sigma	sigma	sigma	
Τ	τ	tau	tau	tau	
Υ	υ	upsilon	upsilon	ípsilon	
Φ	φ	phi	phi	fi	
Χ	χ	chi	khi	ji	
Ψ	ψ	psi	psi	psi	
Ω	ω	omega	oméga	omega	

* letters to be avoided

ANNEX 3

The previous naming scheme for monoclonal antibodies

General policies for monoclonal antibodies

- The common stem for monoclonal antibodies is *-mab*.
- Sub-stems for source of product:

a	rat
axo (pre-sub-stem)	rat-murine hybrid
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
zu	humanized

The distinction between chimeric and humanized antibodies is as follows:

A chimeric antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable region of both heavy and light chains linked to heavy and light constant regions of human origin.

A humanized antibody has segments of foreign-derived amino acids interspersed among variable region segments of human-derived amino acid residues and the humanized heavy-variable and light-variable regions are linked to heavy and light constant regions of human origin.

- Sub-stems for disease or target class:

-ba(c)-	bacterial
-ci(r)-	cardiovascular
-fung-	fungal
-ki(n)- (pre-sub-stem)	interleukin
-le(s)-	inflammatory lesions
-li(m)-	immunomodulator
-os-	bone
-vi(r)-	viral

tumours:

-co(l)-	colon
-go(t)-	testis
-go(v)-	ovary
-ma(r)-	mammary
-me(l)-	melanoma
-pr(o)-	prostate
-tu(m)-	miscellaneous

Whenever there is a problem in pronunciation, the final letter of the sub-stems for diseases or targets may be deleted, e.g. *-vi(r)-, -ba(c)-, -li(m)-, -co(l)-*, etc.

Prefix

Should be random e.g. the only requirement is to contribute to a euphonious and distinctive name.

Second word

If the product is radiolabelled or conjugated to another chemical, such as toxin, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation.

If the monoclonal antibody is used as a carrier for a radioisotope, the latter will be listed first in the INN, e.g. *technetium (^{99m}Tc) pintumomab (86).*

***-toxa-* infix**

For monoclonals conjugated to a toxin, the infix *-toxa-* can be inserted either into the first (main) name or included in the second word.

WHO/EMP/RHT/TSN/2013.1

The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

2013

World Health Organization

WHO/EMP/RHT/TSN/2013.1

The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

2013

International Nonproprietary Names (INN) Programme
Technologies Standards and Norms (TSN)
Regulation of Medicines and other Health Technologies (RHT)
Essential Medicines and Health Products (EMP)

The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances

FORMER DOCUMENT NUMBER: WHO/PHARM S/NOM 15

Printed by the WHO Document Production Services, Geneva, Switzerland

PREFACE

The document *"The Use of Common Stems in the Selection of INNs"* is intended primarily for persons and companies applying to the WHO INN Programme for the selection of an INN for a new pharmaceutical substance and has been designed to assist in the process of devising a suitable proposal. It will also be of assistance to institutions and specialists involved in the review of proposed INNs, including drug regulatory authorities, pharmaceutical manufacturers, patent offices and trade mark officers as well as for scientists, teachers, health professionals and other persons interested generally in drug nomenclature. The document is composed of four main parts and annexes.

Part I *"Introduction"* describes the WHO INN Programme, INN selection procedure, and criteria for name selection and gives general information on the INN stem system.

Part II contains the list of all INN stems. It is composed of two indexes, one entitled *"Alphabetical List of Common Stems"* which presents the list of stems, and another entitled *"Alphabetical List of Common Stems and their definitions"* which includes a definition for each stem.

Part III presents the stem classification system used by the INN Programme to categorize the main activity of pharmaceutical substances. Each category included in the list is given an appropriate code consisting of a capital letter and three digits. When INNs for substances belonging to a given category include a specific stem, appropriate information is included in the table.

Part IV of the document entitled *"Alphabetical List of Stems Together With Corresponding INNs"* serves as a listing of all proposed INNs (published in lists 1 - 109) containing INN stems. The list is organized in alphabetical order (as set out in Part II) and includes all INNs containing individual stems. In addition, under each stem heading information is given on INNs in which the preferred stem has been used but not in accordance with its definition as well as on INNs which belong to the same group of pharmaceutical substances but in which no preferred stem has been used. To facilitate the use of Part IV, the lay-out of information is presented as a diagram on page 6 and is complemented by additional information given at the end of part I *"Introduction"*.

Six annexes attached to the document are intended to be of assistance to users. Annex 1 reproduces the *Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances* as approved by the WHO Executive Board in its resolution EB15.R7 as amended by resolution EB115.R4. Annex 2 reproduces *General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances* as approved by the WHO Executive Board in the above-mentioned resolution, as amended. Annex 3 explains the nomenclature scheme for monoclonal antibodies. Annex 4 explains the nomenclature scheme for Gene Therapy Products. Annex 5 gives reference to the volumes of the *WHO Drug Information* in which proposed lists of INNs have been published. Annex 6 *"Why INN?"* gives general information on the present situation of WHO INN Programme and its achievements.

TABLE OF CONTENTS

PART I

INTRODUCTION

WHO'S INN PROGRAMME

The World Health Organization (WHO) has a constitutional responsibility to "develop, establish and promote international standards with respect to biological, pharmaceutical and similar products". The International Nonproprietary Names (INN) Programme is a core activity embedded in the normative functions of WHO and has served the global public health and medicines community for over fifty years. The Programme was established to assign nonproprietary names to pharmaceutical substances so that each substance would be recognized by a unique name. Such names are needed for the clear identification, safe prescription and dispensing of medicines, and for communication and exchange of information among health professionals. INNs can be used freely because they are in the public domain. In addition to being a basic component of many WHO medicines activities and programmes, INNs are used in regulatory and administrative processes in many countries. They are also intended for use in pharmacopoeias, labelling, and product information and to provide standardized terminology for the international exchange of scientific information.

INN SELECTION PROCEDURE

Each name proposed for designation as an INN is examined and selected in accordance with a formal procedure. Requests for INNs can be submitted directly to WHO (application forms online at http://www.who.int/medicines/services/inn/en/index.html). In some countries where national nomenclature commissions exist, applications may also be made through the national nomenclature authority.

Members of the WHO Expert Panel on the International Pharmacopoeia and Pharmaceutical Preparations (or other Panel as appropriate) are officially designated to select nonproprietary names. Based on the information provided, an agreed name is selected and published as a ***proposed*** INN. During a four month period, any person can make comments or lodge a formal objection to the proposed name. If no objection is raised, this agreed name is published as the ***recommended*** INN.

In 1993, the World Health Assembly endorsed resolution WHA46.19 which states that trademarks should not be derived from INNs and INN stems should not be used in trade marks. The Assembly reasoned that such practice could frustrate the rational selection of INNs and ultimately compromise the safety of patients by promoting confusion in drug nomenclature. Above all, INNs are protected for use in the public domain.

CRITERIA FOR SELECTION

International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and not be liable to confusion with names in common use. Information on the selection procedure and general criteria in devising INNs is set out in Annexes 1 and 2.

INN STEMS

Stems define the pharmacologically related group to which the INN belongs. The present document describes stem use procedure and includes, in Parts II and IV, the list of common stems for which chemical and/or pharmacological categories have been established. These stems and their definitions have been selected by WHO experts and are used when selecting new international nonproprietary names. Because the nomenclature process is on-going and constantly under revision, definitions of older stems are modified as and when newer information becomes available.

Whenever possible, an INN should include the "common stem" expressing the pharmacologically-related group to which the substance belongs. Names that are likely to convey an anatomical, physiological, pathological or therapeutic suggestion are avoided.

In addition, certain rules have been established in devising INNs to facilitate their use internationally. For example, to make pronunciation possible in various languages, the letters "h" and "k" should be avoided; "e" should be used instead of "ae" and "oe", "i" instead of "y", "t" instead of "th" and "f" instead of "ph".

INFORMATION ON USING PART IV "ALPHABETICAL LIST OF STEMS TOGETHER WITH CORRESPONDING INNs"

The following information complements or describes the diagram set out on page 6.

1. The list includes INNs published in *Proposed International Nonproprietary Names Lists 1 - 109* categorized according to the list of stems (see Annex 5).

For each stem, INNs have been classified as:

(a) INNs in which the preferred stem has been used in accordance with its definition;

(b) INNs in which the preferred stem has been used, but not in accordance with its definition;

(c) INNs which belong to the same group of pharmaceutical substances but in which the preferred stem has not been used. (This part of the list is not exhaustive).

2. References to nationally used syllables published in the British Approved Names (BAN) Dictionary and the USP Dictionary of USAN and International Drug Names have also been made wherever applicable. Whenever the BAN or USAN definitions are not identical to the INN definition they are set out in brackets under the INN definition.

3. The codes presented on the diagram as Stem Classification refer to the stem classification system used by the INN Programme described in Part III of the document.

4. Symbol (x) indicates stems included as examples in Article 9 of the *"General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances"* (see Annex 2).

5. Symbol (d) indicates stems that were formerly used, but are no longer formally acknowledged by the INN Programme.

Layout of information

Stem

Stem classification

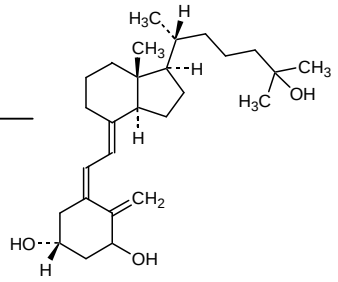
Stem definition

National Name(s)

USAN

calci
N.8.0.0

Vitamin D analogues/derivatives



(a) alfacalcidol (40), calcifediol (26), calcipotriol (61), calcitriol (39), colecalciferol (13), doxercalciferol (82), ergocalciferol (13), falecalcitriol (74), lexacalcitol (71), maxacalcitol (75), paricalcitol (78), secalciferol (62), seocalcitol (78), tacalcitol (65)

(b) calcitonin (31) (polypeptide)

(c) dihydrotachysterol (1)

Graphic Formula

INN (English)

List of proposed INN

Names in which the preferred stem has been used in accordance with its definition

Names in which the preferred stem has been used but not in accordance with its definition

Names which belong to the same group of pharmaceutical substances and in which no preferred stem has been used (this part of the list is not exhaustive)

(x) stems that are included in article 9 of the General Principles

(d) stems that were formerly used, but are no longer formally acknowledged by the INN Programme.

Part II A

ALPHABETICAL LIST OF COMMON STEMS

A
-abine (see -arabine and -citabine)
-ac
-acetam (see -racetam)
-actide
-adol/-adol-
-adom
-afenone
-afil
-aj-
-al
-aldrate
-alol (see -olol)
-alox (see -ox)
-amivir (see vir)
-ampanel
andr
-anib
-anide
-anserin
-antel
-antrone
-apine (see -pine)
-(ar)abine
-arit
-arol
-arone
-arotene
arte-
-ase
-ast
-astine
-azam (see -azepam)
-azenil
-azepam
-azepide
-azocine
-azolam (see -azepam)
-azoline
-azone (see -buzone)
-azosin

B
-bacept (see -cept)
-bactam
-bamate
barb
-begron
-benakin (see -kin)
-bendan (see -dan)
-bendazole
-bercept (see -cept)
-bermin (see -ermin)
-bersat
-betasol (see pred)
bol
-bradine
-brate (see -fibrate)
-bufen
-bulin
-butazone (see -buzone)
-buvir (see vir)
-buzone

C
-caine
-cain-
calci
-capone
-carbef
-carnil (see -azenil)
-castat (see -stat)
-cavir (see vir)
cef-
cell-/cel-
cell-ate (see cell-/cel-)
-cellose (see cell-/cel-)
-cept
-cic
-ciclib
-ciclovir (see vir)
-cidin
-ciguat
-cillide (see -cillin)
-cillin
-cillinam (see -cillin)
-cilpine (see -pine)
-cisteine (see -steine)
-citabine
-clidine/-clidinium
-clone
-cocept (see -cept)
-cog
-cogin
-conazole
cort
-coxib
-crinat
-crine
-cromil
-curium (see -ium)
-cycline

D
-dan
-dapsone
-decakin (see -kin)
-denoson
-dermin (see -ermin)
-dil
-dilol (see -dil)
-dipine
-dismase (see -ase)
-distim (see -stim)
-dodekin (see -kin)
-dopa
-dotril (see -tril/-trilat)
-dox (see -ox/-alox)
-dralazine
-drine
-dronic acid
-dutant (see -tant)
-dyl (see -dil)

E
-ectin
-elestat (see -stat)
-elvekin (see -kin)
-emcinal
-enicokin (see -kin)

-entan
(-)eptacog (see -cog)
erg
-eridine
-ermin
estr
-etanide (see -anide)
-ethidine (see -eridine)
-exakin (see -kin)
-exine

F
-farcept (see -cept)
-fenamate (see -fenamic acid)
-fenamic acid
-fenin
-fenine
-fentanil
-fentrine
-fermin (see -ermin)
-fiban
-fibrate
-filermin (see -ermin)
-flapon
-flurane
-formin
fos
-fosine (see -fos)
-fosfamide (see -fos)
-fovir (see vir)
-fradil
-frine (see -drine)
-fungin
-fylline

G
gab
gado-
-gatran
-gene
gest
-gestr- (see estr)
-giline
-gillin
gli
-gliflozin (see gli)
-gliptin (see gli)
-glitazar (see gli)
-glitazone (see gli)
-glumide
-glutide (see -tide)
-golide
-gosivir (see vir)
-gramostim (see -stim)
-grastim (see -stim)
-grel-/-grel
guan-

I
-ibine (see -ribine)
-icam
-ifene
-igetide (see -tide)
-ilide
imex
-imibe
-imod
-imus
-ine
-inostat (see -stat)
io-
iod-/-io-
-irudin
-isomide
-ium
-izine (-yzine)

K
-kacin
-kalant
-kalim
-kef-
-kin
-ki(n)- (see -mab)
-kinra
-kiren

L
-lefacept (see -cept)
-leukin (see -kin)
-lisib
-listat (see -stat)
-lubant
-lukast (see -ast)
-lutamide
-lutril (see -tril/-trilat)

M
-mab
-mantadine
-mantine (see -mantadine)
-mantone (see -mantadine)
-mapimod (see -imod)
-mastat (see -stat)
-meline
mer-/-mer
-mer
-mesine
-mestane
-metacin
-met(h)asone (see pred)
-micin
-mifene (see -ifene)
-milast (see -ast)
mito-
-monam
-morelin (see -relin)
-mostim (see -stim)
-motide (see -tide)
-motine
-moxin
-mulin
-mustine
-mycin

N
nab
-nabant
-nacept (see -cept)
-nakin (see -kin)
-nakinra (see -kinra)
nal-
-naritide (see -tide)
-navir (see vir)
-nermin (see -ermin)
-nercept (see -cept)
-nertant (see -tant)
-netant (see -tant)
-nicate (see nico-)
-nicline
nico-/nic-/ni-
-nidazole
-nidine (see -onidine)
nifur-
-nil (see -azenil)
nitro-/nitr-/nit-/ni-/-ni-

-nixin
(-)nonacog (see -cog)

O
-octakin (see -kin)
-octadekin (see -kin)
(-)octocog (see -cog)
-ol
-olol
-olone (see pred)
-onakin (see -kin)
-one
-onide
-onidine
-onium (see -ium)
-opamine (see -dopa)
-orex
-orph- (see orphan)
orphan
-otermin (see -ermin)
-ox/-alox
-oxacin
-oxan(e)
-oxanide (see -anide)
-oxef (see cef-)
-oxepin (see -pine)
-oxetine
-oxicam (see -icam)
-oxifene (see -ifene)
-oxopine (see -pine)

P
-pafant
-pamide
-pamil
-parcin
-parib
-parin
-parinux (see -parin)
-patril/-patrilat (see -tril/-trilat)
-pendyl (see -dil)
-penem
perfl(u)-
-peridol (see -perone)
-peridone (see -perone)
-perone
-pidem
-pin(e)
-piprant
-piprazole (see -prazole)
-pirone (see -spirone)
-pirox (see -ox/-alox)
-pitant (see -tant)
-plact
-pladib
-planin
-plase (see -ase)
-plasmid (see -gene)
-platin
-plermin (see -ermin)
-plestim (see -stim and -kin)
-plon
-poetin
-porfin
-poride
-pramine
-prazole
pred
-prenaline (see -terol)
-pressin
-previr (see vir)
-pride
-pril
-prilat (see -pril)
-prim
pris
-pristin
-profen
prost
-prostil (see prost)

Q
-quidar
-quin(e)
-quinil (see -azenil)

R
-racetam
-racil
-relin
-relix
-renone
-restat (see -stat)
retin
-ribine
rifa-
-rinone
-rixin
-rizine (see -izine)
-rolimus (see -imus)
-rozole
-rsen
-rubicin

S
sal
salazo- (see sal)
-salazine/-salazide (see sal)
-salan (see sal)
-sartan
-semide
-sermin (see -ermin)
-serod
-serpine
-sertib
-setron
som-
-sopine (see -pine)
-spirone
-stat/-stat-
-steine
-ster-
-steride (see -ster-)
-stigmine
-stim
sulfa-
-sulfan

T
-tacept (see cept)
-tadine
-tant
-tapide
-taxel
-tecan
-tegrast (see –ast)
-tepa
-tepine (see -pine)
-teplase (see -ase)
-termin (see -ermin)
-terol
-terone
-thiouracil (see -racil)
-tiazem
-tibant
-tide
-tidine

-tilide (see -ilide)
-tiline (see -triptyline)-tinib
-tirelin (see -relin)
-tizide
-tocin
-toin
-trakin (see -kin)
-trakinra (see -kinra)
-tredekin (see -kin)
-trexate
-trexed
-tricin
-tril/-trilat
-triptan
-triptyline
-troban
-trodast (see -ast)
trop

U
-uplase (see -ase)
-uridine

V
-vaptan
-vastatin (see -stat)
-vec (see -gene)
-verine
vin-/-vin-
vir
-vircept (see -cept)
-virine (see vir)
-viroc (see vir)
-virsen
-virumab (see mab)
-vos (see fos)
-vudine (see -uridine)

X
-xaban
-xanox (see -ox/-alox)

Y
-yzine (see -izine)

Z

-zafone
-zepine (see -pine)
-zolast (see -ast)
-zone (see -buzone)
-zomib
-zotan

PART II B

ALPHABETICAL LIST OF COMMON STEMS AND THEIR DEFINITION

A

-abine (see -arabine and -citabine)	arabinofuranosyl derivatives; nucleosides antiviral or antineoplastic agents, cytarabine or azacitidine derivatives
-ac	anti-inflammatory agents, ibufenac derivatives
-acetam (see -racetam)	amide type nootrope agents, piracetam derivatives
-actide	synthetic polypeptide with a corticotropin-like action
-adol/-adol-	analgesics
-adom	analgesics, tifluadom derivatives
-afenone	antiarrhythmics, propafenone derivatives
-afil	inhibitors of phosphodiesterase PDE5 with vasodilator action
-aj-	antiarrhythmics, ajmaline derivatives
-al	aldehydes
-aldrate	antacids, aluminium salts
-alol (see -olol)	aromatic ring related to -olols
-alox (see -ox)	antacids, aluminium derivatives
-amivir (see vir)	neuraminidase inhibitors
-ampanel	antagonists of the ionotropic non-NMDA (*N*-methyl-D-aspartate) glutamate receptors (Namely the AMPA (amino-hydroxymethyl-isoxazole-propionic acid) and/or KA (kainite antagonist) receptors)
andr	steroids, androgens
-anib	angiogenesis inhibitors
-anide	-
-anserin	serotonin receptor antagonists (mostly 5-HT_2)
-antel	anthelminthics (undefined group)
-antrone	antineoplastics; anthraquinone derivatives

-apine (see -pine)	tricyclic compounds
-(ar)abine	arabinofuranosyl derivatives
-arit	antiarthritic substances, acting like clobuzarit and lobenzarit, (mechanism different from anti-inflammatory type substances, e.g. -fenamates or -profens)
-arol	anticoagulants, dicoumarol derivatives
-arone	-
-arotene	arotinoid derivatives
arte-	antimalarial agents, artemisinin related compounds
-ase	enzymes
-ast	antiasthmatics or antiallergics, not acting primarily as antihistaminics
-astine	antihistaminics
-azam (see -azepam)	diazepam derivatives
-azenil	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
-azepam	diazepam derivatives
-azepide	cholecystokinin receptor antagonists, benzodiazepine derivatives
-azocine	narcotic antagonists/agonists related to 6,7-benzomorphan
-azolam (see -azepam)	diazepam derivatives
-azoline	antihistaminics or local vasoconstrictors, antazoline derivatives
-azone (see -buzone)	anti-inflammatory analgesics, phenylbutazone derivatives
-azosin	antihypertensive substances, prazosin derivatives

B

-bacept (see -cept)	B-cell activating factor receptors
-bactam	β-lactamase inhibitors
-bamate	tranquillizers, propanediol and pentanediol derivatives

barb	hypnotics, barbituric acid derivatives
-begron	β_3-adrenoreceptor agonists
-benakin (see -kin)	interleukin-1 analogues and derivatives
-bendan (see -dan)	cardiac stimulants, pimobendan derivatives
-bendazole	anthelminthics, tiabendazole derivatives
-bercept (see -cept)	target: VEGF receptors
-bermin (see -ermin)	vascular endothelial growth factors
-bersat	anticonvulsants, benzoylamino-benzpyran derivatives
-betasol (see pred)	prednisone and prednisolone derivatives
bol	anabolic steroids
-bradine	bradycardic agents
-brate (see -fibrate)	clofibrate derivatives
-bufen	non-steroidal anti-inflammatory agents, arylbutanoic acid derivatives
-bulin	antineoplastics; mitotic inhibitor, tubulin binder
-butazone (see -buzone)	anti-inflammatory analgesics, phenylbutazone derivatives
-buvir (see vir)	RNA polymerase (NS5B) inhibitors
-buzone	anti-inflammatory analgesics, phenylbutazone derivatives

C

-caine	local anaesthetics
-cain-	class I antiarrhythmics, procainamide and lidocaine derivatives
calci	vitamin D analogues/derivatives
-capone	catechol-*O*-methyltransferase (COMT) inhibitors
carbef	antibiotics, carbacephem derivatives
-carnil (see -azenil)	benzodiazepine receptor antagonists/agonists (carboline derivatives)

-castat (see -stat)	dopamine-hydroxylase inhibitors
-cavir (see vir)	carbocyclic nucleosides
cef-	antibiotics, cefalosporanic acid derivatives
cell-/cel-	cellulose derivatives
cell-ate (see cell-/cel-)	cellulose ester derivatives for substances containing acidic residues
-cellose (see cell-/cel-)	cellulose ether derivatives
-cept	receptor molecules, native or modified (a preceding infix should designate the target)
-cic	hepatoprotective substances with a carboxylic acid group
-ciclib	cyclin dependant kinase inhibitors
-ciclovir (see vir)	antivirals, bicyclic heterocycles compounds
-cidin	naturally occurring antibiotics (undefined group)
-ciguat	guanylate cyclase activators and stimulators
-cillide (see -cillin)	antibiotics, 6-aminopenicillanic acid derivatives
-cillin	antibiotics, 6-aminopenicillanic acid derivatives
-cillinam (see -cillin)	antibiotics, 6-aminopenicillanic acid derivatives
-cilpine (see -pine)	tricyclic compounds
-cisteine (see -steine)	mucolytics, other than bromhexine derivatives
-citabine	nucleosides antiviral or antineoplastic agents, cytarabine or azacitidine derivatives
-clidine/-clidinium	muscarinic receptor agonists/antagonists
-clone	hypnotic tranquillizers
-cocept (see -cept)	complement receptors
-cog	blood coagulation factors
-cogin	blood coagulation cascade inhibitors
-conazole	systemic antifungal agents, miconazole derivatives
cort	corticosteroids, except prednisolone derivatives

-coxib	selective cyclo-oxygenase inhibitors
-crinat	diuretics, etacrynic acid derivatives
-crine	acridine derivatives
-cromil	antiallergics, cromoglicic acid derivatives
-curium (see -ium)	curare-like substances
-cycline	antibiotics, protein-synthesis inhibitors, tetracycline derivatives

D

-dan	cardiac stimulants, pimobendan derivatives
-dapsone	antimycobacterials, diaminodiphenylsulfone derivatives
-decakin (see -kin)	interleukin-10 analogues and derivatives
-denoson	adenosine A receptor agonists
-dermin (see -ermin)	epidermal growth factors
-dil	vasodilators
-dilol (see -dil)	vasodilators
-dipine	calcium channel blockers, nifedipine derivatives
-dismase (see -ase)	enzymes with superoxide dismutase activity, see -ase item V
-distim (see -stim)	combination of two different types of colony stimulating factors
-dodekin (see -kin)	interleukin-12 analogues and derivatives
-dopa	dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism/prolactin inhibitors
-dox (see -ox/-alox)	antibacterials, quinazoline dioxide derivatives
-dralazine	antihypertensives, hydrazinephthalazine derivatives
-drine	sympathomimetics
-dronic acid	calcium metabolism regulator, pharmaceutical aid
-dutant (see -tant)	neurokinin NK_2 receptor antagonist
-dyl (see -dil)	vasodilators

E

-ectin	antiparasitics, ivermectin derivatives
-elestat (see -stat)	elastase inhibitors
-elvekin (see -kin)	interleukin-11 analogues and derivatives
-emcinal	erythromycin derivatives lacking antibiotic activity, motilin agonists
-enicokin (see -kin)	interleukin-21 human analogues and derivatives
-entan	endothelin receptor antagonists
(-)eptacog (see -cog)	blood coagulation VII
erg	ergot alkaloid derivatives
-eridine	analgesics, pethidine derivatives
-ermin	growth factors
estr	estrogens
-etanide (see -anide)	diuretics, piretanide derivatives
-ethidine (see -eridine)	analgesics, pethidine derivatives
-exakin (see -kin)	interleukin-6 analogues and derivatives
-exine	mucolytic, bromhexine derivatives

F

-farcept (see -cept)	subgroup of interferon receptors
-fenamate (see -fenamic acid)	"fenamic acid" derivatives
-fenamic acid	anti-inflammatory, anthranilic acid derivatives
-fenin	diagnostic aids; (phenylcarbamoyl)methyl iminodiacetic acid derivatives
-fenine	analgesics, glafenine derivatives (subgroup of fenamic acid group)
-fentanil	opioid receptor agonists, analgesics, fentanyl derivatives
-fentrine	inhibitors of phosphodiesterases

-fermin (see -ermin)	fibroblast growth factors
-fiban	fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)
-fibrate	clofibrate derivatives
-filermin (see -ermin)	leukemia-inhibiting factor
-flapon	5-lipoxygenase-activating protein (FLAP) inhibitor
-flurane	halogenated compounds used as general inhalation anaesthetics
-formin	antihyperglycaemics, phenformin derivatives
fos	insecticides, anthelminthics, pesticides etc., phosphorous derivatives
-fosfamide (see -fos)	alkylating agents of the cyclophosphamide group
-fosine (see -fos)	cytostatic
-fovir (see vir)	phosphonic acid derivatives
-fradil	calcium channel blockers acting as vasodilators
-frine (see -drine)	sympathomimetic, phenethyl derivatives
-fungin	antifungal antibiotics
-fylline	*N*-methylated xanthine derivatives

G

gab	gabamimetic agents
gado-	diagnostic agents, gadolinium derivatives
-gatran	thrombin inhibitor, antithrombotic agent
-gene	gene therapy products
gest	steroids, progestogens
-gestr- (see estr)	estrogens
-giline	monoamine oxydase (MAO)-inhibitors type B
-gillin	antibiotics produced by *Aspergillus* strains

gli	antihyperglycaemics
-gliflozin (see gli)	sodium glucose co-transporter inhibitors, phlorizin derivatives
-gliptin (see gli)	dipeptidyl aminopeptidase–IV inhibitors
-glitazar (see gli)	peroxisome proliferator activating receptor-γ (PPAR-γ) agonists
-glitazone (see gli)	peroxisome proliferator activating receptor-γ (PPAR-γ) agonists, thiazolidinedione derivatives
-glumide	cholecystokinin (CCK) antagonists, antiulcer, anxiolytic agent
-glutide (see -tide)	Glucagon-Like Peptide (GLP) analogues
-golide	dopamine receptor agonists, ergoline derivatives
-gosivir (see vir)	glucoside inhibitors
-gramostim (see -stim)	granulocyte macrophage colony stimulating factor (GM-CSF) types substances
-grastim (see -stim)	granulocyte colony stimulating factor (G-CSF) type substances
-grel-/-grel	platelet aggregation inhibitors
guan-	antihypertensives, guanidine derivatives

I

-ibine (see -ribine)	ribofuranyl-derivatives of the “pyrazofurin” type
-icam	anti-inflammatory, isoxicam derivatives
-ifene	antiestrogens or estrogen receptor modulators, clomifene and tamoxifen derivatives
-igetide (see -tide)	peptides and glycopeptides
-ilide	class III antiarrhythmics, sematilide derivatives
imex	immunostimulants
-imibe	antihyperlipidaemics, acyl CoA: cholesterol acyltransferase (ACAT) inhibitors
-imod	immunomodulators, both stimulant/suppressive and stimulant
-imus	immunosuppressants (other than antineoplastics)

-ine	alkaloids and organic bases
-inostat (see stat)	histone deacetylase inhibitors
io-	iodine-containing contrast media
iod-/-io-	iodine-containing compounds other than contrast media
-irudin	thrombin inhibitors, hirudin derivatives
-isomide	class I antiarrhythmics, disopyramide derivatives
-ium	quaternary ammonium compounds
-izine (-yzine)	diphenylmethyl piperazine derivatives

K

-kacin	antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*)
-kalant	potassium channel blockers
-kalim	potassium channel activators, antihypertensive
-kef-	enkephalin agonists
-kin	interleukin type substances
-ki(n)- (see -mab)	target: interleukin
-kinra (see -kin)	interleukin receptor antagonists
-kiren	renin inhibitors

L

-lefacept (see -cept)	lymphocyte function-associated antigen 3 receptors
-leukin (see -kin)	interleukin-2 analogues and derivatives
-lisib	phosphatidylinositol 3-kinase inhibitors, antineoplastics
-listat (see –stat)	gastrointestinal lipase inhibitors
-lubant	leukotriene B_4 receptor antagonist
-lukast (see –ast)	leukotriene receptor antagonists

-lutamide	non-steroid antiandrogens

M

-mab	monoclonal antibodies
-mantadine	adamantane derivatives
-mantine (see -mantadine)	adamantane derivatives
-mantone (see -mantadine)	adamantane derivatives
-mapimod (see -imod)	mitogen-activated protein (MAP) kinase inhibitors
-mastat (see -stat)	matrix metalloproteinase inhibitors
-meline	cholinergic agents (muscarine receptor agonists/partial antagonists used in the treatment of Alzheimer's disease)
mer-/-mer	mercury-containing drugs, antimicrobial or diuretic
-mer	polymers
-mesine	sigma receptor ligands
-mestane	aromatase inhibitors
-metacin	anti-inflammatory, indometacin derivatives
-met(h)asone (see pred)	prednisone and prednisolone derivatives
-micin	aminoglycosides, antibiotics obtained from various *Micromonospora*
-mifene (see -ifene)	antiestrogens, clomifene and tamoxifen derivatives
-milast (see -ast)	phosphodiesterase IV (PDE IV) inhibitors
mito-	antineoplastics, nucleotoxic agents
-monam	monobactam antibiotics
-morelin (see -relin)	growth hormone release-stimulating peptides
-mostim (see -stim)	macrophage stimulating factors (M-CSF) type substances
-motide (see -tide)	immunological agents for active immunization
-motine	antivirals, quinoline derivatives

-moxin	monoamine oxidase inhibitors, hydrazine derivatives
-mulin	antibacterials, pleuromulin derivatives
-mustine	antineoplastic, alkylating agents, (β-chloroethyl)amine derivatives
-mycin	antibiotics, produced by *Streptomyces* strains (see also -kacin)

N

nab	cannabinoid receptors agonists
-nabant	cannabinoid receptors antagonists
-nacept (see -cept)	interleukin-1 receptors
-nakin (see -kin)	interleukin-1 analogues and derivatives
-nakinra (see -kin)	interleukin-1 receptor antagonists
nal-	opioid receptor antagonists/agonists related to normorphine
-naritide (see -tide)	peptides and glycopeptides
-navir (see vir)	Human Immunodeficiency Virus (HIV) protease inhibitors
-nermin (see -ermin)	tumour necrosis factor
-nercept (see -cept)	tumour necrosis factor receptors
-nertant (see -tant)	neurotensin antagonists
-netant (see -tant)	neurokinin NK_3 receptor antagonists
-nicate (see nico-)	antihypercholesterolaemic and/or vasodilating nicotinic acid esters
-nicline	nicotinic acetylcholine receptor partial agonists / agonists
nico-/nic-/ni-	nicotinic acid or nicotinoyl alcohol derivatives
-nidazole	antiprotozoals and radiosensitizers, metronidazole derivatives
-nidine (see -onidine)	antihypertensives, clonidine derivatives
nifur-	5-nitrofuran derivatives
-nil (see -azenil)	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
nitro-/nitr-/nit-/ni-/-ni-	NO_2 - derivatives

-nixin	anti-inflammatory, anilinonicotinic acid derivatives
(-)nonacog (see -cog)	blood factor IX

O

octakin (see -kin)	interleukin-8 analogues and derivatives
-octadekin (see -kin)	interleukin-18 human analogues and derivatives
(-)octocog (see -cog)	blood factor VIII
-ol	for alcohols and phenols
-olol	β-adrenoreceptor antagonists
-olone (see pred)	steroids other than prednisolone derivatives
-onakin (see -kin)	interleukin-1 analogues and derivatives
-one	ketones
-onide	steroids for topical use, acetal derivatives
-onidine	antihypertensives, clonidine derivatives
-onium (see -ium)	quaternary ammonium compounds
-opamine (see -dopa)	dopaminergic agents dopamine derivatives used as cardiac stimulant/antihypertensives/diuretics
-orex	anorexics
-orph- (see orphan)	opioid receptor antagonists/agonists, morphinan derivates
orphan	opioid receptor antagonists/agonists, morphinan derivates
-otermin (see -ermin)	bone morphogenetic proteins
-ox/-alox	antacids, aluminium derivatives
-oxacin	antibacterials, nalidixic acid derivatives
-oxan(e)	benzodioxane derivatives
-oxanide (see -anide)	antiparasitics, salicylanilides and analogues
-oxef (see cef-)	antibiotics, oxacefalosporanic acid derivatives
-oxepin (see -pine)	tricyclic compounds

-oxetine	serotonin and/or norepinephrine reuptake inhibitors, fluoxetine derivatives
-oxicam (see -icam)	anti-inflammatory, isoxicam derivatives
-oxifene (see -ifene)	antiestrogens or estrogen receptor modulators, clomifene and tamoxifen derivatives
-oxopine (see -pine)	tricyclic compounds

P

-pafant	platelet-activating factor antagonists
-pamide	diuretics, sulfamoylbenzoic acid derivatives (could be sulfamoylbenzamide)
-pamil	calcium channel blocker, verapamil derivatives
-parcin	for glycopeptide antibiotics
-parib	poly-ADP-Ribose polymerase inhibitors
-parin	heparin derivatives including low molecular mass heparins
-parinux (see -parin)	synthetic heparinoids
-pendyl (see -dil)	vasodilators
-penem	analogues of penicillanic acid antibiotics modified in the five-membered ring
perfl(u)-	perfluorinated compounds used as blood substitutes and/or diagnostic agents
-peridol (see -perone)	antipsychotics, haloperidol derivatives
-peridone (see -perone)	antipsychotics, risperidone derivatives
-perone	tranquillizers, neuroleptics, 4'-fluoro-4-piperidinobutyrophenone derivatives
-pidem	hypnotics/sedatives, zolpidem derivatives
-pin(e)	tricyclic compounds
-piprant	prostaglandin receptors antagonists, non-prostanoids
-piprazole (see -prazole)	psychotropics, phenylpiperazine derivatives

-pirone (see -spirone)	anxiolytics, buspirone derivatives
-pirox (see -ox/-alox)	antimycotic pyridone derivatives
-pitant (see -tant)	neurokinin NK_1 (substance P) receptor antagonist
-plact	platelet factor 4 analogues and derivatives
-pladib	phospholipase A_2 inhibitors
-planin	glycopeptide antibacterials (*Actinoplanes* strains)
-plase (see -ase)	enzymes
-plasmid (see -gene)	gene therapy products
-platin	antineoplastic agents, platinum derivatives
-plermin (see -ermin)	platelet-derived growth factor
-plestim (see -stim and -kin)	interleukin-3 analogues and derivatives
-plon	imidazopyrimidine or pyrazolopyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
-poetin	erythropoietin type blood factors
-porfin	benzoporphyrin derivatives
-poride	Na^+/H^+ antiport inhibitor
-pramine	substances of the imipramine group
-prazole	antiulcer, benzimidazole derivatives
pred	prednisone and prednisolone derivatives
-prenaline (see -terol)	bronchodilators, phenethylamine derivatives
-pressin	vasoconstrictors, vasopressin derivatives
-previr (see vir)	Hepatitis Virus C (HVC) protease inhibitors
-pride	sulpiride derivatives
-pril	angiotensin-converting enzyme inhibitors
-prilat (see -pril)	angiotensin-converting enzyme inhibitors
-prim	antibacterials, dihydrofolate reductase (DHFR) inhibitors, trimethoprim derivatives

-pris-	steroidal compounds acting on progesterone receptors (excluding -*gest*- compounds)
-pristin	antibacterials, streptogramins, protein synthesis inhibitors, pristinamycin derivatives
-profen	anti-inflammatory agents, ibuprofen derivatives
prost	prostaglandins
-prostil (see prost)	prostaglandins, anti-ulcer

Q

-quidar	drugs used in multidrug resistance, quinoline derivatives
-quin(e)	quinoline derivatives
-quinil (see -azenil)	benzodiazepine receptor agonists, also partial or inverse (quinoline derivatives)

R

-racetam	amide type nootrope agents, piracetam derivatives
-racil	uracil type antineoplastics
-relin	pituitary hormone-release stimulating peptides
-relix	gonadotropin-releasing-hormone (GnRH) inhibitors, peptides
-renone	aldosterone antagonists, spironolactone derivates
-restat (see -stat)	aldose reductase inhibitors
retin	retinol derivatives
-ribine	ribofuranyl-derivatives of the "pyrazofurin" type
rifa-	antibiotics, rifamycin derivatives
-rinone	cardiac stimulants, amrinone derivatives
-rixin	chemokine CXCR receptors antagonists
-rizine (see -izine)	antihistaminics/cerebral (or peripheral) vasodilators
-rolimus (see -imus)	immunosuppressants, rapamycin derivatives

-rozole	aromatase inhibitors, imidazole-triazole derivatives
-rsen	antisense oligonucleotides
-rubicin	antineoplastics, daunorubicin derivatives

S

sal	salicylic acid derivatives
salazo-	phenylazosalicylic acid derivatives antibacterial
-salan	brominated salicylamide derivatives disinfectant
-sartan	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-semide	diuretics, furosemide derivatives
-sermin (see -ermin)	insulin-like growth factors
-serod	serotonin receptor antagonists and partial agonists
-serpine	derivatives of *Rauwolfia* alkaloids
-sertib	serine/threonine kinase inhibitors
-setron	serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists
som-	growth hormone derivatives
-sopine (see -pine)	tricyclic compounds
-spirone	anxiolytics, buspirone derivatives
-stat/-stat-	enzyme inhibitors
-steine	mucolytics, other than bromhexine derivatives
-ster-	androgens/anabolic steroids
-steride (see -ster-)	androgens/anabolic steroids
-stigmine	acetylcholinesterase inhibitors
-stim	colony stimulating factors
sulfa-	anti-infectives, sulfonamides

-sulfan	antineoplastic, alkylating agents, methanesulfonates
T	
-tacept (see -cept)	cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptors
-tadine	tricyclic histamine-H_1 receptor antagonists, tricyclic compounds
-tant	neurokinin (tachykinin) receptor antagonists
-tapide	microsomal triglyceride transfer protein (MTP) inhibitors
-taxel	antineoplastics; taxane derivatives
-tecan	antineoplastics, topoisomerase I inhibitors
-tegrast (see –ast)	integrin antagonists
-tepa	antineoplastics, thiotepa derivatives
-tepine (see -pine)	tricyclic compounds
-teplase (see -ase)	tissue type plasminogen activators, see -ase item VI
-tercept (see -cept)	transforming growth factors receptors
-termin (see -ermin)	transforming growth factor
-terol	bronchodilators, phenethylamine derivatives
-terone	antiandrogens
-thiouracil (see -racil)	uracil derivatives used as thyroid antagonists
-tiazem	calcium channel blockers, diltiazem derivatives
-tibant	bradykinin receptor antagonists
-tide	peptides and glycopeptides (for special groups of peptides see -actide, -pressin, -relin, -tocin)
-tidine	histamine-H_2-receptor antagonists, cimetidine derivatives
-tilide (see -ilide)	class III antiarrhythmics, sematilide derivatives
-tiline (see -triptyline)	antidepressants, dibenzo[a,d]cycloheptane or cyclopheptene derivatives
-tinib	tyrosine kinase inhibitors
-tirelin (see -relin)	thyrotropin releasing hormone analogues

-tizide	diuretics, chlorothiazide derivatives
-tocin	oxytocin derivatives
-toin	antiepileptics, hydantoin derivatives
-trakin (see -kin)	interleukin-4 analogues and derivatives
-trakinra (see -kinra)	interleukin-4 receptor antagonists
-tredekin (see -kin)	interleukin-13 analogues and derivatives
-trexate	folic acid analogues
-trexed	antineoplastics; thymidilate synthetase inhibitors
-tricin	antibiotics, polyene derivatives
-tril/trilat	endopeptidase inhibitors
-triptan	serotonin ($5HT_1$) receptor agonists, sumatriptan derivatives
-triptyline	antidepressants, dibenzo[a,d]cycloheptane or cyclopheptene derivatives
-troban	thromboxane A_2-receptor antagonists; antithrombotic agents
-trodast (see -ast)	thromboxane A_2-receptor antagonists, antiasthmatics
trop	atropine derivatives

U

-uplase (see -ase)	urokinase type plasminogen activator, see -ase item VII
-ur (see -uridine)	uridine derivatives used as antiviral agents and as antineoplastics
-uridine	uridine derivatives used as antiviral agents and as antineoplastics

V

-vaptan	vasopressin receptor antagonists
-vastatin (see -stat)	antihyperlipidaemic substances, HMG CoA reductase inhibitors
-vec (see -gene)	gene therapy product

-verine	spasmolytics with a papaverine-like action
vin-/-vin-	vinca alkaloids
vir	antivirals (undefined group)
-vircept (see -cept)	antiviral receptors
-virine (see vir)	non-nucleoside reverse transcriptase inhibitors (NNRTI)
-viroc (see -vir)	CCR5 (Chemokine CC motif receptor 5) receptor antagonists
-virsen	antisense oligonucleotides
-vos (see fos)	insecticides, anthelminthics, pesticides etc., phosphorus derivatives
-vudine (see -uridine)	uridine derivatives used as antiviral agents and as antineoplastics

X

-xaban	blood coagulation factor X_A inhibitors, antithrombotics
-xanox (see -ox/-alox)	anti-allergics, tixanox group

Y

-yzine (see -izine)	diphenylmethyl piperazine derivatives

Z

-zafone	alozafone derivatives
-zepine (see -pine)	tricyclic compounds
-zolast (see -ast)	leukotriene biosynthesis inhibitors
-zomib	proteasome inhibitors
-zone (see -buzone)	anti-inflammatory analgesics, phenylbutazone derivatives
-zotan	5-HT_{1A} receptor agonists / antagonists acting primarily as neuroprotectors

Acknowledgements

The INN Secretariat extends its thanks to Dr R. Boudet-Dalbin, France, for the graphic representations of the chemical formulae in this document.

PART III

Stem classification with corresponding examples of stems and their definition

A000	**CNS DEPRESSANTS**		
A100	**General anaesthetics**		
A110	General anaesthetics, volatile	*-flurane*	halogenated compounds used as general inhalation anaesthetics
A120	General anaesthetics, other		
A200	**Hypnotics - sedatives**		
A210	Barbiturates	*barb*	hypnotics, barbituric acid derivatives
A220	Hypnotic sedatives, other	*-clone*	hypnotic tranquillizers
A220		*-plon*	imidazopyrimidine or pyrazolopyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
A240	Chloral derivatives, hypnotic sedatives		
A300	**Centrally acting voluntary muscle tone modifying drugs**		
A310	Antiepileptics	*-bersat*	anticonvulsants, benzoylamino-benzpyran derivatives
A311	Hydantoins, Antiepileptics	*-toin*	antiepileptics, hydantoin derivatives
A312	Acetylureas, Antiepileptics		
A313	Oxazolidinediones, Antiepileptics		
A314	Succinimides, Antiepileptics		
A315	Barbiturates, Antiepileptics		
A316	Antiepileptics, other		
A320	Central anticholinergics		

A330	Centrally acting voluntary-muscle relaxants		
A400	**Analgesics and antipyretics,** please see AA code here below.		
A500	**Antivertigo drugs**		

AA- ANALGESICS AND ANTIPYRETICS*

* The stems here below have been extracted from the A-CNS depressant category since not all analgesics are CNS depressants. In this context, a subcategory "AA- Analgesics and antipyretics" has been created to better reflect this information.

A400	**Analgesics**		
A410	**Opioids**	-adol or -adol-	analgesics
A410		-azocine	narcotic antagonists/agonists related to 6,7-benzomorphan
A410		-eridine	analgesics, pethidine derivatives
A410		-ethidine	see -eridine
A410		-fentanil	opioid receptor agonists, analgesics, fentanyl derivatives
A410		nal-	opioid receptor antagonists/agonists related to normorphine
A410		orphan	opioid receptor antagonists/agonists, morphinan derivates; -orphine, -orphinol, -orphone
A420	**Analgesics - Antipyretics**	-ac	anti-inflammatory agents, ibufenac derivatives
A420		-adol or -adol-	analgesics
A420		-arit	antiarthritic substances, acting like clobuzarit and lobenzarit (mechanism different from anti-inflammatory type substances, e.g. -fenamates or -profens)

A420		-bufen	non-steroidal anti-inflammatory agents, arylbutanoic acid derivatives
A420		-butazone	-buzone: anti-inflammatory analgesics, phenylbutazone derivatives
A420		-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
A420		-coxib	selective cyclo-oxygenase inhibitors
A420		-fenamate	"-fenamic acid" derivatives
A420		-fenamic acid	anti-inflammatory, anthranilic acid derivatives
A420		-icam	anti-inflammatory, isoxicam derivatives
A420		-metacin	anti-inflammatory, indometacin derivatives
A420		-nixin	anti-inflammatory, anilinonicotinic acid derivatives
A420		-profen	anti-inflammatory agents, ibuprofen derivatives
A430	**Analgesics, other**	-adom	analgesics, tifluadom derivatives
A430		-fenine, phenine	analgesics, glafenine derivatives - (subgroup of fenamic acid group)
A440	**Central antiemetics**		

B000	**CNS STIMULANTS**	*-ampanel*	antagonists of the ionotropic non-NMDA (*N*-methyl-D-aspartate) glutamate receptors (Namely the AMPA (amino-hydroxymethyl-isoxazole-propionic acid) and/or KA (kainite antagonist) receptors)
B100	**Analeptics**	*-fylline*	*N*-methylated xanthine derivatives
B100		*-racetam*	amide type nootrope agents, piracetam derivatives

B100		*vin-* (and *-vin-*)	vinca alkaloids
B200	**Opioid receptor antagonists**	*nal-*	narcotic antagonists/agonists related to normorphine
B200		*orphan*	opioid receptor antagonists/agonists, morphinan derivates
B300	**Benzodiazepine receptor antagonists**		

C000	**PSYCHOPHARMACOLOGICS**	*-piprazole*	psychotropics, phenylpiperazine derivatives *(future use is discouraged due to conflict with the stem –prazole)*
C000		*-pride*	sulpiride derivatives
C000		*-racetam*	amide type nootrope agents, piracetam derivatives
C000		*-triptan*	serotonin (5-HT_1) receptor agonists, sumatriptan derivatives
C000		*-zotan*	serotonin 5-HT_{1A} receptor agonists/antagonists acting primarily as neuroprotectors
C100	**Anxiolytic sedatives**	*-azenil*	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
C100		*-azepam*	diazepam derivatives
C100		*-bamate*	tranquillizers, propanediol and pentanediol derivatives
C100		*-carnil*	benzodiazepine receptor antagonists/agonists (carboline derivatives)
C100		*-peridone*	see *-perone*: antipsychotics, risperidone derivatives

C100		*-perone*	tranquillizers, neuroleptics, 4'-fluoro-4-piperidino-butyrophenone derivatives
C100		*-pidem*	hypnotics/sedatives, zolpidem derivatives
C100		*-plon*	imidazopyrimidine or pyrazolopyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
C100		*-quinil*	benzodiazepine receptor agonists also partial or inverse (quinoline derivatives), see *-azenil*
C100		*-spirone*	anxiolytics, buspirone derivatives
C100		*-zafone*	alozafone derivatives
C200	**Antipsychotics (neuroleptics)**	*-perone*	tranquillizers, neuroleptics, 4'-fluoro-4-piperidinobutyrophenone derivatives; *-peridol*: antipsychotics, haloperidol derivatives; *-peridone*: antipsychotics, risperidone derivatives
C210	Brain amine depleters		
C220	Central adrenoreceptor antagonists		
C300	**Antidepressants**	*-oxetine*	serotonin and/or norepinephrine reuptake inhibitors, fluoxetine derivatives
C310	MAO inhibitors	*-giline*	MAO-inhibitors type B
C310		*-moxin*	monoamine oxidase inhibitors, hydrazine derivatives
C320	Tricyclic antidepressants	*-pin(e)*	tricyclic compounds; *dipine*: see *-dipine*; *-zepine*: antidepressant/ neuroleptic; C.0.0.0 *-apine*: psychoactive; A.3.1.0 *cilpine*: antiepileptic; *-oxepin, -oxopine, -sopine, -tepine*

C320		*-pramine*	substances of the imipramine group
C320		*-triptyline*	antidepressants, dibenzo[a,d]cycloheptane or cyclopheptene derivatives
C330	Tetracyclic antidepressants		
C340	Bicyclic antidepressants		
C400	**Indirect releasers of catecholamines**		
C500	**Psychodysleptics (hallucinogens)**		
C600	**CNS metabolites**		
C700	**Serotonin receptor antagonists**	*-anserin*	serotonin receptor antagonists (mostly 5-HT_2)
C700		*erg*	ergot alkaloid derivatives
C700		*-setron*	serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists, see *-anserin*

E000	**DRUGS ACTING AT SYNAPTIC AND NEUROEFFECTOR JUNCTIONAL SITES**	*gab*	gabamimetic agents
E000		*-nabant*	cannabinoid receptors antagonists
E000	Local anaesthetics	*-caine*	local anaesthetics
E100	**Cholinergic agents**	*-meline*	cholinergic agents (muscarinic receptor agonists/partial antagonists used in the treatment of Alzheimer's disease)
E100		*-clidine/ -clidinium*	muscarinic receptor agonists/antagonists

E110	Dopaminergic receptor agonists	*-dopa*	dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism/prolactin inhibitors
E110		*-golide*	dopamine receptor agonists, ergoline derivatives
E111	Muscarinic receptor agonists		
E112	Nicotinic receptor agonists	*-nicline*	nicotinic acetylcholine receptor partial agonists / agonists
E120	Anticholinesterase agents	*-stigmine*	anticholinesterases
E200	**Cholinergic antagonists**	*trop*	atropine derivatives
E210	Peripheral cholinergic antagonists		
E220	Ganglionic antagonists		
E300	**Neuromuscular blocking agents**	*-curium*	curare-like substance; see *-ium*
E300		*-ium*	quaternary ammonium compounds; *-curium*: curare-like substances; *-onium*
E400	**Adrenergic agents**	*-azoline*	antihistaminics or local vasoconstrictors, antazoline derivatives
E400		*-drine*	sympathomimetics; *-frine*: sympathomimetic, phenethyl derivatives
E400		*-frine*	sympathomimetic, phenethyl derivatives
E400		*-terol*	bronchodilators, phenethylamine derivatives [previously *-prenaline* or *-terenol*]
E410	Beta adrenoreceptor agonists		
E420	Alpha adrenoreceptor agonists		

E500	**Adrenoreceptor antagonists**		
E510	Alpha adrenoreceptor antagonists	*-oxan(e)*	benzodioxane derivatives
E520	Beta adrenoreceptor antagonists	*-alol*	aromatic ring -CHOH-CH_2-NH-R related to -ololS
E520		*-olol*	beta-adrenoreceptor antagonists; *-alol*: aromatic ring -CH-CH_2-NH-R related to -ololS
E530	Catecholamines false transmitters		
E540	Adrenergic neurone blocking agents	*-serpine*	derivatives of *Rauwolfia* alkaloids

F000	**AGENTS ACTING ON SMOOTH MUSCLES**		
F100	**Spasmolytics, general**	*-verine*	spasmolytics with a papaverine-like action
F200	**Vasodilators**	*-afil*	inhibitors of PDE5 with vasodilator action
F200		*-ciguat*	guanylate cyclase activators and stimulators
F200		*-dil*	vasodilators
F200		*-entan*	endothelin receptor antagonists
F210	Coronary vasodilators, also calcium channel blockers	*-dipine*	calcium channel blockers, nifedipine derivatives
F210		*-fradil*	calcium channel blockers acting as vasodilators
F210		*-pamil*	calcium channel blockers, verapamil derivatives
F210		*-tiazem*	calcium channel blockers, diltiazem derivatives
F220	Peripheral vasodilators	*-nicate*	antihypercholesterolaemic and/or vasodilating nicotinic acid esters

F300	**Smooth muscle stimulants**		
F310	Vasoconstrictor agents		
F400	**Agents acting on the uterus**	*erg*	ergot alkaloid derivatives

G000	**HISTAMINE AND ANTIHISTAMINICS**		
G100	**Histamine and histamine-like drugs**		
G200	**Antihistaminics**	*-astine*	antihistaminics
G210	Histamine H_1-receptor antagonists	*-tadine*	histamine-H_1 receptor antagonists, tricyclic compounds
G220	Histamine H_2-receptor antagonists	*-tidine*	histamine-H_2-receptor antagonists, cimetidine derivatives
G230	Histamine H_3-receptor antagonists		
G300	**Histamine metabolism agents**		

H000	**CARDIOVASCULAR AGENTS**	*-bradine*	bradycardic agents
H000		*-denoson*	adenosine A receptor agonists
H000		*-vaptan*	vasopressin receptor antagonists
H100	**Cardiac glycosides and drugs with similar action**	*-dan*	cardiac stimulants, pimobendan derivatives
H100		*-rinone*	cardiac stimulants, amrinone derivatives
H200	**Antiarrhythmics**	*-afenone*	antiarrhythmics, propafenone derivatives
H200		*-aj-*	antiarrhythmics, ajmaline derivatives
H200		*-cain-*	Class I antiarrhythmics, procainamide and lidocaine derivatives (antifibrillants with local anaesthetic activity)

H200		*-ilide*	Class III antiarrhythmics, sematilide derivatives
H200		*-isomide*	class I antiarrhythmics, disopyramide derivatives
H200		*-kalant*	potassium channel blockers
H300	**Antihypertensives**	*-azosin*	antihypertensive substances, prazosin derivatives
H300		*-dralazine*	antihypertensives, hydrazinephthalazine derivatives
H300		*guan-*	antihypertensives, guanidine derivatives
H300		*-kalim*	potassium channel activators, antihypertensive
H300		*-kiren*	renin inhibitors
H300		*-(o)nidine*	antihypertensives, clonidine derivatives
H300		*-pril(at)*	angiotensin-converting enzyme inhibitors
H300		*-sartan*	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
H400	**Antihyperlipidaemic drugs**	*-fibrate*	clofibrate derivatives
H400		*-nicate*	antihypercholesterolaemic and/or vasodilating nicotinic acid esters
H400		*-tapide*	microsomal triglyceride transfer protein (MTP) inhibitors
H400		*-vastatin*	see *-stat*; antihyperlipidaemic substances, HMG CoA reductase inhibitors
H500	**Antivaricose drugs**		
H510	Sclerosing drugs		

H600	**Capillary-active drugs, haemostyptics**		
H700	**Calcium channel blockers**		
H800	**Agents influencing the renin-angiotensin system**		
H810	Angiotensin converting enzyme inhibitors		
H820	Angiotensin receptor antagonists		

I000	**BLOOD AND AGENTS ACTING ON THE HAEMOPOIETIC SYSTEM (EXCL. CYTOSTATICS)**		
I100	**Antianaemic agents**		
I110	Iron preparations		
I120	Haematinics, other (Vit. B-12, folic acid, etc.)		
I130	Miscellaneous antianaemic agents		
I200	**Agents influencing blood coagulation**	*-cog*	*(-)eptacog:* blood coagulation VII, *(-)octocog:* blood factor VIII, *(-)nonacog:* blood factor IX
I200		*-cogin*	blood coagulation cascade inhibitors
I200		*-fiban*	fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)
I200		*-gatran*	thrombin inhibitor, antithrombotic agents
I200		*-parin*	heparin derivatives including low molecular mass heparins
I210	Anticoagulants	*-arol*	anticoagulants, dicoumarol derivatives

I210		*-grel-* or *-grel*	platelet aggregation inhibitors
I210		*-irudin*	hirudin derivatives
I210		*-pafant*	platelet-activating factor antagonists
I210		*-troban*	thromboxane A_2-receptor antagonists; antithrombotic agents
I220	Prothrombin inhibitors		
I230	Prothrombin synthesis inhibitors		
I240	Anticoagulant inhibitors		
I250	Agents affecting fibrinolysis		
I260	Coagulation promoting agents		
I261	Blood clotting factors		
I300	**Blood proteins and their fractions**	*-poetin*	erythropoietin type blood factors
I310	Blood substitutes (macromolecular)		
I400	**Platelet-function regulators**		
I500	**Colony stimulating factors**	*-stim*	colony stimulating factors: *-distim*: combination of two different types of CSF; *-gramostim*: granulocyte macrophage colony stimulating factor (GM-CSF) type substances; *-grastim*: granulocyte colony stimulatory factor (G-CSF) type substances; *-mostim:* macrophage stimulating factors (M-CSF) type substances; *-plestim:* interleukin-3 analogues and derivatives

I500	Granulocyte stimulating factors	*-grastim*	see *-stim*
I500	Macrophage stimulating factor	*-mostim*	macrophage stimulating factors (M-CSF) type substances; see *-stim*

J000	**AGENTS INFLUENCING THE GASTROINTESTINAL TRACT**	*-emcinal*	erythromycin derivatives lacking antibiotic activity, motilin agonists
J000		*-glumide*	cholecystokinine antagonists, antiulcer, anxiolytic agents
J000		*-prazole*	antiulcer, benzimidazole derivatives
J000		*-serod*	serotonin receptor antagonists and partial agonists
J100	**Drugs acting on gastrointestinal system**	*-azepide*	cholecystokinin receptor antagonists
J100		*-pride*	sulpiride derivatives
J120	Choleretics (and hepatoprotective agents)	*-cic*	hepatoprotective substances with a carboxylic acid group
J130	Digestive enzymes		
J200	**Emetics**		
J300	**Hepato-protective agents**		
J400	**Gastro-intestinal anti-infectives (see S000)**		
J500	**Antidiarrhoeals**		

K000	**AGENTS INFLUENCING THE RESPIRATORY TRACT AND ANTIALLERGICS**	*-ast*	antiasthmatics or antiallergics, not acting primarily as antihistaminics; *-lukast*: leukotriene receptor antagonist; *-milast*: phosphodiesterase IV (PDE IV) inhibitors; *-trodast*: thromboxane A_2 receptor antagonists, antiasthmatics, *-zolast*: leukotriene biosynthesis inhibitors
K000		*-cromil*	antiallergics, cromoglicic acid derivatives
K000		*-exine*	mucolytic, bromhexine derivatives
K000		*-fentrine*	inhibitors of phosphodiesterases
K000		*-lukast*	leukotriene receptor antagonists, see *-ast*
K000		*-steine*	mucolytics, other than bromhexine derivatives
K000		*-trodast*	thromboxane A_2 receptor antagonists, antiasthmatics ;see *-ast*
K000		*-xanox*	antiallergic respiratory tract drugs, xanoxic acid derivatives
K100	**Antitussives**		
K110	Antitussives - central		
K120	Antitussives - peripheral		
K200	**Expectorants**		

L000	**CYTOTOXICS, TARGETED THERAPIES AND HORMONES IN CANCER THERAPY**	*-anib*	angiogenesis inhibitors
L000		*-antrone*	antineoplastics; anthraquinone derivatives
L000		*-(ar)abine*	arabinofuranosyl derivatives
L000		*-bulin*	antineoplastics; mitotic inhibitors, tubulin binders
L000		*-mestane*	aromatase inhibitors
L000		*mito-*	antineoplastics, nucleotoxic agents
L000		*-platin*	antineoplastic agents, platinum derivatives
L000		*-quidar*	drugs used in multidrug resistance; quinoline derivatives
L000		*-racil*	uracil type antineoplastics
L000		*-ribine*	ribofuranil-derivatives of the "pyrazofurin" type
L000		*-rozole*	aromatase inhibitors, imidazole-triazole derivatives
L000		*-sertib*	serine/threonine kinase inhibitors
L000		*-taxel*	antineoplastics; taxane derivatives
L000		*-tecan*	antineoplastics, topoisomerase I inhibitors
L000		*-tinib*	tyrosine kinase inhibitors
L000		*-trexed*	antineoplastics; thymidiylate synthetase inhibitors

L100	**Immunosuppressants**		
L200	**Alkylating agents**	*-mustine*	antineoplastic, alkylating agents, (beta-chloroethyl)amine derivatives
L200		*-sulfan*	antineoplastic, alkylating agents, methanesulfonates
L200		*-tepa*	antineoplastics, thiotepa derivatives
L300	**Radioisotopes (except diagnostics)**		
L310	Radioisotopes - systemic		
L320	Radioisotopes - locally applied		
L400	**Antineoplastics - antimetabolites**	*-abine*	see *-arabine, -citabine*
L400		*-citabine*	nucleosides antiviral or antineoplastic agents, cytarabine or azacitidine derivatives
L400		*-trexate*	folic acid analogues
L400		*-uridine*	uridine derivatives used as antiviral agents and as antineoplastics; also *-udine*
L410	Ornithine decarboxylase inhibitors		
L500	**Antineoplastics - natural products (incl. antibiotics)**	*-rubicin*	antineoplastics, daunorubicin derivatives
L500		*vin-* or *-vin-*	vinca alkaloids
L600	**Antineoplastics - sex hormone analogues and inhibitors**		
L610	Aromatase inhibitors		
L620	Luteinizing hormone-releasing hormone agonists		

M000	**METABOLISM AND NUTRITION (EXCL. WATER AND MINERAL METABOLISM)**	*-stat* (or *-stat-*)	enzyme inhibitors; *-lipastat*: pancreatic lipase inhibitors; *-restat* or *-restat-*: aldose-reducing inhibitors; *-vastatin*: antihyperlipidaemic substances, HMG CoA reductase inhibitors
M100	**Anorectics**	*-orex*	anorectics
M200	**Dietetics and antiadipositas drugs**		
M210	Bulk forming drugs		
M300	**Agents influencing lipid and fat metabolism**	*-imibe*	antihyperlipidaemics, acyl CoA:cholesterol acyltransferase (ACAT) inhibitors,
M300		*-listat*	see *-stat*
M310	Antiatherosclerosis agents		
M320	Lipotropic agents		
M321		*-begron*	β_3-adrenoreceptor agonists
M330	Lipogenesis inducing agents		
M400	**Agents influencing protein metabolism**		
M410	Anabolic steroids	*bol*	anabolic steroids
M420	Catabolic agents		
M430	Amino acids		
M500	**Agents influencing carbohydrate metabolism**	*-restat* (or *-restat-*)	see *-stat*; aldose-reductase inhibitors
M510	Insulins		
M520	Oral antidiabetics - islet mediated	*-formin*	antihyperglycaemics, phenformin derivatives

M520		*gli-, -gli-*	previously *gly-*; antihyperglycaemics
M520		*-gliptin*	dipeptidyl aminopeptidase-IV inhibitors
M520		*-glitazar*	peroxisome proliferator activating receptor-γ (PPAR) agonists
M520		*-glitazone*	peroxisome proliferator activating receptor-γ (PPAR) agonists, thiazolidinedione derivatives
M530	Oral antidiabetics - extra pancreatic	*gli*	antihyperglycaemics
M540	Gluconeogenesis influencing agents		
M600	**Agents influencing uric acid metabolism**		
M610	Uricosurics		
M620	Uric acid synthesis inhibitors		
M630	Agents influencing oxalic acid metabolism		
M700	**Thyroid and antithyroids**		
M710	Thyroid and thyroid hormones		
M720	Thyroid stimulators		
M730	Antithyroids	*-thiouracil*	uracil derivatives used as thyroid antagonists
M740	Radioactive iodine agents (for therapy)		
M800	**Enzymes**		
M810	Enzyme inhibitors		
M820	Enzyme stimulators		

N000	**AGENTS INFLUENCING WATER AND MINERAL METABOLISM**		
N100	**Diuretics**		
N110	Carbonic anhydrase inhibitors	*-semide*	diuretics, furosemide derivatives
N120	Saluretics	*-anide*	N.1.2.0 *-etanide*: diuretics, piretanide derivatives; S.3.0.0 *-oxanide*: antiparasitic, salicylanilides and analogues
N120		*-etanide*	diuretics, piretanide derivatives; see *-anide*
N120		*-pamide*	diuretics, sulfamoylbenzoic acid derivatives (could be sulfamoylbenzamide)
N121	Thiazide derivatives	*-tizide*	diuretics, chlorothiazide derivatives
N122	Ethacrynic acid derivatives	*-crinat*	diuretics, etacrynic acid derivatives
N123	Chlortalidone derivatives		
N129	Saluretics, other		
N130	Mercurial diuretics	*mer-* (or *-mer-*)	mercury-containing drugs, antimicrobial or diuretic [*mer-* and *-mer-* can be used for any type of substances and are no longer restricted to use in INNs for mercury-containing drugs; *-mer*: polymers]
N170	Purines and other diuretics		
N180	Aldosterone inhibitors	*-renone*	aldosterone antagonists, spironolactone derivates
N200	**Acidifiers**		
N400	**Saline cathartics**		

N500	**Alkalizers**		
N510	Parenteral alkalizer solutions		
N520	Oral antacids	*-aldrate*	antacids, aluminium salts
N520		*-alox*	see *-ox*
N600	**Fluid and electrolyte replacement therapy**		
N610	Electrolyte and carbohydrate solutions		
N700	**Mineral salts**		
N710	Ion exchange resins		
N800	**Vitamin D group and calcium metabolism drugs**	*calci*	Vitamin D analogues/derivatives
N800		*-dronic acid*	calcium metabolism regulator, pharmaceutical aid

P000	**VITAMINS**		
P100	**Vitamin A**	*-arotene*	arotinoid derivatives
P100		*retin*	retinol derivatives
P200	**Vitamin B1**		
P300	**Vitamin B2**		
P400	**Vitamin B6**		
P500	**Vitamin C**		
P600	**Vitamin E**		
P700	**Nicotinic acid derivatives**	*nic-*.	nicotinic acid or nicotinoyl alcohol derivatives
P800	**Vitamins, other**		

Q000	**HORMONES OR HORMONE RELEASE-STIMULATING PEPTIDES**	*-morelin*	see *-relin*; pituitary hormone release-stimulating peptides
Q000		*prost*	prostaglandins; *-prostil*: prostaglandins, anti-ulcer
Q000		*-relin*	pituitary hormone-release stimulating peptides: *-morelin*: growth hormone release-stimulating peptides; *-tirelin*: thyrotropin releasing hormone analogues
Q000		*som-*	growth hormone derivatives
Q000		*-tirelin*	see *-relin*; thyrotropin releasing hormone analogues
Q100	**Hypophysis hormones**		
Q110	Hypophysis anterior lobe		
Q111	Hypophysis anterior lobe hormones	*-actide*	synthetic polypeptides with a corticotropin-like action
Q112	Hypophysis anterior lobe inhibitors		
Q120	Hypophysis posterior lobe (incl. other oxytocics)	*-pressin*	vasoconstrictors, vasopressin derivatives
Q120		*-tocin*	oxytocin derivatives
Q200	**Sex hormones and analogues**	*-pris-*	steroidal compounds acting on progesterone receptors (excluding *–gest-* compounds)
Q210	Estrogens, also interceptive contraceptive agents e.g. epostane	*estr*	estrogens
Q210		*-ifene*	antiestrogens or estrogen receptor modulators, *clomifene* and *tamoxifen* derivatives
Q220	Progestogens	*gest*	steroids, progestogens

Q230	Androgens	*andr* or *–stan-* or *–ster-*	steroids, androgens
Q230		*-ster-*	androgens/anabolic steroids: *-testosterone*, *-sterone, -ster-, -gesterone, -sterone, sterol, ster, -(a)steride*
Q231	Androgens	*-terone*	antiandrogens
Q240	Gonadotrophins and gonadotrophin secretion stimulating drugs		
Q241	Antigonadotrophins		
Q300	**Adrenocortical hormones and analogues**	*cort*	corticosteroids, except prednisolone derivatives
Q300		*-olone*	steroids other than prednisolone derivatives
Q300		*-onide*	steroids for topical use, acetal derivatives
Q310	Mineralosteroids		
Q320	Mineralosteroid antagonists		
Q330	Glucosteroids	*pred*	prednisone and prednisolone derivatives; *-methasone* or *-metasone*, *-betasol*, *-olone*
Q340	Glucosteroids antagonists		

S000	**ANTI-INFECTIVES AND DRUGS ACTING ON IMMUNITY**		
S100	**Ectoparasiticides**		
S200	**Antiseptics and disinfectants**		
S210	Antiseptics (excl. heavy metal antiseptics)	*-nifur-*	5-nitrofuran derivatives

S220	Heavy metal antiseptics	*-mer-*	mercury-containing drugs, antimicrobial or diuretic [*mer-* and *-mer-* can be used for any type of substances and are no longer restricted to use in INNs for mercury-containing drugs]
S230	Detergent antiseptics		
S300	**Chemotherapeutics of parasitic diseases**	*-ectin*	antiparasitics, ivermectin derivatives
S300		*-oxanide*	antiparasitics, salicylanilides and analogues; see *-anide*
S310	Anthelminthics (excl. antinematode agents)	*-antel*	anthelminthics (undefined group)
S310		*-bendazole*	anthelminthics, tiabendazole derivatives
S310		*-fos (-vos)*	insecticides, anthelmintics, pesticides etc., phosphorous derivatives
S310		*-fos-* or *fos-*	various pharmacological categories belonging to *-fos* (other than above)
S320	Antinematode agents		
S330	Antiprotozoal agents (incl. all arsphenamines)	*arte-*	antimalarial agents, artemisinin related compounds
S330		*-nidazole*	antiprotozoals and radiosensitizers, metronidazole derivatives
S400	**Chemotherapeutics of fungal diseases**	*-conazole*	systemic antifungal agents, miconazole derivatives
S410	Antifungal agents		
S420	Fungicides		
S430	Antifungal antibiotics		

S500	**Antibiotics, antibacterial and antiviral agents**	*-planin*	glycopeptide antibacterials (*Actinoplanes* strains)
S510	Sulfonamides	*sulfa-*	anti-infectives, sulfonamides
S520	Antimycobacterials	*-dapsone*	antimycobacterials, diaminodiphenylsulfone derivatives
S520		*-pirox*	see *-ox*
S530	Antiviral	*-arabine*	arabinofuranosyl derivatives
S530		*-motine*	antivirals, quinoline derivatives
S530		*-ribine*	ribofuranil-derivatives of the *pyrazofurin* type
S530		*-uridine*	uridine derivatives used as antiviral agents and as antineoplastics; *-udine*
S530		*vir*	antivirals (undefined group): *-amivir, -cavir, -ciclovir, -fovir, -gosivir, -navir, -virsen, -virumab*
S550	Antibacterial/other	*-citabine*	nucleosides antiviral or antineoplastic agents, cytarabine or azacitidine derivatives
S550		*-oxacin*	antibacterials, nalidixic acid derivatives
S550		*-prim*	antibacterials, dihydrofolate reductase (DHFR) inhibitors, trimethoprim derivatives
S600	**Antibiotics (except antineoplastic antibiotics)**	*-cidin*	naturally occurring antibiotics (undefined group)
S600		*-fungin*	antifungal antibiotics
S600		*-gillin*	antibiotics produced by *Aspergillus* strains

S600		*-monam*	monobactam antibiotics
S600		*-mycin*	antibiotics, produced by *Streptomyces* strains (see also *-kacin*)
S600		*-parcin*	for glycopeptide antibiotics
S600		*-penem*	analogues of penicillanic acid antibiotics modified in the five-membered ring
S600		*-pristin*	antibacterials, streptogramins, protein-synthesis inhibitors, pristinamycin derivatives
S610	Antibiotics acting on the bacterial cell wall	*-carbef*	antibiotics, carbacephem derivatives
S610		*cef-*	antibiotics, cefalosporanic acid derivatives
S610		*-cillin*	antibiotics, 6-aminopenicillanic acid derivatives
S610		*-oxef*	see *cef-*; antibiotics, oxacefalosporanic acid derivatives
S620	Antibiotics affecting cell membrane and with detergent effect	*-tricin*	antibiotics, polyene derivatives
S630	Antibiotics affecting protein synthesis	*-cycline*	antibiotics, protein-synthesis inhibitors, tetracycline derivatives
S630		*-kacin*	antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*); S.6.5.0: *-micin*: aminoglycosides, antibiotics obtained from *various Micromonospora*
S640	Antibiotics affecting nucleic acid metabolism	*rifa-*	antibiotics, rifamycin derivatives

S650	Antibiotics-action unclassified (including β-lactamase inhibitors)	*-bactam*	β-lactamase inhibitors
S650		*-micin*	see *-kacin*; aminoglycosides, antibiotics obtained from various *Micromonospora*
S700	**Immunomodulators and immunostimulants (incl. gamma globulins)**	*-cept*	receptor molecules, native or modified (a preceeding infix should designate the target)
S700		*imex*	immunostimulants
S700		*-imod*	immunomodulators, both stimulant/suppressive and stimulant
S700		*-imus*	immunosuppressants (other than antineoplastics)
S700		*-kin*	interleukin type substances: *-nakin, -leukin, -trakin, -exakin, -octakin, -decakin, -elvekin, -dodekin, tredekin, -octadekin*
S700		*-kinra*	interleukin-receptors antagonists: *- nakinra, -trakinra*
S700		*-mab*	monoclonal antibodies (see also Annex)
S710	Interferons and immunomodulators		

T000	**LOCALLY ACTING AGENTS (INCL. DERMATOLOGIC AND INTERNALLY USED DRUGS)**		
T100	**Locally acting externally-applied agents**		
T110	Vasodilators (external) - rubefaciens		

T200	**Locally acting internally-applied agents**		
T210	Adsorbents, astringents		
T220	Lubricant cathartics		
T230	Irritant cathartics		
T240	Gastro-intestinal anti-infectives, non-resorbed		
T250	Saponins		
T260	Detergents		
T300	**Intravaginal contraceptives**		

U000	**MISCELLANEOUS DRUGS**		*-ermin*: growth factors; *-dermin*: epidermal growth factors; *-fermin*: fibrino-blast growth factors; *-nermin*: tumour necrosis factor; *-sermin*: insulin-like growth factors
U000		*gado-*	diagnostic agents, gadolinium derivatives
U100	**Diagnostic aids**	*-fenin*	diagnostic aids; (phenyl-carbamoyl)methyl iminodiacetic acid derivatives
U110	Radiocontrast media	*io-*	iodine-containing contrast media
U110		*-io-* or *iod-*	iodine-containing compounds other than contrast media
U120	Diagnostic aids, other		
U130	Diagnostic radioisotopes		
U200	**Chelating agents, detoxicants, etc.**		
U210	Alcohol deterrents		

U300	**Anti-inflammatory agents**	*-lubant*	phospholipase A_2 inhibitors
U310	Non-antipyretic antirheumatics		
U320	Anti-inflammatory agents, other		
U400	**Pharmaceutical adjuncts**	*cell-* or *cel-*	cellulose derivatives; (*cell-ate* and *-cellose*)
U400		*-dronic acid*	calcium metabolism regulator, pharmaceutical aid

V000	**UNCLASSIFIED PHARMACOLOGICAL MECHANISMS**		
V100	**Intrauterine contraceptive device**		
V200	**Medicinal plants**		
V300	**Homoeopathic preparations**		

W000	**ENZYMES AND VARIOUS**	*-ase*	enzymes; *-dismase, -teplase, -uplase*
W000		*-pladib*	phospholipase A_2 inhibitors
W000		*-stat*	enzyme inhibitors

Y000	**VETERINARY DRUGS**	*-nidazole*	antiprotozoals and radiosensitizers, metronidazole derivatives

Z000	**GENE THERAPY PRODUCTS**	*-gene*	gene therapy products, please refer to Annex 4

PART IV

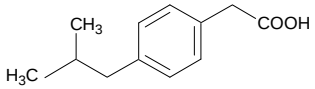
ALPHABETICAL LIST OF STEMS TOGETHER WITH CORRESPONDING INNS

-abine **see -arabine, -citabine**

USAN

-ac (x) **anti-inflammatory agents, ibufenac derivatives**

A.4.2.0 (USAN: anti-inflammatory agents (acetic acid derivatives))



(a) -clofenac: aceclofenac (52), alclofenac (23), diclofenac (28), fenclofenac (30)
-dolac: dexpemedolac (71), etodolac (45), pemedolac (58)
-fenac: amfenac (38), bromfenac (55), furofenac (40), ibufenac (14), lexofenac (38), nepafenac (78)
-zolac: bufezolac (39), isofezolac (39), lonazolac (34), mofezolac (64), pirazolac (43), trifezolac (34)
others: anirolac (52), bendazac (22), cinfenoac (41), clidanac (39), clofurac (42), clopirac (30), eltenac (53), felbinac (54), fenclorac (33), fentiazac (32), isoxepac (37), ketorolac (51), oxepinac (36), oxindanac (54), (quinclorac, ISO name for a herbicide), sulindac (33), tianafac (31), tifurac (57), tiopinac (40), zomepirac (37)

(b) bufexamac (20) (anti-inflammatory; acetohydroxamic acid group instead of acetic acid group)

(c) amtolmetin guacil (65), clamidoxic acid (17), fenclozic acid (22), metiazinic acid (20), prodolic acid (29), tolmetin (23)

-acetam **see -racetam**

USAN

-actide **synthetic polypeptides with a corticotropin-like action**

Q.1.1.1 (USAN: synthetic corticotropins)

(a) alsactide (45), codactide (24), giractide (29), norleusactide (18), seractide (31), tetracosactide (18), tosactide (24), tricosactide (44), tridecactide (97)

BAN, USAN

-adol (x) or -adol- **analgesics**

A.4.1.0
A.4.2/3.0 (USAN: analgesics (mixed opiate receptor agonists/antagonists))

(a) A.4.1.0: acetylmethadol (5), alimadol (39), alphacetylmethadol (5), alphamethadol (5), axomadol (87), betacetylmethadol (5), betamethadol (5), indantadol (94), levacetylmethadol (27), noracymethadol (12), tapentadol (87)

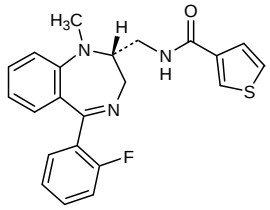
A.4.2/3.0: apadoline (74), asimadoline (74), befiradol (99), bromadoline (49), cebranopadol (107), ciprefadol (41), ciramadol (39), cloracetadol (16), dibusadol (24), dimenoxadol (7), diproxadol (34), eluxadoline (109), enadoline (68), faxeladol (97), filenadol (47), flumexadol (36), furadoline (48), gaboxadol (48), insalmadol (92), levonantradol (43), lexanopadol (109), lorcinadol (57), moxadolen (45), (deleted in List 48: moxifadol (47)), myfadol (17), nafoxadol (50), nantradol (42), nerbacadol (56), oxapadol (40), picenadol (47), pinadoline (50), pipradimadol (42), pipramadol (42), pravadoline (60), vadoline (60), profadol (20), radolmidine (82), ruzadolane (71), spiradoline (53), tazadolene (52), tolpadol (48), tramadol (22), veradoline (47)

(b) alfadolone (27), hexapradol (12) (CNS stimulant), nadolol (34), quinestradol (15) (estrogenic)

(c) A.4.1.0: dimepheptanol (5)

-adom **analgesics, tifluadom derivatives**

A.4.3.0

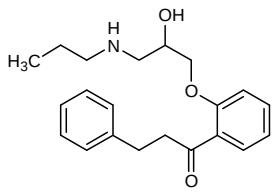


(a) lufuradom (50), tifluadom (48)

USAN

-afenone **antiarrhythmics, propafenone derivatives**

H.2.0.0



(a) alprafenone (62), berlafenone (63), diprafenone (48), etafenone (19), propafenone (29)

USAN

-afil **inhibitors of phosphodiesterase PDE5 with vasodilator action**

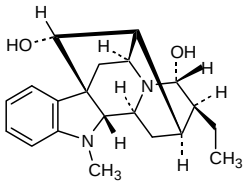
F.2.0.0 (USAN: PDE5 inhibitors)

(a) avanafil (92), beminafil (90), dasantafil (91), gisadenafil (101), lodenafil carbonate (94), mirodenafil (95), sildenafil (75), tadalafil (85), udenafil (93), vardenafil (82)

USAN

-aj- **antiarrhythmics, ajmaline derivatives**

H.2.0.0



(a) detajmium bitartrate (34), lorajmine (34), prajmalium bitartrate (23)

-al (d) **aldehydes**

USAN

-aldrate **antacids, aluminium salts**

N.5.2.0

(a) carbaldrate (53), potassium glucaldrate (14), magaldrate (49), simaldrate (15), sodium glucaspaldrate (17)

algeldrate (15), almadrate sulfate (15), almagodrate (52)

(c) alexitol sodium (45), almagate (41), almasilate (43), dosmalfate (75), glucalox (13), hydrotalcite (23), lactalfate (53), sucralox (13)

USAN

-alol **see -olol**

-alox **see -ox**

-amivir **see -vir**

USAN

-ampanel **antagonists of the ionotropic non-NMDA (*N*-methyl-D-aspartate) glutamate receptors (Namely the AMPA (amino-hydroxymethyl-isoxazole-propionic acid) and/or KA (kainite antagonist) receptors)**

B.0.0.0 (USAN: ionotropic non-NMDA glutamate receptors (AMPA and/or KA receptors) antagonists)

(a) becampanel (90), dasolampanel (105), fanapanel (80), irampanel (82), perampanel (97), selurampanel (104), talampanel (80), tezampanel (95), zonampanel (85)

USAN

andr (d) **steroids, androgens**

Q.2.3.0 (USAN: -andr- androgens)

(a) i. andr: androstanolone (4), methandriol (1), nandrolone (22), norethandrolone (6), ovandrotone albumin (52), silandrone (18)

ii. -stan- (d): androstanolone (4), drostanolone (13), epitiostanol (31), mestanolone (10), stanozolol (18), epostane (51) (contraceptive)

iii. -ster- (d): calusterone (23), cloxotestosterone (12), fluoxymesterone (6), mesterolone (15), methyltestosterone (4), oxymesterone (12), penmesterol (14), prasterone (23), testosterone (4), testosterone ketolaurate (16), tiomesterone (14)

(b) i. andr: oxandrolone (12), propetandrol (13)

ii. ster: aldosterone (6), bolasterone (13), dihydrotachysterol (1), dimethisterone (8), ethisterone (4), norethisterone (6), norvinisterone (6), stercuronium iodide (21) (neuromuscular blocking agent)

(c) metandienone (12), oxymetholone (11), trestolone (25) (antineoplastic androgen)

USAN

-anib **angiogenesis inhibitors**

L.0.0.0

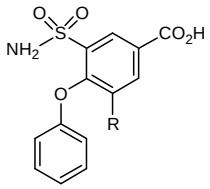
(a) beloranib (100), bevasiranib (108), brivanib alaninate (97), cediranib (95), crenolanib (105), motesanib (97), nintedanib (105), linifanib (102), lucitanib (107), pazopanib (94), pegaptanib (88), pegdinetanib (103), semaxanib (85), tivozanib (102), toceranib (100), trebananib (106), vandetanib (91), vatalanib (84)

USAN

-anide

-etanide diuretics, piretanide derivatives

N.1.2.0 (USAN: diuretics (piretanide type))

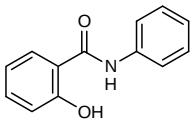


(a) bumetanide (24), piretanide (33)

(c) besunide (30)

-oxanide antiparasitics, salicylanilides and analogues

S.3.0.0 (USAN: antiparasitics (salicylanilide derivatives))



(a) bromoxanide (31), clioxanide (19), rafoxanide (24)

thioanalogues: brotianide (24)

related: diloxanide (8), nitazoxanide (45)

(b) closantel (36), flurantel (25), niclosamide (13), resorantel (23), salantel (29)

(c) oxyclozanide (16)

other *–anides*: aurothioglycanide (1) (antiarthritic; gout-remedy), ceforanide (39) (antibiotic), oglufanide (86) (immunomodulator), polihexanide (24) (antibacterial), tiprostanide (48) (antihypertonic)

BAN, USAN

-anserin **serotonin receptor antagonists (mostly 5-HT_2)**

C.7.0.0 (USAN: serotonin 5-HT_2 receptor antagonists)

(a) adatanserin (70), altanserin (50), blonanserin (76), butanserin (51), eplivanserin (80), fananserin (69), flibanserin (75), iferanserin (89), ketanserin (46), lidanserin (62), nelotanserin (101), pelanserin (57), pimavanserin (97), pruvanserin (90), seganserin (56), trelanserin (97), tropanserin (55), volinanserin (95)

(b) serotonin receptor antagonists, psychoactive: cinanserin (17), glemanserin (68), mianserin (20), ritanserin (51)

USAN

-antel **anthelminthics (undefined group)**

S.3.1.0

(a) amidantel (40), carbantel (35), closantel (36), derquantel (99), epsiprantel (57), febantel (38), flurantel (25), monepantel (98), morantel (22), oxantel (3l), pexantel (22), praziquantel (34), pyrantel (l7), resorantel (23), salantel (29), zilantel (33), antelmycin (15)

USAN

-antrone **antineoplastics; anthraquinone derivatives**

L.0.0.0/ L.5.0.0

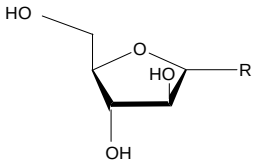
(a) ametantrone (45), banoxantrone (90), butantrone (49), ledoxantrone (76), losoxantrone (68), mitoxantrone (44), nortopixantrone (87), piroxantrone (59), pixantrone (89), sepantronium bromide (105), teloxantrone (68), topixantrone (87)

-apine **see -pine**

USAN

-(ar)abine **arabinofuranosyl derivatives**

L.4.0.0/
S.5.3.0 (USAN: -arabine: antineoplastic (arabinofuranosyl derivatives))



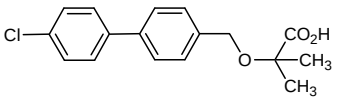
(a) clofarabine (90), cytarabine (14), fazarabine (56), fludarabine (48), nelarabine (80), vidarabine (23)
See also the stem -citabine: ancitabine (36), apricitabine (95), capecitabine (73), decitabine (61), dexelvucitabine (95), elvucitabine (89), emtricitabine (80), enocitabine (46), fiacitabine (59), flurocitabine (38), galocitabine (65), gemcitabine (62), ibacitabine (57), mericitabine (108), sapacitabine (94), tezacitabine (84), torcitabine (87), troxacitabine (81), valopicitabine (93), valtorcitabine (90), zalcitabine (66)

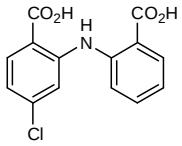
(c) S.5.3.0: ribavirin (31), taribavirin (95)

USAN

-arit **antiarthritic substances, acting like clobuzarit and lobenzarit (mechanism different from anti-inflammatory type substances, e.g. -fenamates or -profens)**

A.4.2.0 (USAN: antirheumatic (lobenzarit type))





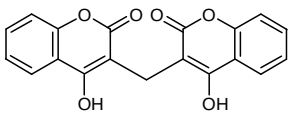
(a) actarit (62), bindarit (64), clobuzarit (44), lobenzarit (46), romazarit (60)

(c) tarenflurbil (97)

USAN

-arol (d) **anticoagulants, dicoumarol derivatives**

I.2.1.0 (USAN: anticoagulants (dicoumarol type))



(a) acenocoumarol (6), clocoumarol (31), coumetarol (13), dicoumarol (23), tioclomarol (31), xylocoumarol (15)

(b) cloridarol (29) (coron. vasodil.), fluindarol (16) (anticoag. of indonedione-type)

(c) diarbarone (15), ethyl biscoumacetate (4), phenprocoumon (11), tecarfarin (101), warfarin (23)

USAN

-arone

(USAN: antiarrhythmics)

amiodarone (16) (antiarrhythmic), benzarone (13), benzbromarone (13) (uricosuric), benziodarone (11), brinazarone (64) (calcium channel blocker), bucromarone (48) (antiarrhythmic), budiodarone (101), celivarone (94), diarbarone (15), dronedarone (75) (antianginal, antiarrhythmic), etabenzarone (17), fantofarone (65) (calcium channel blocker), furidarone (19), inicarone (27), mecinarone (30), pyridarone (16), rilozarone (58)

USAN

-arotene **arotinoid derivatives**

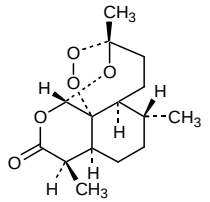
P.1.0.0

(a) adarotene (100), amsilarotene (98), betacarotene (38), bexarotene (80), etarotene (64), linarotene (65), mofarotene (70), palovarotene (99), sumarotene (64), tamibarotene (73), tazarotene (72), temarotene (54), trifarotene (107)

USAN

arte- **antimalarial agents, artemisinin related compounds**

S.3.3.0



(a) artefenomel (109), arteflene (70), artemether (61), artemisone (95), artemisinin (56), artemotil (80), artenimol (81), arterolane (97), artesunate (61)

USAN

-ase **enzymes**

W.0.0.0

(a) agalsidase alfa (84), agalsidase beta (84), alglucerase (68), alglucosidase alfa (91), brinase (22), asfotase alfa (104), bucelipase alfa (95), calaspargase pegol (105), cocarboxylase (1), condoliase (106), crisantaspase (107), dornase alfa (70), elosulfase alfa (108), eufauserase (84), galsulfase (92), glucarpidase (92), hyalosidase (50), hyaluronidase (1), idursulfase (90), kallidinogenase (22), ocrase (28), pegaspargase (64), penicillinase (10), promelase (47), rizolipase (22), serrapeptase (31), sfericase (40), streptodornase (6), streptokinase (6), tilactase (50), urokinase (48)

(c) batroxobin (29), bromelains (18), chymopapain (26), chymotrypsin (10), defibrotide (44), fibrinolysin (human) (10), orgotein (31), sutilains (18), ubidecarenone (48)

Classification of enzymes

I proteinase

(a) with -*ase* suffix:

INN	**origin**	**use, action**
crisantaspase (107)	*Erwinia chrysanthemi*	asparaginase
brinase (22)	*Aspergillus oryzae*	fibrinolytic
calaspargase pegol (105)	*Escherichia coli*	asparaginase
kallidinogenase (22)	pancreas or urine of mammals	splitting kinin, kallidin from kininogen (vasodilator)
ocrase (28)	*Aspergillus ochraceus*	fibrinolytic (topically: cleaning wounds)
pegaspargase (64)		asparaginase
promelase (46)	*Aspergillus melleus*	proteinase (chronic bronchitis)

	serrapeptase (31)	*Serratia sp.* E15	proteinase (chronic paranasal sinusitis etc.)
	sfericase (40)	*Bacillus sphaericus*	proteinase (chronic paranasal sinusitis etc.)
	streptokinase (6)	*Streptococcus haemolyticus*	changing plasminogen into plasmine (activator of fibrinolysis)
	urokinase (48)	human origin	plasminogen activator
	urokinase alfa (27)	recombinant material	plasminogen activator
(c)	without *-ase* suffix:		
	batroxobin (29)	the venom of the serpent *Bothopsatrox*	thrombin like enzyme
	bromelains (18)	*Ananas comosus* Merr.	fibrin depolymerizing (anti-inflammatory)
	chymopapain (26)	papaya late	proteolytic (chemonucleosis)
	chymotrypsin (10)	mammalian pancreas	proteolytic (anti-inflammatory, antioedema)
	defibrotide (44)	mammalian pancreas	proteolytic (anti-inflammatory, antioedema)
	fibrinolysin (human) (10)	human	fibrinolytic
	sutilains (18)	*Bacillus subtilis*	proteolytic
II	*-lipase*		
	bucelipase alfa (95)	human origin	lipase
	rizolipase (22)	*Rhizopus arrhizus* var. Delemar	lipase
III	co-enzymes		
(a)	cocarboxylase (1)	chemically defined	co-enzyme in the metabolism of pyruvic acid
(c)	ubidecarenone (48)	chemically defined	naturally occurring co-enzyme, a component in the electron transfer system in mitochondria (congestive heart failure)

				USAN
IV	*-dismase* enzymes with superoxide dismutase activity			
	(USAN: superoxide dismutase activity (exception: orgotein))			
(a)	ledismase (70), sudismase (58)			
(c)	isomerase			
	orgotein (31)	mammalian tissue (liver, red blood cell etc.)	superoxide dismutase activity (anti-inflammatory)	
	pegorgotein (72)			
V	*-diplase* plasminogen activator combined with another enzyme			
	amediplase (79)			
				USAN
VI	*-teplase* tissue-type plasminogen activators			
(a)	alteplase (59), desmoteplase (80), duteplase (62), lanoteplase (76), monteplase (71), nateplase (73), pamiteplase (78), reteplase (69), silteplase (65), tenecteplase (79)			
(c)	anistreplase (59)			
				USAN
VII	*-uplase* urokinase-type plasminogen activators			
(a)	nasaruplase (68), nasaruplase beta (85), saruplase (58)			
VIII	others			
	agalsidase alfa (84)	human origin	treatment of deficiency of alpha-galactosidase activity (Fabry's disease)	
	agalsidase beta (84)	hamster	treatment of deficiency of alpha-galactosidase activity (Fabry's disease)	
	alfimeprase (85)	*Agkistrodon contrix contrix*	antithrombotic	
	alglucerase (68)	human origin (placenta isoenzyme)	glucocerebrosidase	
	alglucosidase alfa (91)	recombinant	treatment of Pompe's disease	
	asfotase alfa (104)	recombinant	phosphatase	
	condoliase (106)	*Proteus vulgaris*	endolyase	
	dornase alfa (70)	human origin	treatment of cystic fibrosis	

elosulfase alfa (108)	CHO cells	*N*-acetylgalactosamine-6-sulfatase
epafipase (85)	human origin	antiallergic, antiasthmatic
eufauserase (84)	*Euphausia superba*	digests proteins and selected cell surface adhesion molecules (wound healing; viginal/oral candidosis)
galsulfase (92)	recombinant	Maroteaux-Lamy syndrome
glucarpidase (92)	*Pseudomonadadaceae gen. sp.*	adjunctive treatment of patients at risk of methotrexate toxicity
hyalosidase (50)		hyaluronoglucosaminidase (treatment of myocardial infarction)
hyaluronidase (1)	various origins	depolymerizing hyaluronic acid (cellular diffusion factor)
idursulfase (90)		treatment of Hunter Syndrome (Mucopolysaccharidosis Type II), degrades glycosaminoglycans heparan and dermatan sulfate
imiglucerase (72)	human origin (placenta isoenzyme)	
laronidase (85)	human origin	
pegademase (63)	Origin should be indicated	
pegadricase (105)	*Candida utilis*	urate oxidase
pegloticase (98)	*Sus scrofa*	uricase
penicillinase (10)	*Bacillus cereus*	inactivating penicillin
ranpirnase (81)	*Rana pipiens*	ribonuclease (antineoplastic)
rasburicase (81)	*Aspergillus flavus*	urate oxidase (hyperuricaemia)
streptodornase (6)	*Streptococcus haemolyticus*	hydrolysing desoxyribonucleoprotein
taliglucerase alfa (101)	recombinant	beta-glucocerebrosidase
tilactase (50)		β-D-glactosidase
velaglucerase alfa (98)		beta-glucocerebrosidase

		BAN; USAN
-ast (x)	**antiasthmatics or antiallergics, not acting primarily as antihistaminics**	
K.0.0.0	(BAN: antiasthmatics, antiallergics when not acting primarily as antihistamines) (USAN: antiasthmatics / antiallergics: not acting primarily as antihistamines)	
(a)	acitazanolast (72), acreozast (77), andolast (67), asobamast (63), ataquimast (82), bamaquimast, (76), batebulast (66), bunaprolast (60), dametralast (54), dazoquinast (54), doqualast (48), eflumast (61), enofelast (67), enoxamast (52), fenprinast (48), filaminast (75), ibudilast (58), idenast (58), loxanast (46), melquinast (62), oxalinast (49), pemirolast (61), picumast (47), pirodomast (64), quinotolast (64), raxofelast (68), repirinast (55), revenast (51), scopinast (76), suplatast tosilate (64), tazanolast (59), tiacrilast (52), tibenelast (58), tioxamast (53), tiprinast (50), tranilast (46), zaprinast (46)	
-lukast	**leukotriene receptor antagonists**	USAN
(a)	ablukast (61), cinalukast (70), iralukast (70), masilukast (94), montelukast (73), pobilukast (70), pranlukast (67), ritolukast (64), sulukast (63), tipelukast (95), tomelukast (59), verlukast (65), zafirlukast (71)	
-milast	**phosphodiesterase IV (PDE IV) inhibitors**	USAN
(a)	apremilast (97), catramilast (95), cilomilast (82), lirimilast (86), oglemilast (94), piclamilast (73), revamilast (102), roflumilast (77), elbimilast (107), tetomilast (91), tofimilast (85)	
-tegrast	**integrin antagonists**	USAN
(a)	carotegrast (102), firategrast (96), lifitegrast (107), valategrast (93), zaurategrast (101)	
-trodast	**thromboxane A_2 receptor antagonists, antiasthmatics** (USAN: thromboxane A_2 receptor antagonists)	USAN
(a)	imitrodast (70), seratrodast (70)	
-zolast	**leukotriene biosynthesis inhibitors** (USAN: benzoxazole derivatives)	USAN
(a)	binizolast (60), eclazolast (55), ontazolast (72), quazolast (55), tetrazolast (67)	
(c)	bufrolin (34), oxarbazole (38), pirolate (44)	
		BAN, USAN
-astine (x)	**antihistaminics**	
G.2.0.0	(BAN: antihistamines, not otherwise classifiable) (USAN: antihistaminics (histamine-H_1 receptor antagonists))	
(a)	acrivastine (51), alinastine (74), azelastine (36), bamirastine (91), barmastine (59),. bepiastine (19), bepotastine (78), bilastine (82), cabastinen (50), carebastine (52), clemastine (22), dorastine (23), ebastine (52), emedastine (59), epinastine (55),	

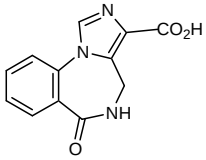
flezelastine (67), levocabastine (50), linetastine (74), mapinastine (72), mizolastine (64), moxastine (15), noberastine (59), octastine (37), perastine (15), piclopastine (22), rocastine (57), setastine (39), talastine (18), temelastine (54), zepastine (26)

(b) cloperastine (18) (antitussive), vinblastine (12) (vinca-alkaloid)

(c) astemizole (45), carbinoxamine (4)

-azam **see - azepam**

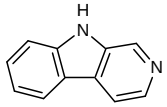
-azenil **benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)**
C.1.0.0 (USAN: benzodiazepine receptor antagonists/agonists)



(a) bretazenil (60), flumazenil (55), iomazenil ^{123}I (66), sarmazenil (59)

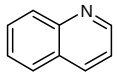
(b) nabazenil (49)

-carnil **benzodiazepine receptor antagonists/agonists (carboline derivatives)**



(a) abecarnil (60), gedocarnil (61)

-quinil **benzodiazepine receptor agonists, also partial or inverse (quinoline derivatives)**
(USAN: benzodiazepine receptor agonists, partial agonists, inverse agonists (quinoline derivatives)

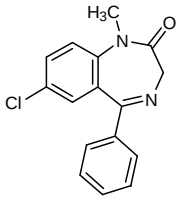


(a) lirequinil (72), radequinil (93) (replaces resequin (90)) , terbequinil (63)

BAN; USAN

-azepam (x) **diazepam derivatives**

C.1.0.0 (BAN: substances of the diazepam group)
(USAN: antianxiety agents (diazepam type))



(a) bromazepam (22), camazepam (30), carburazepam (39), cinolazepam (46), clonazepam (22), cyprazepam (16), delorazepam (40), diazepam (12), doxefazepam (43), elfazepam (36), fletazepam (31), fludiazepam (36), flunitrazepam (24), flurazepam (20),

flutemazepam (58), flutoprazepam (45), fosazepam (27), halazepam (29), iclazepam (37), lorazepam (23), lormetazepam (38), meclonazepam (44), medazepam (20), menitrazepam (22), metaclazepam (46), motrazepam (31), nimetazepam (26), nitrazepam (16), nordazepam (39), nortetrazepam (20), oxazepam (13), pinazepam (32), pivoxazepam (34), prazepam (14), proflazepam (31), quazepam (36), reclazepam (53), sulazepam (14), temazepam (22), tetrazepam (17), tolufazepam (51), tuclazepam (40), uldazepam (30)

not true benzodiazepines: bentazepam (33), clotiazepam (30), lopirazepam (36), premazepam (45), ripazepam (33), zolazepam (28)

related: adinazolam (45), alprazolam (30), arfendazam (39), clazolam (29), climazolam (51), clobazam (25), clobenzepam (25), cloxazolam (29), ecopipam (80), estazolam (3l), flutazolam (32), haloxazolam (38), ketazolam (26), levotofisopam (92), lofendazam (36), loprazolam (44), mexazolam (40), midazolam (40), nefopam (25), oxazolam (25), razobazam (52), remimazolam (102), tofisopam (26), trepipam (38), triazolam (30), triflubazam (28), zapizolam (43), zomebazam (49)

(c) brotizolam (40), chlordiazepoxide (11), ciclotizolam (40), demoxepam (23), dipotassium clorazepate (17), ethyl carfluzepate (43), ethyl dirazepate (44), ethyl loflazepate (43), etizolam (40), potassium nitrazepate (17)

not related: anxiolytic: fenobam (36), muscle relax.: xilobam (36)

USAN

-azepide **cholecystokinin receptor antagonists, benzodiazepine derivatives**

J.1.0.0 (USAN: cholecystokinin receptor antagonists)

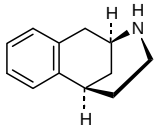
(a) devazepide (62), pranazepide (75), netazepide (106), tarazepide (68)

(c) lorglumide (56)

USAN

-azocine **narcotic antagonists/agonists related to 6,7-benzomorphan**

A.4.1.0 (USAN: narcotic antagonists/agonists, 6,7-benzomorphan derivatives)



(a) anazocine (30), bremazocine (43), butinazocine (53), carbazocine (16), cogazocine (36), cyclazocine (14), eptazocine (45), gemazocine (29), ibazocine (36), ketazocine (34), metazocine (9), moxazocine (38), pentazocine (14), phenazocine (9), quadazocine (54), tonazocine (46), volazocine (19)
related compounds: dezocine (35)

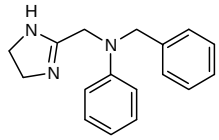
(b) streptozocin (33)

-azolam **see -azepam**

USAN

-azoline **antihistaminics or local vasoconstrictors, antazoline derivatives**

E.4.0.0 (USAN: antihistamines/local vasoconstrictors (antazoline type))



(a) antazoline (1), cilutazoline (61), cirazoline (38), clonazoline (18), coumazoline (26), domazoline (30), fenoxazoline (12), indanazoline (42), metrafazoline (33), naphazoline (1), nemazoline (63), oxymetazoline (13), phenamazoline (6), prednazoline (22), talazoline (01), tefazoline (24), tinazoline (39), tramazoline (15), xylometazoline (8)

(b) cefazolin (25) (antibiotic)

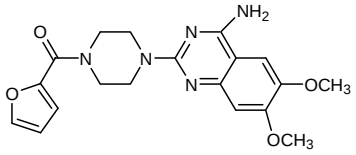
(c) tetryzoline (6), metizoline (22)

-azone **see -buzone**

USAN

-azosin **antihypertensive substances, prazosin derivatives**

H.3.0.0 (USAN: antihypertensives (prazosin type))



(a) bunazosin (50), doxazosin (47), neldazosin (60), prazosin (22), quinazosin (17), terazosin (44), tiodazosin (41), trimazosin (31)

related: alfuzosin (49), tamsulosin (65), tipentosin (55)

-bacept see -cept

BAN; USAN

-bactam **β-lactamase inhibitors**

S.6.5.0

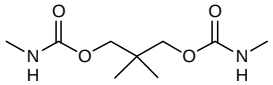
(a) brobactam (53), sulbactam (44), tazobactam (60)

(c) clavulanic acid (44)

BAN, USAN

-bamate **tranquillizers, propanediol and pentanediol derivatives**

C.1.0.0 (USAN: tranquilizers/antiepileptics (propanediol and pentanediol groups))



(a) carisbamate (96), cyclarbamate (13), felbamate (54), meprobamate (6), nisobamate (21), pentabamate (13), tybamate (14)

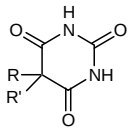
(b) difebarbamate (16), febarbamate (12), lorbamate (24), phenprobamate (10)

(c) mebutamate (12), metaglycodol (12) (not a carbamate)

BAN, USAN

barb (d) **hypnotics, barbituric acid derivatives**

A.2.l.0 (BAN: -barb, -barb-: for barbiturates)
(USAN: -barb; or -barb-: barbituric acid derivatives)



(a) allobarbital (1), amobarbital (1), aprobarbital (1), barbexaclone (16), barbital (4), barbital sodium (4), benzobarbital (25), brallobarbital (41), carbubarb (14), cyclobarbital (1), difebarbamate (16), eterobarb (32), febarbamate (12), heptabarb (14), hexobarbital (1), methylphenobarbital (1), nealbarbital (11), pentobarbital (1), phenobarbital (4), phenobarbital sodium (4), probarbital sodium (1), proxibarbal (33), secbutabarbital (12), secobarbital (4), tetrabarbital (4), thialbarbital (4), thiotetrabarbital (4), vinbarbital (1)

(c) butalbital (4), buthalital sodium (8), metharbital (1), methitural (6), methohexital (8), phetharbital (10), talbutal (17), thiopental sodium (4), vinylbital (12)

(c) prazitone (19) (barbituric acid derivative used as antidepressive), bucolome (17) (barbituric acid derivative used as anti-inflammatory uricosuric)

USAN

-begron **β_3-adrenoreceptor agonists**

M.3.2.1

(a) amibegron (94), fasobegron (98), lubabegron (109), mantabegron (88), mirabegron (98), rafabegron (88), ritobegron (91), solabegron (90), talibegron (86), vibegron (108)

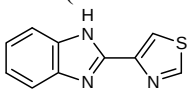
-benakin **see -kin**

-bendan **see -dan**

USAN

-bendazole **anthelminthics, tiabendazole derivatives**

S.3.l.0 (USAN: anthelmintics (tiabendazole type))



(a) albendazole (35), albendazole oxide (56), bisbendazole (29), cambendazole (24), ciclobendazole (31), dribendazole (49), etibendazole (49), fenbendazole (29), flubendazole (34), lobendazole (28), luxabendazole (52), mebendazole (24), oxibendazole (30), parbendazole (19), subendazole (31), tiabendazole (13), triclabendazole (45)

(b) bendazol (l2) (vasodilator, also benzimidazole derivative)
L.0.0.0: nocodazole (36), procodazole (36) (also benzimidazole derivative)

(c) oxfendazole (35), tioxidazole (39)

related: furodazole (37) (S.3.l.0)

-bercept **see -cept**

-bermin **see -ermin**

-betasol **see pred**

USAN

-bersat **anticonvulsants, benzoylamino-benzpyran derivatives**

A.3.1.0 (USAN: anticonvulsants; antimigraine (benzoylamino-benzpyran derivatives))

(a) carabersat (85), tidembersat (84), tonabersat (85)

BAN, USAN

bol (x) **anabolic steroids**

M.4.1.0 (BAN: steroids, anabolic)
(USAN: bol- or -bol- : anabolic steroids)

(a) bolandiol (16), bolasterone (13), bolazine (21), boldenone (20), bolenol (19), bolmantalate (16), clostebol (22), enestebol (22), furazabol (16), mebolazine (21), mibolerone (27), norboletone (15), norclostebol (22)
-bolone: formebolone (31), mesabolone (29), metribolone (17), oxabolone cipionate (14), quinbolone (14), roxibolone (40), stenbolone (17), tibolone (22), trenbolone (24)

(c) ethylestrenol (13), hydroxystenozole (10), metandienone (12), metenolone (12), oxandrolone (12), propetandrol (13), tiomesterone (14)

-bradine **bradycardic agents**

H.0.0.0

(a) cilobradine (63), ivabradine (75), zatebradine (62)

-brate **see -fibrate**

USAN

-bufen **non-steroidal anti-inflammatory agents, *arylbutanoic acid* derivatives**

A.4.2.0 (USAN: non-steroidal anti-inflammatory agents, fenbufen derivatives)

(a) butibufen (32), fenbufen (30), furobufen (30), indobufen (39), metbufen (43)

USAN

-bulin **antineoplastics; mitotic inhibitors, tubulin binders**

L.0.0.0

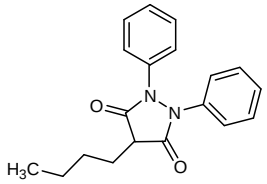
(a) batabulin (90), cevipabulin (96), crolibulin (104), denibulin (95), eribulin (97), fosbretabulin (100), indibulin (91), lexibulin (105), mivobulin (77), ombrabulin (99), plinabulin (102), rosabulin (95), taltobulin (91), verubulin (103)

(b) thyroglobulin (26)

-butazone **see -buzone**

-buzone **anti-inflammatory analgesics, phenylbutazone derivatives**

A.4.2.0



(a) feclobuzone (27), kebuzone (19), pipebuzone (25), suxibuzone (24), tribuzone (33)

-butazone (USAN: anti-inflammatory analgesics (phenylbutazone type)) USAN

mofebutazone (15), oxyphenbutazone (8), phenylbutazone (1)

-azone aminophenazone (13), bisfenazone (33), famprofazone (21), morazone (12), nifenazone (15), nimazone (20), niprofazone (29), phenazone (4), propyphenazone (1), sulfinpyrazone (8)

-zone clofezone (17), proxifezone (24)

related: azapropazone (18), benhepazone (15), bumadizone (24), cinnopentazone (17), isamfazone (37), metamfazone (12), osmadizone (26), ruvazone (26)

(c) benzpiperylone (12), butopyrammonium iodide (8), dibupyrone (17), metamizole sodium (53), metazamide (16), piperylone (11)

BAN, USAN

-caine (x) **local anaesthetics**

E.0.0.0

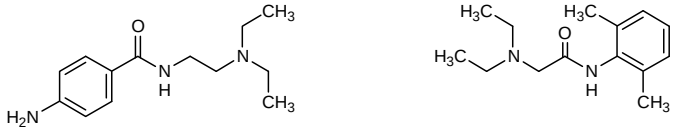
(a) ambucaine (6), amoxecaine (1), aptocaine (21), articaine (47) (previously carticaine (27)), benzocaine (42), betoxycaine (13), bucricaine (49), bumecaine (25), bupivacaine (17), butacaine (4), butanilicaine (16), chloroprocaine (6), cinchocaine (1), clibucaine (14), clodacaine (13), clormecaine (17), cyclomethycaine (6), dexivacaine (20), diamocaine (22), edronocaine (84), elucaine (29), etidocaine (29), fexicaine (25), fomocaine (18), hexylcaine (4), hydroxyprocaine (1), hydroxytetracaine (1), ipravacaine (85), ketocaine (15), leucinocaine (17), levobupivacaine (74), lidocaine (1), lotucaine (27), mepivacaine (11), meprylcaine (4), myrtecaine (15), octacaine (14), oxetacaine (13), oxybuprocaine (8), parethoxycaine (l), paridocaine (8), phenacaine (4), pinolcaine (32), piperocaine (l), piridocaine (l), pramocaine (4), pribecaine (32), prilocaine (14), procaine (10), propanocaine (6), propipocaine (16), propoxycaine (4) proxymetacaine (6), pyrrocaine (13), quatacaine (18), quinisocaine (4), risocaine (26), rodocaine (27), ropivacaine (50), tetracaine (4), tolycaine (16), trapencaine (56), trimecaine (11), vadocaine (57)

(c) amolanone (6), benzyl alcohol (l), cryofluorane (6), diperodon (l), dyclonine (6), midamaline (6)

BAN

-cain- (x) **Class I antiarrhythmics, procainamide and lidocaine derivatives**

H.2.0.0 (BAN: antifibrillants with local anaesthetic activity)



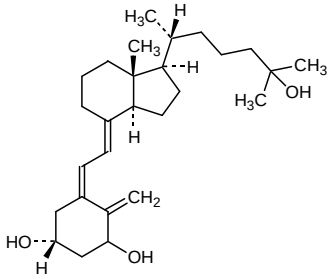
(a) acecainide (39), asocainol (47), barucainide (52), bucainide (35), carcainium chloride (36), carocainide (46), droxicainide (47), encainide (40), epicainide (40), erocainide (50), flecainide (37), guafecainol (38), indecainide (48) (originally ricainide (47)), itrocainide (54), ketocainol (32), lorcainide (38), milacainide (77), modecainide (63), murocainide (46), nicainoprol (46), nofecainide (44), pilsicainide (62), pincainide (49), procainamide

(1), quinacainol (50), recainam (54), solpecainol (55), stirocainide (47), suricainide (55), tocainide (36), transcainide (51), (verocainine (42) - replaced by tiapamil in List 43), zocainone (4l)

USAN

calci **Vitamin D analogues/derivatives**

N.8.0.0 (USAN: calci- or -calci-: Vitamin D analogues)



(a) alfacalcidol (40), atocalcitol (88), becocalcidiol (92), calcifediol (26), calcipotriol (61), calcitriol (39), colecalciferol (13), doxercalciferol (82), ecalcidene (85), eldecalcitol (97), elocalcitol (95), ergocalciferol (13), falecalcitriol (74), inecalcitol (87), lexacalcitol (71), lunacalcipol (102), maxacalcitol (75), paricalcitol (78), pefcalcitol (107), secalciferol (62), seocalcitol (78), tacalcitol (65)

(b) calcitonin (31) (polypeptide)

(c) dihydrotachysterol (1)

USAN

-capone **catechol-*O*-methyltransferase (COMT) inhibitors**

entacapone (65), nebicapone (96), nitecapone (62), opicapone (103), tolcapone (66)

USAN

-carbef **antibiotics, carbacephem derivatives**

S.6.1.0

(a) loracarbef (60)

-carnil **see -azenil**

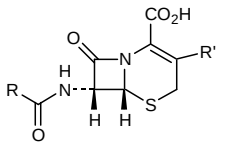
-castat **see -stat**

-cavir **see vir**

BAN, USAN

cef- (x) **antibiotics, cefalosporanic acid derivatives**

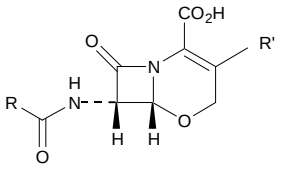
S.6.1.0 (USAN: cephalosporins)



(a) cefacetrile (25), cefaclor (36), cefadroxil (33), cefalexin (18), cefaloglycin (16), cefalonium (16), cefaloram (16), cefaloridine (15), cefalotin (14), cefamandole (30), cefaparole (33), cefapirin (23), cefatrizine (34), cefazaflur (36), cefazedone (36), cefazolin (25), cefbuperazone (48), cefcanel (60), cefcanel daloxate (59), cefcapene (68), cefclidin (64), cefdaloxime (64), cefdinir (61), cefditoren (66), cefedrolor (53), cefempidone (58), cefepime (57), cefetamet (49), cefetecol (63), cefetrizole (44), cefivitril (52), cefixime (53), cefluprenam (71), cefmatilen (81), cefmenoxime (44), cefmepidium chloride (57), cefmetazole (39), cefminox (53), cefodizime (44), cefonicid (42), cefoperazone (42), ceforanide (39), cefoselis (71), cefotaxime (42), cefotetan (48), cefotiam (40),cefovecin (87), cefoxazole (34), cefoxitin (29), cefozopran (66), cefpimizole (50), cefpiramide (47), cefpirome (50), cefpodoxime (58), cefprozil (62), cefquinome (59), cefradine (26), cefrotil (34), cefroxadine (42), cefsulodin (38), cefsumide (38), ceftaroline fosamil (97), ceftazidime (44), cefteram (55), ceftezole (34), ceftibuten (60), ceftiofur (53), ceftiolene (49), ceftioxide (43), ceftizoxime (59), ceftizoxime alapivoxil (77), ceftobiprole (92), ceftobiprole medocaril (92), ceftolozane (105), ceftriaxone (44), cefuracetime (45), cefuroxime (34), cefuzonam (55)

-oxef **antibiotics, oxacefalosporanic acid derivatives**

S.6.1.0 (USAN: antibiotic, oxacefalosporanic acid derivatives)



(a) flomoxef (55), latamoxef (46)

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cell- or cel- **cellulose derivatives [cel- in Spanish]**

U.4.0.0

(a) celucloral (40)

(c) celiprolol (35)

cell-ate **cellulose ester derivatives for substances containing acidic residues**

U.4.0.0 **[cel-ato in Spanish]**

(a) cellaburate (23), cellacefate (18)

-cellose **cellulose ether derivatives**

U.4.0.0 **[-celosa in Spanish]**

(a) -

(c) carmellose (45), croscarmellose (48), ethylcellulose (80), hyetellose (80), hymetellose (80), hyprolose (80), hypromellose (18), methylcellulose (4)

USAN

-cept **receptor molecules, native or modified (a preceding infix should designate the target)**

S.7.0.0

(a)

-ba- B-cell activating factor receptors
briobacept (98)

-ber- vascular endothelial growth factor (VEGF) receptors
aflibercept (96), conbercept (105)

-co- complement receptors
mirococept (91)

-far- subgroup of interferon receptors
bifarcept (86)

-lefa- lymphocyte function-associated antigen 3 receptors
alefacept (84)

-na- interleukin-1 receptors
rilonacept (95)

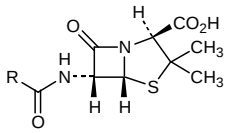
-ner- Tumour Necrosis Factor (TNF) receptors
baminercept (99), etanercept (81), lenercept (72), onercept (82), pegsunercept (87)

-ta- cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) receptors
abatacept (91), belatacept (93)

-ter- transforming growth factor receptors
dalantercept (105), ramatercept (108), sotatercept (104)

-vir- antiviral receptors
alvircept sudotox (69)

other: atacicept (95), ipafricept (109)

		USAN
-cic	**hepatoprotective substances with a carboxylic acid group**	
J.1.2.0	(USAN: hepatoprotectives (timonacic group))	
(a)	limazocic (69), tidiacic (33), timonacic (33), (tiofacic (45) replaced by stepronin (46))	
(b)	bisorcic (34) (psychostimulant)	
(c)	stepronin (46)	
		USAN
-ciclib	**cyclin dependant kinase inhibitors**	
L.0.0.0	dinaciclib (102), milciclib (105), palbociclib (109), riviciclib (109), roniciclib (109), seliciclib (92), voruciclib (109)	
-ciclovir	see -vir	
		USAN
-cidin	**naturally occurring antibiotics (undefined group)**	
S.6.0.0	(USAN: natural antibiotics (undefined group))	
(a)	brilacidin (108), candicidin (17), gramicidin (1), gramicidin S (26), methocidin (6)	
(b)	guancidine (18) (hypotensive)	
-ciguat	**guanylate cyclase activators and stimulators**	
F.2.0.0	(USAN: guanaline cyclase activators)	
(a)	ataciguat (88), cinaciguat (97), etriciguat (88), lificiguat (95), nelociguat (105), riociguat (98), vericiguat (109)	
-cillide	**see -cillin**	
		BAN, USAN
-cillin (x)	**antibiotics, 6-aminopenicillanic acid derivatives**	
S.6.1.0	(USAN: penicillins)	
		
(a)	adicillin (14), almecillin (14), amantocillin (17), amoxicillin (27), ampicillin (13), apalcillin (39), aspoxicillin (50), azidocillin (19), azlocillin (36), bacampicillin (32), benethamine penicillin (1), benzathine benzylpenicillin (18), benzylpenicillin (53), carbenicillin (20), carfecillin (30), carindacillin (29), ciclacillin (22), clemizole penicillin (8), clometocillin (12), cloxacillin (13), dicloxacillin (16), epicillin (25), fenbenicillin (13), fibracillin (30),	

flucloxacillin (17), fomidacillin (55), fumoxicillin (47), furbucillin (31), fuzlocillin (47), hetacillin (16), isopropicillin (12), lenampicillin (50), levopropicillin (12), metampicillin (20), meticillin (12), mezlocillin (34), nafcillin (13), oxacillin (l5), oxetacillin (33), penamecillin (16), pheneticillin (11), phenoxymethyl penicillin (6), phenyracillin (8), piperacillin (38), pirbenicillin (35), piridicillin (43), piroxicillin (49), pivampicillin (23), prazocillin (27), propicillin (13), quinacillin (14), rotamicillin (35), sarmoxicillin (41), sarpicillin (36), sulbenicillin (26), sultamicillin (48), suncillin (25), talampicillin (31), tameticillin (35), temocillin (46), ticarcillin (29), tifencillin (12), tobicillin (78)

(b) xantocillin (12)

(c) penimepicycline (l6), penimocycline (22)

-cillide

S.6.1.0 libecillide (32)

-cillinam

S.6.1.0 bacmecillinam (38), mecillinam (32), pivmecillinam (32)

-cillinam **see -cillin**

-cilpine **see -pine**

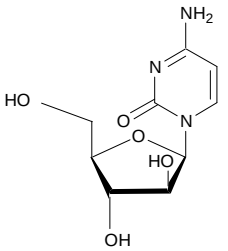
-cisteine **see -steine**

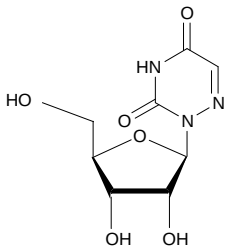
USAN

-citabine **nucleosides antiviral or antineoplastic agents, cytarabine or azacitidine derivatives**

(USAN: nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives)

L.4.0.0/S.5.5.0





(a) ancitabine (36), apricitabine (95), capecitabine (73), decitabine (61), dexelvucitabine (95), elvucitabine (89), emtricitabine (80), enocitabine (46), fiacitabine (59), flurocitabine (38), galocitabine (65), gemcitabine (62), gemcitabine elaidate (106), ibacitabine (57), mericitabine (108), sapacitabine (94), tezacitabine (84), torcitabine (87), troxacitabine (81), valopicitabine (93), valtorcitabine (90), zalcitabine (66)

(c) cytarabine (14), azacitidine (40)

USAN

-clidine/-clidinium muscarinic receptors agonists/antagonists

E.1.0.0

aceclidine (13), benzoclidine (25), eticyclidine (44), gacyclidine (76), phencyclidine (11), procyclidine (01), rolicyclidine (44), talsaclidine (72), tenocyclidine (44), vedaclidine (76)
aclidinium bromide (100), clidinium bromide (06), droclidinium bromide (33) umeclidinium bromide (106)

USAN

-clone hypnotic tranquillizers

A.2.2.0 (USAN: hypnotics / tranquillizers (zopiclone type))

(a) barbexaclone (16), eszopiclone (87), pagoclone (74), pazinaclone (70), suproclone (46), suriclone (43), suproclone (46), zopiclone (39)

(b) gestaclone (23), pimeclone (20)

-cocept see -cept

-cog blood coagulation factors

I.2.0.0

(-)eptacog blood coagulation VII:	eptacog alfa (activated) (77), eptacog alfa pegol (activated) (101), oreptacog alfa (activated) (109), vatreptacog alfa (activated) (98)
(-)octocog blood factor VIII:	beroctocog alfa (98), damoctocog alfa pegol (109), moroctocog alfa (72), octocog alfa (73), simoctocog alfa (104), turoctocog alfa (108), turoctocog alfa pegol (108)
(-)nonacog blood factor IX:	albutrepenonacog alfa (109), eftrenonacog alfa (109), nonacog alfa (77), nonacog beta pegol (103), nonacog gamma (108), trenonacog alfa (107)
(-)tridecacog blood factor XIII:	catridecacog (99)
Other:	vonicog alfa (102)

-cogin blood coagulation cascade inhibitors

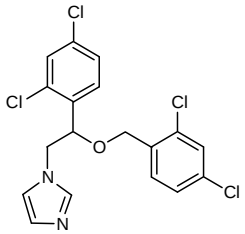
I.2.0.0

drotrecogin alfa (activated) (86), pegnivacogin (106), taneptacogin alfa (90), tifacogin (78)

BAN; USAN

-conazole (x) systemic antifungal agents, miconazole derivatives

S.4.0.0 (BAN: systemic antifungals of the miconazole group)
(USAN: systemic antifungals (miconazole type))



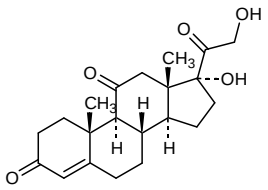
(a) albaconazole (87), aliconazole (43), alteconazole (53), arasertaconazole (93), azaconazole (45), becliconazole (65), brolaconazole (58), butoconazole (40), cisconazole (59), croconazole (55), (cyproconazole (ISO)), democonazole (42), (diniconazole (ISO $C_{17}H_{17}Cl_2N_3O$)), doconazole (37), eberconazole (64), econazole (27), efinaconazole (104), embeconazole (92), enilconazole (44), (etaconazole (ISO)), fenticonazole (44), fluconazole (54), fosfluconazole (83), (furconazole (ISO/TC 81 N 872 $C_{15}H_{14}Cl_2F_3N_3O_2$)), (hexaconazole (ISO $C_{14}H_{17}Cl_2N_3O$)), isavuconazole (96), isoconazole (30), itraconazole (50), ketoconazole (43), lanoconazole (66), luliconazole (86), miconazole (22), neticonazole (63), omoconazole (45), orconazole (40), oxiconazole (42), parconazole (39), (penconazole, (ISO)), posaconazole (82), (propiconazole (ISO)), pramiconazole (95), ravuconazole (83), saperconazole (59), sertaconazole (56), sulconazole (38), (tebuconazole (ISO $C_{16}H_{22}ClN_3O$)), terconazole (45) (originally triaconazole), tioconazole (40), (uniconazole (ISO $C_{15}H_{18}ClN_3O$)), valconazole (40), voriconazole (73), zinoconazole (50), zoficonazole (43)

(c) bifonazole (44), isavuconazonium chloride (96)

BAN, USAN

cort (x) corticosteroids, except prednisolone derivatives

Q.3.0.0 (USAN: -cort-: cortisone derivatives)



(a) amebucort (54), anecortave (80), butixocort (63), cicortonide (28), corticotropin (68), corticotropin-zinc hydroxide (68), cortisone (1), cortisuzol (30), cortivazol (23), cortodoxone (15), deflazacort (39) (previously azacort (38)), desoxycortone (4), fluazacort (30), fludrocortisone (6), fludroxycortide (12), fluocortin (31), formocortal (18),

hydrocortamate (6), hydrocortisone (1), hydrocortisone aceponate (54), locicortolone dicibate (60), naflocort (50), nicocortonide (40), nivacortol (24), resocortol (74), tixocortol (38)

(b) prednisolone derivatives: clocortolone (16), difluocortolone (18), fluocortolone (15), halocortolone (31)

(c) aldosterone (6), algestone (22) (also progest. when used as algestone acetophenide), medrysone (16)

USAN

-coxib (x) **selective cyclo-oxygenase inhibitors**

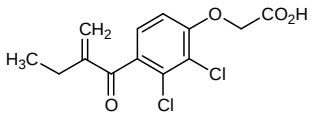
A.4.2.0 (USAN: cyclooxygenase-2 inhibitors)

(a) apricoxib (99), celecoxib (80), cimicoxib (89), deracoxib (80), etoricoxib (84), firocoxib (89), lumiracoxib (87), mavacoxib (94), parecoxib (80), robenacoxib (91), rofecoxib (80), tilmacoxib (84), valdecoxib (80)

USAN

-crinat **diuretics, etacrynic acid derivatives**

N.1.2.2 (USAN: diuretics (ethacrynic acid derivatives))

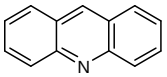


(a) brocrinat (51), sulicrinat (52)

(c) etacrynic acid (14), furacrinic acid (29), indacrinone (51), tienilic acid (25)

USAN

-crine (d) **acridine derivatives**



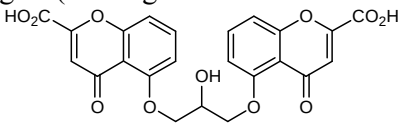
(a) antineoplastics: amsacrine (44), nitracrine (35)
anthelminthics; antimalarials: floxacrine (34), mepacrine (4)
antidepressants: dimetacrine (19), monometacrine (19)
antiparkinsonian: botiacrine (38)
acetylcholinesterase inhibitors: ipidacrine (73), suronacrine (61), tacrine (8), velnacrine (61)

(c) acridorex (2l), acriflavinium chloride (l), acrisorcin (l3), aminoacridine (l), ethacridine (l), proflavine (l)

USAN

-cromil **antiallergics, cromoglicic acid derivatives**

K.0.0.0 (USAN: antiallergics (cromoglicic acid derivatives))



(a) ambicromil (48) (replacement of probicromil (46)), isocromil (39), minocromil (50), nedocromil (50), proxicromil (39), terbucromil (38), texacromil (58)

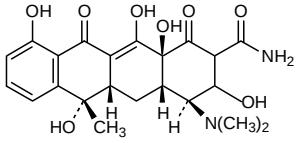
(c) cromitrile (46), cromoglicate lisetil (72), cromoglicic acid (l8)

-curium **see -ium**

BAN; USAN

-cycline (d) **antibiotics, protein-synthesis inhibitors, tetracycline derivatives**

S.6.3.0 (BAN: antibiotics of the tetracycline group)
(USAN: antibiotics (tetracycline derivatives))



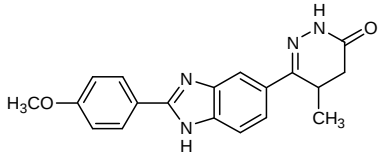
(a) amicycline (14), apicycline (17), cetocycline (39), chlortetracycline (4), clomocycline (16), colimecycline (33), demeclocycline (25), demecycline (14), doxycycline (16), eravacycline (108), etamocycline (18), guamecycline (22), lymecycline (14), meclocycline (14), meglucycline (22), metacycline (12), minocycline (14), nitrocycline (14), omadacycline (102), oxytetracycline (1), pecocycline (15), penimepicycline (16), penimocycline (22), pipacycline (12), rolitetracycline (11), sarecycline (109), sancycline (15), tetracycline (4), tigecycline (86)

related: carubicin (40), daunorubicin (20), detorubicin (41), doxorubicin (25), zorubicin (39)

USAN

-dan **cardiac stimulants, pimobendan derivatives**

H.1.0.0 (USAN: positive inotropic agents (pimobendan type))



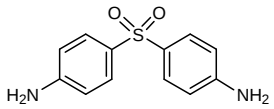
(a) adibendan (57), bemorodan (61), imazodan (55), indolidan (57), levosimendan (68), meribendan (62), pimobendan (46), prinoxodan (64), senazodan (85), siguazodan (60), simendan (66)

(b) nitrodan (15), tyromedan (15)

USAN

-dapsone **antimycobacterials, diaminodiphenylsulfone derivatives**

S.5.2.0 (USAN: antimycobacterial (diaminodiphenylsulfone derivatives))



(a) acedapsone (22), amidapsone (28), dapsone (23)

-decakin **see -kin**

USAN

-denoson **adenosine A receptor agonists**

H.0.0.0

apadenoson (94), binodenoson (90), capadenoson (95), evodenoson (108), regadenoson (91), selodenoson (91), sonedenoson (101), tecadenoson (87), trabodenoson (107)

-dermin **see –ermin**

USAN

-dil **vasodilators**

F.2.0.0
F.2.1./2.0 (USAN: -dil; or -dil-: vasodilators (undefined group))

F.2.0.0
(a) alprostadil (39), aviptadil (78), belfosdil (61), benfurodil hemisuccinate (16), biclodil (52), buflomedil (33), burodiline (26), carprazidil (45), cetiedil (27), cinepaxadil (50), dopropidil (59), eliprodil (66), fasudil (64), fenoxedil (27), flosatidil (64), fostedil (51), fronepidil (59), ifenprodil (27), levosemotiadil (72), manozodil (47), mefenidil (48), minoxidil (25), naftopidil (52), naminidil (87), nesapidil (52),perfomedil (60), pinacidil (46), piribedil (23), pitenodil (37), podilfen (22), radiprodil (98), ripasudil (109), stevaladil (34), suloctidil (30), tipropidil (44), traxoprodil (86), urapidil (27), viquidil (25)

(c) dilmefone (33)

F.2.1.0

(a) coronary vasodilators: bepridil (30), bumepidil (44), ecipramidil (40), fendiline (24), fenetradil (30), floredil (28), hexadiline (13), ipramidil (51), mepramidil (27), metrifudil (23), nicorandil (44), pirozadil (33), pretiadil (27), razinodil (38), semotiadil (64), sinitrodil (74), terodiline (16), tixadil (l8), trapidil (29)

(c) dilazep (22), diltiazem (30)

-dilol carvedilol (50), dioxadilol (53), dramedilol (57), flavodilol (48), mindodilol (52), nipradilol (50) (previously nipradolol), oberadilol (77), parodilol (57), prizidilol (44), tribendilol (54)

(b) diloxanide (8) (amebicide), methdilazine (10) (antihistaminic), phenobutiodil (6) (contrast medium), prodilidine (12) (analgesic)

-fradil **calcium channel blockers acting as vasodilators** USAN

(a) mibefradil (72)

-pendyl cloxypendyl (15), isothipendyl (6), oxypendyl (13), prothipendyl (6)

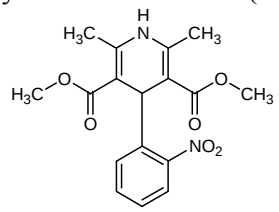
-dyl bisacodyl (13) (laxative), bunamiodyl (10), iofendylate (12), trihexyphenidyl (l) (antiparksonian)

-dilol **see -dil**

BAN; USAN

-dipine (x) **calcium channel blockers, nifedipine derivatives**

F.2.1.0 (BAN: calcium ion channel antagonists)
(USAN: phenylpyridine vasodilators (nifedipine type))



(a) amlodipine (53), clevidipine (75), darodipine (51) (replaces dazodipine (49)), dexniguldipine (67), elgodipine (61), elnadipine (59), felodipine (44), flordipine (48), isradipine (55), lacidipine (57), lemildipine (69), levamlodipine (98), levniguldipine (67), mesudipine (40), nicardipine (42), nifedipine (27), niguldipine (60), niludipine (38), nilvadipine (52), nimodipine (40), nisoldipine (42), nitrendipine (42), olradipine (69), oxodipine (52), riodipine (51), sagandipine (64), teludipine (64) (previously taludipine (61))
-nidipine: aranidipine (69), azelnidipine (69), barnidipine (64), benidipine (58), cilnidipine (66), cronidipine (61), efonidipine (66), furnidipine (67), iganidipine (70), lercanidipine

(69) (previously masnidipine), manidipine (59), palonidipine (64), pranidipine (66), sornidipine (58), vatanidipine (77)

(b) budipine (36) (central stimulant, antidepressant and antiparkinsonian), prodipine (29) (central stimulant antiparkinsonian)

-dismase **enzymes with superoxide dismutase activity, see -ase item V**

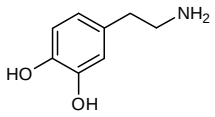
-distim **see -stim**

-dodekin **see -kin**

USAN

-dopa **dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism/ prolactin inhibitors**

E.1.1.0 (USAN: dopamine receptor agonists)



(a) carbidopa (37), ciladopa (52), dopamantine (31), droxidopa (57), etilevodopa (80), fluorodopa (^{18}F) (64), levodopa (21), melevodopa (83), methyldopa (12)

-opamine **dopaminergic agents dopamine derivatives used as cardiac stimulant/ antihypertensives/diuretics**

(USAN: -pamine: dopaminergics (butopamine type))

(a) butopamine (43), cliropamine (59), denopamine (50), dopamine (18), fosopamine (69), ibopamine (43), octopamine (32), oxidopamine (37) (glaucoma), ractopamine (54) (1 of 4 isomers of butopamine)

(b) tiopropamine (36) (gastric and duodenal ulcers), tolpropamine (13) (antihistaminic)

(c) dobutamine (29), docarpamine (59), dopexamine (50), fenoldopam (53), levdobutamine (65), methyldopa (12) (alpha-2 adrenoreceptor agonist, cardiotonic), zelandopam (84)

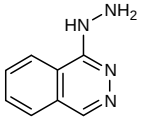
-dotril **see -tril/trilat**

-dox **see -ox/-alox**

USAN

-dralazine **antihypertensives, hydrazinephthalazine derivatives**

H.3.0.0 (USAN: antihypertensives (hydrazine-phthalazines))



(a) budralazine (33), cadralazine (41), dihydralazine (4), endralazine (39), hydralazine (1), mopidralazine (52), oxdralazine (38), picodralazine (18), pildralazine (48), todralazine (26)

-drine **sympathomimetics**

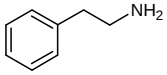
E.4.0.0 (USAN: -drine: sympathomimetics)

(a) alifedrine (49), bedoradrine (95), butidrine (16), cafedrine (14), cinnamedrine (19), corbadrine (1), dioxethedrin (6), dioxifedrine (41), etafedrine (14), meluadrine (78), methoxyphedrine (6), midodrine (27), norbudrine (17), oxyfedrine (16), pholedrine (1), pseudoephedrine (11), racephedrine (66), ritodrine (22), theophylline ephedrine (14), tinofedrine (32), trecadrine (53)
not phenethylamine derivatives: levopropylhexedrine (37), octodrine (19), propylhexedrine (6)

(b) bufenadrine (13) (antiemetic) related chemically, chlormerodrin (4) (diuretic), chlormerodrin (^{197}Hg) (24), dieldrin (10) (insecticide), orphenadrine (8) (spasmolytic)

-frine **sympathomimetic, phenethyl derivatives**

E.4.0.0



(a) amidefrine mesilate (15), berefrine (68), ciclafrine (33), dimetofrine (27), dipivefrine (39), epinephrine (16), etilefrine (18), etilefrine pivalate (50), gepefrine (38), norepinephrine (45), norfenefrine (16), oxilofrine (62), phenylephrine (1), pivenfrine (42), racepinefrine (41)

USAN

-dronic acid **calcium metabolism regulator, pharmaceutical aid**

N.8.0.0
U.4.0.0 (USAN: -dronate: calcium metabolism regulators)

(a) alendronic acid (61), butedronic acid (59), clodronic acid (37), etidronic acid (22), ibandronic acid (71), incadronic acid (70), lidadronic acid (84), medronic acid (39), minodronic acid (78), neridronic acid (61), olpadronic acid (71), oxidronic acid (42), pamidronic acid (59), piridronic acid (58), risedronic acid (62), tiludronic acid (60), zoledronic acid (71)

-dutant **see -tant**

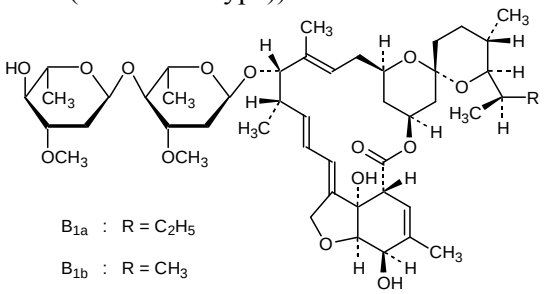
-dyl **see -dil**

USAN

-ectin **antiparasitics, ivermectin derivatives**

(USAN: antiparasitics (ivermectin type))

S.3.0.0



(a) abamectin (53), dimadectin (73), doramectin (63), eprinomectin (73), fuladectin (71), ivermectin (44), latidectin (88), moxidectin (61), nemadectin (60), selamectin (81)

-elestat **see -stat**

-elvekin **see -kin**

USAN

-emcinal **erythromycin derivatives lacking antibiotic activity, motilin agonists**

J.0.0.0

(a) alemcinal (84), idremcinal (81), mitemcinal (86)

-enicokin **see -kin**

USAN

-entan (x) **endothelin receptor antagonists**

F.2.0.0

(a) ambrisentan (85), atrasentan (83), avosentan (93), bosentan (70), clazosentan (90), darusentan (82), edonentan (86), enrasentan (80), fandosentan (87), feloprentan (85), macitentan (107), nebentan (90), sitaxentan (83), tezosentan (81), zibotentan (94)

(-)eptacog **see -cog**

USAN

erg **ergot alkaloid derivatives**

F.4.0.0
C.7.0.0 (USAN: -erg-: ergot alkaloid derivatives)

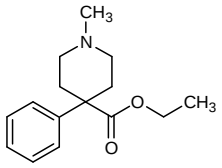
(a) acetergamine (18), amesergide (67), brazergoline (37), bromerguride (51), cabergoline (54), cianergoline (47), delergotrile (42), dihydroergotamine (16), disulergine (45), dosergoside (54), ergometrine (4), ergotamine (4), etisulergine (47), lergotrile (32), lysergide (8), mergocriptine (54), mesulergine (47), metergoline (18), metergotamine (29), methylergometrine (l), methysergide (11), nicergoline (26), pergolide (41), propisergide (35), proterguride (50), romergoline (66), sergolexole (60), terguride (50), tiomergine (42), voxergolide (61)

(b) ergocalciferol (l3)

USAN

-eridine **analgesics, pethidine derivatives**

A.4.1.0 (USAN: analgesics (meperidine type))



(a) anileridine (5), carperidine (11), etoxeridine (6), morpheridine (6), oxpheneridine (5), pheneridine (5), phenoperidine (11), properidine (5), sameridine (68), trimeperidine (6)

(b) diaveridine (l8) (coccidiostat.), eseridine (53), nexeridine (34) (somewhat related)

(c) benzethidine (9), butoxylate (14), diphenoxylate (10), fetoxilate (21), furethidine (9), hydroxypethidine (5), pethidine (4), piminodine (9)

USAN

-ermin **growth factors**

U.0.0.0

-bermin **vascular endothelial growth factors**
(a) telbermin (85)

-dermin **epidermal growth factors**
(a) murodermin (63), nepidermin (97)

-fermin	**fibroblast growth factors**
(a)	ersofermin (66), palifermin (86), repifermin (82), sprifermin (105), trafermin (74), velafermin (94)
-filermin	**leukemia-inhibiting factor**
(a)	emfilermin (82)
-nermin	**tumour necrosis factor**
(a)	ardenermin (88), dulanermin (99), plusonermin (73), sonermin (68), tasonermin (76)
-plermin	**platelet-derived growth factor**
(a)	becaplermin (74)
-sermin	**insulin-like growth factors**
(a)	mecasermin (66), mecasermin rinfabate (91)
-termin	**transforming growth factor**
(a)	cetermin (74), liatermin (81)
-otermin	**bone morphogenic proteins**
(a)	avotermin (77), dibotermin alfa (89), eptotermin alfa (89), nebotermin (109), radotermin (92)
Others:	dapiclermin (93)

BAN; USAN

estr	**estrogens**
Q.2.1.0	(USAN: estr-; or -estr-: estrogens)
(a)	almestrone (24), benzestrol (1), broparestrol (8), cloxestradiol (12), dienestrol (1), diethylstilbestrol (4), epiestriol (12), epimestrol (22), (eptamestrol/etamestrol (49) deleted), estradiol (4), estradiol benzoate (4), estradiol undecylate (16), estradiol valerate (35), estramustine (24), estrapronicate (34), estrazinol (16), estriol succinate (14), estrofurate (25), estrone (4), ethinylestradiol (1), fenestrel (18), fosfestrol (15), furostilbestrol (1), hexestrol (1), mestranol (12), methallenestril (6), methestrol (1), moxestrol (24), nilestriol (32), orestrate (17), polyestradiol phosphate (36), promestriene (31), quinestradol (15), quinestrol (14)
(b) Q.2.2.0	alfatradiol (84) (topical), allylestrenol (10) (progest.), ethylestrenol (13) (anabol.), fulvestrant (78) (estrogens receptor antagonist), lynestrenol (13) (progest.)
-gestr-:	edogestrone (22), levonorgestrel (30), megestrol (13), melengestrol (13), norgestrel (17), norgestrienone (18), pentagestrone (14), quingestrone (13)
(c)	chlorotrianisene (6), clomifene (12), enclomifene (33), zuclomifene (33) (antiestrogens)

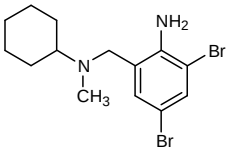
-etanide **see -anide**

-ethidine **see -eridine**

-exakin **see -kin**

-exine **mucolytic, bromhexine derivatives**

K.0.0.0



(a) adamexine (36), bromhexine (20), brovanexine (31), cistinexine (54), dembrexine (56), neltenexine (62), oxabrexine (40)

(b) enefexine (54) (antidepressant), gamfexine (17) (antidepressant)

(c) ambroxol (32) (dembrexol (50): replaced by dembrexine (56))

-farcept **see -cept**

-fenamate **see -fenamic acid**

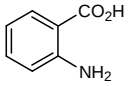
USAN

-fenamic acid **anti-inflammatory, anthranilic acid derivatives**

-fenamate **"fenamic acid" derivatives**

(USAN: -fenamic acid: anti-inflammatory (anthranilic acid derivatives); -fenamate: "fenamic acid" ester or salt derivatives)

A.4.2.0



(a) clofenamic acid (13), enfenamic acid (45), flufenamic acid (13), meclofenamic acid (17), mefenamic acid (13), tolfenamic acid (24)

colfenamate (29), etofenamate (29), prefenamate (36), terofenamate (32), ufenamate (50)

(b) clantifen (24), oxyfenamate (13)

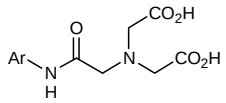
phonetically close: clofenamide (13), diclofenamide (13) (N.1.1.0)

(c) flutiazin (22)

USAN

-fenin **diagnostic aids; (phenylcarbamoyl)methyl iminodiacetic acid derivatives**

U.1.0.0



(a) arclofenin (52), butilfenin (41), disofenin (43), etifenin (43), galtifenin (59), lidofenin (39), mebrofenin (47)

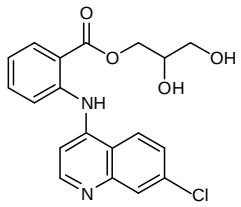
USAN

-fenine **analgesics, glafenine derivatives (subgroup of fenamic acid group)**

phenine

(USAN: -fenine: analgesics (fenamic acid subgroup))

A.4.3.0



(a) antrafenine (35), floctafenine (24), florifenine (50), glafenine (15), nicafenine (40)

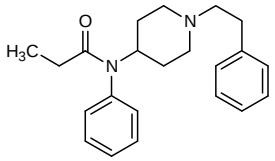
(b) spasmolytic diphenylacetates: adiphenine (1), drofenine (26)
other: buphenine (8) (vasodilator), cinfenine (27) (antidepressant)

USAN

-fentanil **opioid receptor agonists, analgesics, fentanyl derivatives**

(USAN: -fentanil: narcotic analgesics (fentanyl derivatives))

A.4.1.0



(a) alfentanil (43), brifentanil (62), carfentanil (39), fentanyl (14), lofentanil (43), mirfentanil (64), ocfentanil (61), remifentanil (67), sufentanil (36), trefentanil (67)

USAN

-fentrine **inhibitors of phosphodiesterases**

K.0.0.0

(a) benafentrine (44), pumafentrine (86), tolafentrine (70)

-fermin **see -ermin**

USAN

-fiban **fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)**

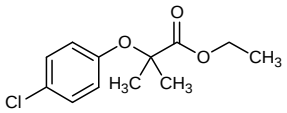
I.2.0.0

carafiban (78), elarofiban (83), fradafiban (72), gantofiban (80), lamifiban (72), lefradafiban (75), lotrafiban (78), orbofiban (75), roxifiban (77), sibrafiban (77), tirofiban (73), xemilofiban (74)

BAN, USAN

-fibrate **clofibrate derivatives**

H.4.0.0 (BAN: substances of the clofibrate group)
(USAN: -fibrate, -fibric acid: antihyperlipidaemics (clofibrate type))



(a) bezafibrate (35), biclofibrate (28), binifibrate (44), choline fenofibrate (97), ciprofibrate (36), clinofibrate (39), dulofibrate (43), etofibrate (31), fenirofibrate (49), fenofibrate (35), lifibrate (30), nicofibrate (31), picafibrate (35), ponfibrate (37), ronifibrate (55), salafibrate (41), serfibrate (34), simfibrate (22), sitofibrate (32), tiafibrate (33), timofibrate (40), tocofibrate (33), urefibrate (37), xantifibrate (31)

clofibric acid (20), clofibrate (13), aluminium clofibrate (31), calcium clofibrate (34), cinnarizine clofibrate (38), etofylline clofibrate (38), magnesium clofibrate (3l)
clofibride (28), plafibride (39)

related: arhalofenate (101), beclobrate (35), eniclobrate (39), gemfibrozil (34), halofenate (20), lifibrol (62), metibride (53), terbufibrol (35), tibric acid (33), (fibrafylline (43) deleted)

(b) bromebric acid (25) (prophylaxis of migraine), fibracillin (30) (antibiotic)

(c) nafenopin (24), treloxinate (25)

-filermin **see -ermin**

USAN

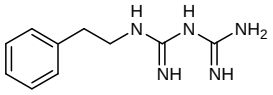
-flapon **5-lipoxygenase-activating protein (FLAP) inhibitors**

K.0.0.0
J.0.0.0

fiboflapon (105), quiflapon (72), veliflapon (95)

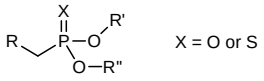
		USAN
-flurane	**halogenated compounds used as general inhalation anaesthetics**	
A.1.1.0	(USAN: general inhalation anesthetics (halogenated alkane derivatives))	
(a)	aliflurane (36), cryofluorane (6), desflurane (62), enflurane (25), isoflurane (28), methoxyflurane (11), norflurane (20), roflurane (12), sevoflurane (25), teflurane (12)	
(b)	apaflurane (73)	
(c)	fluroxene (12), halothane (6)	

		USAN
-formin (d)	**antihyperglycaemics, phenformin derivatives**	
M.5.2.0	(USAN: hypoglycemics (phenformin type))	



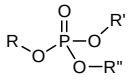
(a)	benfosformin (29), buformin (17), etoformin (34), metformin (21), metformin glycinate (103), phenformin (10), tiformin (22)	

		USAN
-fos (-vos)	**insecticides, anthelminthics, pesticides etc., phosphorous derivatives**	
S.3.1.0 (Y.0.0.0)	(USAN: -fo(s)-: phosphoro-derivatives)	
1.	organophosphorous derivatives:	



(a)	vet. insecticides:	
	quintiofos (25)	
(b)	toldimfos (23) (vet. phosphorous source)	
(c)	vet. insecticides and anthelminthics:	
	metrifonate (16)	
	anthelmintic: butonate (30)	

2. phosphates:



(a) vet. insecticides: clofenvinfos (23)

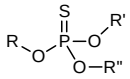
vet. anthelminthics: bromofenofos (43), dichlorvos (28), naftalofos (16)

anthelminthics: vincofos (28)

(b) triclofos (l3) (hypnotic, sedative)

(c) vet. anthelminthics: fospirate (21), haloxon (16)

3. phosphorothioates:

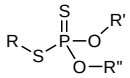


vet. insecticides:

(a) bromofos (25), coumafos (16), fenclofos (23), temefos (31)

(c) dimpylate (16), phoxim (20) (vet. insecticide and anthelmintic), pyrimitate (16)

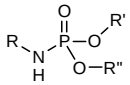
4. phosphorodithioates:



(a) benoxafos (22) (vet. pesticide)

(c) carbofenotion (23) (vet. insecticide), dioxation (l6) (vet. insecticide), (malathion (46) (deleted!))

5. phosphoramidates



crufomate (16), uredofos (37)

anthelminthic:
imcarbofos (44)

-fos- or fos- **various pharmacological categories belonging to fos (other than those above):**

-fos-

alafosfalin (41), amifostine (44), belfosdil (61), benfosformin (29), butafosfan (38), cifostodine (50), creatinolfosfate (20), dexfosfoserine (68), ferpifosate sodium (69), furifosmin (70), mono*phospho*thiamine (8), sodium picofosfate (37), sofosbuvir (108), sparfosic acid (46), technetium (^{99m}Tc) furifosmin (70), tetrofosmin (66), trifosmin (74)

-fosfamide: alkylating agents of the cyclophosphamide group
(USAN: isophosphoramide mustard derivatives)
canfosfamide (92), cyclophosphamide (10), defosfamide (12), glufosfamide (77), ifosfamide (23), mafosfamide (51), palifosfamide (99), perfosfamide (66), sufosfamide (36), trofosfamide (23)

-fosine cytostatic
edelfosine (59), ilmofosine (56), miltefosine (61), perifosine (78)

fos-
fosalvudine tidoxil (95), fosamprenavir (83), fosaprepitant (94), fosarilate (53), fosazepam (27), fosbretabulin (100), foscarnet sodium (42), foscolic acid (12), fosdevirine (103), fosenazide (48), fosfestrol (15), fosfluconazole (83), fosfluridine tidoxil (93), fosfocreatinine (50), fosfomycin (25), fosfonet sodium (35), fosfosal (37), fosfructose (81), fosinopril (69), fosinoprilat (62), fosmenic acid (49), fosmidomycin (46), fosopamine (69), fosphenytoin (62), fospirate (21), fospropofol (100), fosquidone (64), fostamatinib (100), fostedil (51), fostriecin (55), fosveset (83)

-fovir **see vir**

USAN

-fradil **see -dil**

-frine **see -drine**

USAN

-fungin **antifungal antibiotics**

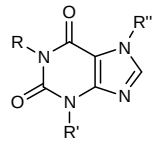
S.6.0.0 (USAN: antifungal antibiotics (undefined group))
S.4.3.0

(a) abafungin (74), anidulafungin (81), basifungin (72), caspofungin (80), cilofungin (60), fusafungine (15), kalafungin (20), micafungin (84), nifungin (24), oxifungin (40), sinefungin (39), triafungin (40)

USAN

-fylline ***N*-methylated xanthine derivatives**

B.1.0.0 (USAN: theophylline derivatives)



(a) acefylline clofibrol (44), acefylline piperazine (14), albifylline (66), aminophylline (4), apaxifylline (71), arofylline (75), bamifylline (15), cipamfylline (71), denbufylline (55),

derenofylline (102), dimabefylline (19), diniprofylline (18), diprophylline (1), doxofylline (47), enprofylline (44), etamiphylline (6), etofylline (14), etofylline clofibrate (38), fibrafylline (43) (deleted), flufylline (48), fluprofylline (50), furafylline (48), guaifylline (16), isbufylline (62), istradefylline (89), laprafylline (60), lisofylline (72), lomifylline (37), mercurophylline (1), metescufylline (15), mexafylline (48), midaxifylline (79), naxifylline (86), nestifylline (64), pentifylline (29), pentoxifylline (29), perbufylline (58), pimefylline (2l), propentofylline (46), proxyphylline (10), pyridofylline (14), rolofylline (98), spirofylline (58), stacofylline (73), tazifylline (52), theophylline ephedrine (14), tonapofylline (102), torbafylline (56), triclofylline (19), verofylline (43), visnafylline (24), choline theophyllinate (8), fenetylline (16)

(c) cafedrine (14), dimenhydrinate (1), dimethazan (8), meralluride (1), mercumatilin sodium (4), piprinhydrinate (8), promethazine teoclate (10), protheobromine (14), theodrenaline (14), xantifibrate (31), xantinol nicotinate (16)

radicals and groups: teprosilate (29)

USAN

gab (x) **gabamimetic agents**

E.0.0.0

(a) atagabalin (102), fengabine (53), gabapentin (46), gabapentin enacarbil (94), gaboxadol (48) (used as analgesic), imagabalin (101), lesogaberan (100), mirogabalin (109), pivagabine (66), pregabalin (78), progabide (43) (used as antiepileptic), retigabine (76), tiagabine (63), tolgabide (53), vigabatrin (52) (anticonvulsants)

(b) gabexate (35) (proteolytic)

USAN

gado- (x) **diagnostic agents, gadolinium derivatives**

U.0.0.0 (USAN: gadolinium derivatives (principally for diagnostic use))

(a) gadobenic acid (64), gadobutrol (66), gadocoletic acid (85), gadodenterate (91), gadodiamide (63), gadofosveset (86), gadomelitol (85), gadopenamide (60), gadopentetic acid (50), gadoterdol (70), gadoteric acid (59), gadoversetamide (71), gadoxetic acid (71)

USAN

-gatran (x) **thrombin inhibitors, antithrombotic agents**

I.2.0.0 (USAN: thrombin inhibitors (argatroban type))

(a) atecegatran (103), atecegatran metoxil (105), dabigatran (83), dabigatran etexilate (87), efegatran (71), flovagatran (97), inogatran (72), melagatran (74), napsagatran (72), sofigatran (95), ximelagatran (84)

(c) argatroban (57)

USAN

-gene **gene therapy products** (see also Annex 4)

Z.0.0.0 A two-word name approach has been selected:

Word 1	*-gene*		*gene component*
		-cima-	cytosine deaminase
		-ermin-	growth factor
		-kin-	interleukin
		-lim-	immunomodulator
		-lip-	human lipoprotein lipase
		-mul-	multiple gene
		-stim-	colony stimulating factor
		-tima-	thymidine kinase
		-tusu-	tumour suppression
Word 2	*-vec*		*vector component is a virus*
	-repvec		*replicating viral vector*
		-adeno-	adenovirus
		-cana-	canarypox virus
		-foli-	fowlpox virus
		-herpa-	herpes virus
		-lenti-	lentivirus
		-morbilli-	paramoxyviridae morbillivirus
		-parvo-	adeno-associated virus (parvoviridae dependovirus)
		-retro-	other retrovirus
		-vaci-	vaccinia virus
	-plasmid		*in case the vector is a plasmid*

In case of non-plasmid naked DNA, there is no need for a second word in the name.
In case of antisense nucleotides, please refer to the already existing stem *-rsen.*

(a) alferminogene tadenovec (95), alipogene tiparvovec (99), amolimogene bepiplasmid (98), beperminogene perplasmid (95), contusugene ladenovec (97), golnerminogene pradenovec (101), pexastimogene devacirepvec (108), riferminogene pecaplasmid (100), rilimogene galvacirepvec (107), rilimogene glafolivec (107), sitimagene ceradenovec (97), taberminogene vadenovec (100), talimogene laherparepvec (104), tipapkinogene sovacivec (102), velimogene aliplasmid (97), vocimagene amiretrorepvec (107)

BAN, USAN

gest (x) **steroids, progestogens**

Q.2.2.0 (USAN: -gest-: progestins)

(a) altrenogest (46), anagestone (16), cingestol (20), clogestone (21), clomegestone (20), demegestone (24), desogestrel (38), dexnorgestrel (30), dienogest (49), dydrogesterone (12), edogestrone (22), etonogestrel (65), flugestone (16), gestaclone (23), gestadienol (22),

gestodene (37), gestonorone caproate (16), gestrinone (39), haloprogesterone (11), hydroxyprogesterone (8), hydroxyprogesterone caproate (8), levonorgestrel (33) (previously dexnorgestrel), medrogestone (15), medroxyprogesterone (10), medrogestone (l5), megestrol (l3), melengestrol (13), metogest (33), nomegestrol (49), norelgestromin (83), norgesterone (14), norgestimate (35), norgestomet (32), norgestrel (17), norgestrienone (18), oxogestone (19), pentagestrone (14), progesterone (4), proligestone (28), promegestone (38), quingestanol (15), quingestrone (13), segesterone (89), tigestol (20), tosagestin (86), trengestone (22), trimegestone (66)

(b) algestone (22) (glucorticoid)

(c) allylestrenol (10), chlormadinone (12), cismadinone (12), delmadinone (23), dimethisterone (8), ethisterone (4), ethynerone (17), etynodiol (13), hydromadinone (12), lynestrenol (13), metynodiol (27), norethisterone (6), noretynodrel (13), norvinisterone (10)

clometerone (15) (antiestrogen), dimepregnen (24) (antiestrogen)

-gestr- **see estr**

USAN

-giline **monoamine oxydase (MAO)-inhibitors type B**

C.3.1.0

(a) pargyline (13)
clorgiline (23), mofegiline (69), rasagiline (70), selegiline (39)

USAN

-gillin **antibiotics produced by *Aspergillus* strains**

S.6.0.0

(a) fumagillin (1), mitogillin (17)

(c) mitosper (24), nifungin (24)

BAN, USAN

gli (x) **antihyperglycaemics**
(previously gly-)

M.5.2./3.0 (BAN: sulphonamide hypoglycaemics)
(USAN: gli-: antihyperglycaemics)

(a) **1. sulfonamide derivatives:** gliamilide (33), glibenclamide (18), glibornuride (22), glibutimine (31), glicaramide (28), glicetanile (37), gliclazide (25), (deleted: glidanile (23)), glicondamide (44), glidazamide (24), gliflumide (33), glimepiride (53), glipalamide (62), glipizide (27), gliquidone (28), glisamuride (45), glisentide (58) (previously glipentide (27)), glisindamide (43), glisolamide (43), glisoxepide (24), glybuthiazol (8), glybuzole (15), glyclopyramide (17), glycyclamide (12), glyhexamide (15), glymidine sodium (15), glyoctamide (14), glyparamide (USAN only), glypinamide (13), glyprothiazol (8), glysobuzole (12)

2. other than sulfonamide derivatives: camiglibose (67), deriglidole (66), emiglitate (55), fasiglifam (107), imeglimin (98), ingliforib (85), isaglidole (61), limiglidole (100), linogliride (48), managlinat dialanetil (96), meglitinide (34), midaglizole (57), miglitol (55), mitiglinide (78), naglivan (65), nateglinide (77), piragliatin (97), pirogliride (40), repaglinide (65), teglicar (91), tibeglisene (64), voglibose (65)

3. peptide: seglitide (57)

(b) cromoglicate lisetil (72), cromoglicic acid (18), ioglicic acid (33), ioxaglic acid (37), sulglicotide (29) (treatment of peptic ulcers), tropigline (08)

(c) acetohexamide (12), butadiazamide (10), carbutamide (36), chlorpropamide (8), heptolamide (12), metahexamide (10), palmoxiric acid (48), thiohexamide (12), tolazamide (12), tolbutamide (6), tolpentamide (12), tolpyrramide (13)

gly- *prior to revision of the General Principles*

(a) glybuthiazol (08), glybuzole (15), glyclopyramide (17), glycyclamide (13), glyhexamide (15), glymidine sodium (15), glyoctamide (14), glypinamide (13), glyprothiazol (08), glysobuzole (12)

(c) glycerol (4), glycobiarsol (l), glycopyrronium bromide (12)

-gliflozin **sodium glucose co-transporter inhibitors, phlorizin derivatives** USAN
(USAN: phlorozin derivatives, phenolic glycosides)

atigliflozin (100), canagliflozin (102), dapagliflozin (97), empagliflozin (104), ertugliflozin (107), ipragliflozin (103), luseogliflozin (104), remogliflozin etabonate (98), sergliflozin etabonate (98), tofogliflozin (103)

-gliptin **dipeptidyl aminopeptidase–IV inhibitors** USAN
M.5.2.0

(a) alogliptin (96), anagliptin (103), bisegliptin (103), carmegliptin (98), denagliptin (94), dutogliptin (100), evogliptin (107), gemigliptin (103), gosogliptin (101), linagliptin (99), melogliptin (99), omarigliptin (107), saxagliptin (92), sitagliptin (94), teneligliptin (99), trelagliptin (106), vildagliptin (90)

-glitazar **peroxisome proliferator activating receptor-γ (PPAR-γ) agonists** USAN
M.5.2.0 (USAN: PPAR agonists (not thiazolidene derivatives))

(a) aleglitazar (95), cevoglitazar (94), farglitazar (84), imiglitazar (91), indeglitazar (100), muroglitazar (90), naveglitazar (92), oxeglitazar (88), peliglitazar (92), pemaglitazar (92), ragaglitazar (85), reglitazar (87), saroglitazar (108), sipoglitazar (93), sodelglitazar (95), tesaglitazar (85)

-glitazone **peroxisome proliferator activating receptor-γ (PPAR-γ) agonists, thiazolidinedione derivatives** USAN
M.5.2.0 (USAN: PPST agonists (thiazolidene derivatives))

(a) ciglitazone (50), balaglitazone (84), darglitazone (69), edaglitazone (91), englitazone (64), lobeglitazone (95), netoglitazone (85), pioglitazone (60), rivoglitazone (87), rosiglitazone (78), troglitazone (69)

(c) efatutazone (102)

-gliflozin **see gli**

-gliptin **see gli**

-glitazar **see gli**

-glitazone **see gli**

USAN

-glumide **cholecystokinine antagonists, antiulcer, anxiolytic agents**

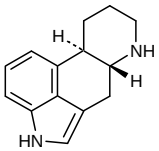
J.0.0.0/C.1.0.0

(a) amiglumide (85), dexloxiglumide (65), itriglumide (82), lorglumide (56), loxiglomide (57), proglumide (16), spiroglumide (70), tomoglumide (56)

-glutide **see tide**

-golide **dopamine receptor agonists, ergoline derivatives**

E.1.1.0



(a) adrogolide (82), naxagolide (60), pergolide (41), quinagolide (62), voxergolide (61)

(c) rotigotine (83)

-gosivir **see vir**

-gramostim **see -stim**

-grastim **see -stim**

USAN

-grel-
-grel **platelet aggregation inhibitors**

I.2.1.0 (USAN: -grel- or -grel: platelet aggregation inhibitors, primarily platelet P2Y12 receptor antagonists)

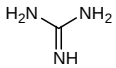
(a) anagrelide (42), camonagrel (61), cangrelor (97), clopidogrel (57), dazmegrel (51), elinogrel (101), furegrelate (53), isbogrel (59), itazigrel (56), midazogrel (53), nafagrel (64), nicogrelate (48), oxagrelate (47), ozagrel (55), pamicogrel (70), parogrelil (94),

pirmagrel (53), prasugrel (91), rafigrelide (106), regrelor (97), ridogrel (59), rolafagrel (65), samixogrel (72), sarpogrelate (63), satigrel (67), sunagrel (52), temanogrel (103), terbogrel (75), ticagrelor (95), trifenagrel (53)

USAN

guan- **antihypertensives, guanidine derivatives**

H.3.0.0



(a) guanabenz (26), guanacline (l6), guanadrel (20), guanazodine (27), guancidine (18), guanclofine (36), guanethidine (11), guanfacine (35), guanisoquine (15), guanoclor (15), guanoctine (16), guanoxan (15), guanoxabenz (31), guanoxyfen (16), guabenxan (32)

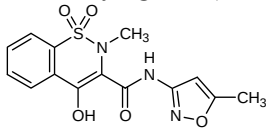
(c) guabenxan (32)

-ibine **see -ribine**

USAN

-icam **anti-inflammatory, isoxicam derivatives**

A.4.2.0 (USAN: anti-inflammatory agents (isoxicam type))



(a) ampiroxicam (56), droxicam (52), enolicam (45), isoxicam (30), lornoxicam (59),

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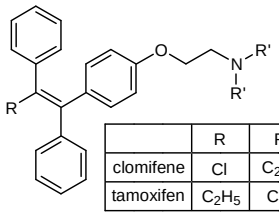
USAN

-ifene **antiestrogens or estrogen receptor modulators, clomifene and tamoxifen derivatives**

(USAN: -ifen(e): antiestrogens of the clomifene and tamoxifen groups)

(Q.2.1.0 L.6.0.0)



	R	R'
clomifene	Cl	C_2H_5
tamoxifen	C_2H_5	CH_3

(a) acolbifene (86), clomifenoxide (54), tesmilifene (81)
-oxifene: afimoxifene (95), arzoxifene (80), bazedoxifene (86), droloxifene (53), idoxifene (68), lasofoxifene (81), levormeloxifene (73), miproxifene (74), ormeloxifene (69), pipendoxifene (84), raloxifene (54), tamoxifen (28), trioxifene (41), zindoxifene (54)
-mifene: clomifene (12), enclomifene (33), fispemifene (89), nitromifene (33), ospemifene (85), panomifene (58), sivifene (99), toremifene (53), zuclomifene (33)

(b) dextropropoxyphene (7), levopropoxyphene (7), suloxifen (30) (bronchodilator)

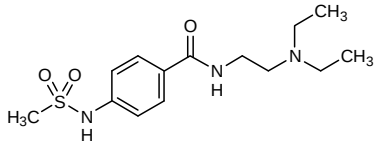
(c) nafoxidine (16)

-igetide **see -tide**

USAN

-ilide **class III antiarrhythmics, sematilide derivatives**

H.2.0.0 (USAN: class III antiarrhythmic agents)



(a) ambasilide (59), artilide (67), azimilide (72), dofetilide (65), ersentilide (72), ibutilide (63), ipazilide (62), risotilide (62), sematilide (58), trecetilide (79)

(b) bromacrylide (13), ftaxilide (32), gliamilide (33)

USAN

imex (d) **immunostimulants**

S.7.0.0

(a) azimexon (40), forfenimex (55), imexon (37), roquinimex (53), ubenimex (56)

USAN

-imibe **antihyperlipidaemics, acyl CoA: cholesterol acyltransferase (ACAT) inhibitors,**

M.3.0.0

(a) avasimibe (80), canosimibe (100), eflucimibe (84), eldacimibe (76), ezetimibe (83), lecimibide (70), octimibate (52), pactimibe (89)

USAN

-imod **immunomodulators, both stimulant/suppressive and stimulant**

S.7.0.0 (USAN: immunomodulators)

(a) agatolimod (98), apilimod (95), atiprimod (75), blisibimod (107), ceralifimod (109), cridanimod (83), defoslimod (79), entolimod (108), epetirimod (97), esonarimod (79), fingolimod (91), forigerimod (104), golotimod (97), glaspimod (74), iguratimod (86), imiquimod (66), ivarimod (60), laquinimod (85), litenimod (96), paquinimod (94), pidotimod (63), ponesimod (103), rabeximod (97), resiquimod (82), rintatolimod (102), siponimod (106), sotirimod (94), susalimod (73), tasquinimod (93), tiprotimod (57)

-mapimod **mitogen-activated protein (MAP) kinase inhibitors** USAN

(a) balamapimod (96), bentamapimod (98), dilmapimod (102), doramapimod (88), losmapimod (101), pamapimod (96), talmapimod (99), semapimod (89)

USAN

-imus **immunosuppressants (other than antineoplastics)**

S.7.0.0 (USAN: immunosuppressives)

(a) abetimus (81), anisperimus (82), gusperimus (68), laflunimus (70), manitimus (93), napirimus (60), tresperimus (75), vidofludimus (103)

-rolimus **immunosuppressants, rapamycin derivatives** USAN

(a) everolimus (82), olcorolimus (105), pimecrolimus (81), ridaforolimus (108), sirolimus (69), tacrolimus (66), temsirolimus (94), umirolimus (103), zotarolimus (94)

-ine (d) **alkaloids and organic bases**

(a) 1669 (18.9%) INNs ending in *-ine* in Lists 1-109 of proposed INNs

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-inostat **see stat**

BAN, USAN

io- (x) **iodine-containing contrast media**

U.1.1.0

(a) iobenzamic acid (14), iobitridol (68), iobutoic acid (20), iocarmic acid (22), iocetamic acid (18), iodamide (15), iodecimol (51), iodetryl (1), iodixanol (53), iodophthalein sodium (1), iodoxamic acid (26), iofendylate (12), ioforminol (103), iofratol (67), ioglicic acid (33), ioglucol (41), ioglucomide (41), ioglunide (40), ioglycamic acid (15), iohexol (43), iolidonic acid (26), iolixanic acid (26), iomeglamic acid (26), iomeprol (54), iomorinic acid (37), iopamidol (40), iopanoic acid (1), iopentol (52), iophenoic acid (4), ioprocemic acid (39), iopromide (44), iopronic acid (28), iopydol (14), iopydone (14), iosarcol (54), iosefamic acid (14), ioseric acid (33), iosimenol (88), iosimide (50), iosulamide (39), iosumetic acid (33), iotalamic acid (13), iotasul (43), iotetric acid (37), iotranic acid (28), iotriside (60), iotrizoic acid (22), iotrolan (51), iotroxic acid (32), ioversol (56), ioxabrolic acid (53), ioxaglic acid (37), ioxilan (59), ioxitalamic acid (22), ioxotrizoic acid (33), iozomic acid (24)

(c) adipiodone (4), bunamiodyl (10), dimethiodal sodium (1), diodone (1), ethyl cartrizoate (12), methiodal sodium (1), metrizamide (26), pheniodol sodium (1), phenobutiodil (6), propyl docetrizoate (10), propyliodone (1), sodium acetrizoate (4), sodium amidotrizoate (4), sodium diprotrizoate (6), sodium metrizoate (13), sodium tyropanoate (12)

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io(d)-/-io- **radiopharmaceuticals, iodine-contained**

(a) ethiodized oil (^{131}I) (24), iobenguane (^{131}I) (57), iocanlidic acid (^{123}I) (77), iodinated (^{125}I) human serum albumin (24), iodinated (^{131}I) human serum albumin (24), iodine (^{124}I) girentuximab (101), iodocetylic acid (^{123}I) (47), iodocholesterol (^{131}I) (39), iodofiltic acid (^{123}I) (95), iofolastat (^{123}I) (105), iofetamine (^{123}I) (51), ioflubenzamide (^{131}I) (103), ioflupane (^{123}I) (75), iolopride (^{123}I) (73), iomazenil (^{123}I) (66), iometin (^{125}I) (24), iometin (^{131}I) (24), iometopane (^{123}I) (76), sodium iodide (^{125}I) (24), sodium iodide (^{131}I) (24), sodium iodohippurate (^{131}I) (24), sodium iotalamate (^{125}I) (24), sodium iotalamate (^{131}I) (24)

(c) fibrinogen (^{125}I), macrosalb (^{131}I) (33), rose bengal (^{131}I) sodium (24), tolpovidone (^{131}I) (24)

USAN

-irudin **hirudin derivatives**

I.2.1.0 (USAN: anticoagulants (hirudin type))

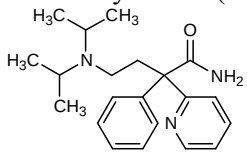
bivalirudin (72), desirudin (70), lepirudin (73), pegmusirudin (77)

USAN

-isomide **class I antiarrhythmics, disopyramide derivatives**

(USAN: -isomide: antiarrhythmics (disopyramide derivatives))

H.2.0.0



(a) actisomide (60), bidisomide (63), pentisomide (59)

(c) disopyramide (12)

BAN, USAN

-ium **quaternary ammonium compounds**

(USAN: -ium or -onium: quaternary ammonium derivatives)

E.3.0.0 **neuromuscular blocking agents with a flexible structure**

(a) azamethonium bromide (1), decamethonium bromide (1), dicolinium iodide (25), dimecolinium iodide (14), fubrogonium iodide (18), hexamethonium bromide (1), mebezonium iodide (16), oxapropanium iodide (1), oxydipentonium chloride (1), pentamethonium bromide (1), pentolonium tartrate (4), prodeconium bromide (6), stilonium iodide (32), suxamethonium chloride (1), suxethonium chloride (1), tetrylammonium bromide (1), tiametonium iodide (15), trepirium iodide (25)

(c) gallamine triethiodide (1)

E.3.0.0 **neuromuscular blocking agents with rigid structure**

(USAN: -curium, also -curonium; neuromuscular blocking agents)

(a) -curonium: alcuronium chloride (17), candocuronium iodide (70), dacuronium bromide (21), pancuronium bromide (19), pipecuronium bromide (69), rapacuronium bromide (78), rocuronium bromide (66), stercuronium iodide (21), vecuronium bromide (46)

-curium (d) (curare-like substances): atracurium besilate (42) , cisatracurium besilate (73), doxacurium chloride (58), gantacurium chloride (91), mivacurium chloride (58), truxicurium iodide (22), truxipicurium iodide (22)

-others: dimethyltubocurarinium chloride (1), fazadinium bromide (32), hexafluronium bromide (12), laudexium metilsulfate (4), pentacynium chloride (6), phenactropinium chloride (8), piprocurarium iodide (11), thiazinamium metilsulfate (37), trimethidinium methosulfate (8)

(c) tubocurarine chloride (1)

E.1.0.0 **cholinergic agents**

(a) aclatonium napadisilate (44), ambenonium chloride (6), benzpyrinium bromide (1), carpronium chloride (23), demecarium bromide (10), furtrethonium iodide (1)

(c) acetylcholine chloride (4), charbacol (4), choline alfoscerate (29), choline chloride (4), choline gluconate (1), choline salicylate (15) (analgesic), choline theophyllinate (8) (smooth muscle relaxant), methacholine chloride (1), nitricholine perchlorate (6) (antihypertensive), distigmine bromide (16), ecothiopate iodide (6), neostigmine bromide (4), obidoxime chloride (16), pralidoxime iodide (10), pyridostigmine bromide (6)

E.2.0.0 **anticholinergic agents**

(a) aclidinium bromide (100), benzilonium bromide (13), benzopyrronium bromide (12), beperidium (57), bevonium metilsulfate (19), butropium bromide (30), ciclonium bromide (19), ciclotropium bromide (50), cimetropium bromide (51), clidinium bromide (6), cyclopyrronium bromide (12), dimetipirium bromide (37), diponium bromide (15), dotefonium bromide (24), droclidinium bromide (33), emepronium bromide (18), etipirium iodide (22), fenclexonium metilsulfate (20), fenpiverinium bromide (26), fentonium bromide (29), flutropium bromide (50), glycopyrronium bromide (12), heteronium bromide (14), hexasonium iodide (15), hexocyclium metilsulfate (6), hexopyrronium bromide (13), ipratropium bromide (31), methanthelinium bromide (1), methylbenactyzium bromide (34), metocinium iodide (26), nolinium bromide (37), otilonium bromide (38), oxapium iodide (26), oxitefonium bromide (18), oxitropium bromide (36), oxyphenonium bromide (1), oxypyrronium bromide (13), oxysonium iodide (15), pentapiperium metilsulfate (26), prifinium bromide (20), ritropirronium bromide (33), sintropium bromide (47), sultroponium (18), tematropium metilsulfate (64), tiemonium iodide (13), timepidium bromide (29), tiotropium bromide (67), tiquizium bromide (47), trantelinium bromide (24), trospium chloride (25), umeclidinium bromide (106), xenytropium bromide (15)

(c) atropine methonitrate (4), buzepide metiodide (14), chlorisondamine chloride (6), diphemanil metilsulfate (4), homatropine methylbromide (1), isopropramide iodide (8), mepenzolate bromide (10), octatropine methylbromide (10), parapenzolate bromide (14), pipenzolate bromide (6), poldine metilsulfate (11), propantheline bromide (1), propyromazine bromide (12), tridihexethyl iodide (6), tropenziline bromide (11), thihexinol methylbromide (1), tricyclamol chloride (4)

S.2.3.0 **surfactants used as antibacterials and antiseptics**

(a) acriflavinium chloride (1), amantanium bromide (39), benzalkonium chloride (1), benzethonium chloride (1), benzododecinium chloride (1), benzoxonium chloride (36), cefalonium (16), cefmepidium chloride (57), cetalkonium chloride (15), cethexonium chloride (36), cetrimonium bromide (1), cetylpyridinium chloride (1), chlorphenoctium amsonate (8), deditonium bromide (15), denatonium benzoate (15), dequalinium chloride (8), disiquonium chloride (55), dodeclonium bromide (16), dofamium chloride (21), fludazonium chloride (33), furazolium chloride (15), halopenium chloride (10), hedaquinium chloride (8), lapirium chloride (27), lauralkonium chloride (62), laurcetium bromide (70), laurolinium acetate (12), mecetronium etilsulfate (51), metalkonium chloride (60), methylbenzethonium chloride (1), methylrosanilinium chloride (1), methylthioninium chloride (1), miripirium chloride (63), miristalkonium chloride (41), octafonium chloride (16), opratonium iodide (76), penoctonium bromide (20), pirralkonium bromide (19), polidronium chloride (67), polixetonium chloride (70), prolonium iodide (14), sanguinarium chloride (68), sepazonium chloride (34), tetradonium bromide (18), tibezonium iodide (32), tiodonium chloride (36), toliodium chloride (36), toloconium metilsulfate (17), tonzonium bromide (14), triclobisonium chloride (10)

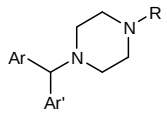
(c) domiphen bromide (23)

other agents

alagebrium chloride (91), albitiazolium bromide (101), amezinium metilsulfate (36), amprolium chloride (16), azaspirium chloride (25), bephenium hydroxynaphthoate (11), bibenzonium bromide (12), bidimazium iodide (27), bretylium tosilate (10), butopyrammonium iodide (8), carcainium chloride (36), clofilium phosphate (42), datelliptium chloride (57), detajmium bitartrate (34), dibrospidium chloride (51), ditercalinium chloride (49), edrophonium chloride (4), elliptinium acetate (43), emilium tosilate (37), enisamium iodide (101), famiraprinium chloride (58), feniodium chloride (23), gallium (^{67}Ga) citrate (33), homidium bromide (36), isavuconazonium chloride (96) isometamidium chloride (18), mefenidramium metilsulfate (52), meldonium (86), mequitamium iodide (61), nolpitantium besilate (75), pinaverium bromide (32), pirdonium bromide (28), prajmalium bitartrate (23), pranolium chloride (32), pretamazium iodide (29), propagermanium (65), prospidium chloride (22), pyritidium bromide (16), pyrvinium chloride (6), quindonium bromide (14), quinuclium bromide (40), repagermanium (63), rimazolium metilsulfate (26), roxolinium metilsulfate (33), samarium (^{153}Sm) lexidronam (74), sepantronium bromide (105), sevitropium mesilate (56), spirogermanium (43), stilbazium iodide (13), thenium closilate (12), tipetropium bromide (42), tolonium chloride (4), trazium esilate (54), trethinium tosilate (14), troxonium tosilate (13), troxypyrrolium tosilate (13)

(c) alazanine triclofenate (13) (anthelminthic), colfosceril palmitate (64) (pulmonary surfactant), dithiazanine iodide (8) (anthelminthic), hexadimethrine bromide (8) (heparin antagonist)

-izine (-yzine) **diphenylmethyl piperazine derivatives**



(a) antihistaminics: G.2.0.0: buclizine (4), cetirizine (51), chlorcyclizine (1), clocinizine (15), cyclizine (1), efletirizine (71), elbanizine (60), flotrenizine (48), levocetirizine (78), lomerizine (68), pibaxizine (62), trenizine (48)

homochlorcyclizine (10) (serotonin antagonist)

tranquillizers: etodroxizine (18), hydroxyzine (6)

various: benderizine (40) (antiarrhythmic), decloxizine (19) (respiratory insufficiency), ropizine (36) (anticonvulsant)

-rizine **antihistaminics/cerebral (or peripheral) vasodilators**

belarizine (36), buterizine (42), cinnarizine (11), dotarizine (50), flunarizine (22), lifarizine (66), tagorizine (72), tamolarizine (66), trelnarizine (62)

chemically related: pipoxizine (32) (respiratory insufficiency)

(b) phenothiazine derivatives: chloracyzine (12) (vasodilator), fluacizine (25) (sedative), moracizine (25) (antiarrhythmic), tiracizine (62) (antiarrhythmic)

benzilate esters: benactyzine (6) (tranquillizer), benaprizine (26) (anti-parkinsonian)

phenylpiperazine: dimetholizine (10) (antiallergic), dropropizine (18)/levodropropizine (64) (antitussive)
antibiotic "cef": cefatrizine (34)

pyrazine derivatives: ampyzine (15) (central nervous stimulant), triampyzine (15) (anticholinergic)

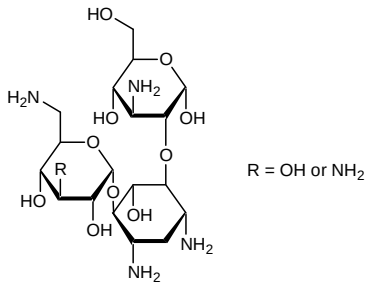
indoloquinolines (anticholinergic): metoquizine (17), toquizine (17)

(c) medibazine (16)

USAN

-kacin **antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*)**

S.6.3.0 (USAN: antibiotics obtained from *Streptomyces kanamyceticus* (related to kanamycin))



(a) amikacin (30), arbekacin (56), butikacin (4l), dibekacin (31), propikacin (43)

(c) bekanamycin (24), kanamycin (10)

other aminoglycoside antibiotics:

Strept. griseus: dihydrostreptomycin (1) (semisynthetic), streptomycin (1), streptoniazid (13) (semisynthetic)

Strept. tenebrarius: apramycin (31), nebramycin (19) (mixture of several antibiotics, including apramycin and tobramycin), tobramycin (28)

Bacillus circularis: butirosin (25)

USAN

-kalant **potassium channel blockers**

(USAN: potassium channel antagonists)

H.2.0.0

(a) adekalant (83), almokalant (64), clamikalant (81), inakalant (95), nifekalant (75), pinokalant (82), terikalant (66), vernakalant (96)

BAN, USAN

-kalim **potassium channel activators, antihypertensive**

(USAN: potassium channel agonists)

H.3.0.0

(a) aprikalim (64), bimakalim (64), cromakalim (58), levcromakalim (66), emakalim (66), mazokalim (75), rilmakalim (65), sarakalim (81)

USAN

-kef- **enkephalin agonists**

(USAN: enkephalin agonists (various indications))

casokefamide (65), frakefamide (81), metenkefalin (97), metkefamide (44)

USAN

-kin **interleukin type substances**

S.7.0.0

(a)

IL-1 :	*-nakin*	interleukin-1 analogues and derivatives *-onakin:* interleukin-1 α analogues and derivatives: pifonakin (77) *-benakin:* interleukin-1 β analogues and derivatives: mobenakin (72)
IL-2 :	*-leukin*	interleukin-2 analogues and derivatives: adargileukin alfa (89), aldesleukin (63), celmoleukin (65), denileukin diftitox (78), teceleukin (54) pegaldesleukin (74), tucotuzumab celmoleukin (95)
IL-4 :	*-trakin*	interleukin-4 analogues and derivatives: binetrakin (82)
IL-6 :	*-exakin*	interleukin-6 analogues and derivatives: atexakin alfa (72)
IL-8 :	*-octakin*	interleukin-8 analogues and derivatives: emoctakin (74)
IL-10 :	*-decakin*	interleukin-10 analogues and derivatives: ilodecakin (81)
IL-11 :	*-elvekin*	interleukin-11 analogues and derivatives: oprelvekin (76)
IL-12 :	*-dodekin*	interleukin-12 analogues and derivatives: edodekin alfa (79)
IL-13:	*-tredekin*	interleukin-13 analogues and derivatives: cintredekin besudotox (92)
IL-18 :	*-octadekin*	interleukin-18 human analogues and derivatives: iboctadekin (92) tadekinig alfa (90) (fraction of IL-18 human)
Il-21	*-enicokin*	interleukin -21 human analogues and derivatives: denenicokin (99)

(c) IL-3: *-plestim***:** interleukin-3 analogues and derivatives:
muplestim (72), daniplestim (76)

USAN

-kinra **interleukin receptor antagonists**

S.7.0.0

IL-1	*-nakinra*	interleukin-1 receptor antagonists: anakinra (72)
IL-4	*-trakinra*	interleukin-4 receptor antagonists: pitrakinra (84)

		USAN
-kiren	**renin inhibitors**	
H.3.0.0		
(a)	aliskiren (83), ciprokiren (69), ditekiren (62), enalkiren (61), remikiren (66), terlakiren (66), zankiren (70)	
-lefacept	**see -cept**	
-leukin	**see -kin**	
		USAN
-lisib	**phosphatidylinositol 3-kinase inhibitors, antineoplastics**	
L.0.0.0	(USAN: phosphatidylinositol 3-kinase inhibitors)	
	acalisib (109), apitolisib (108), buparlisib (106), copanlisib (108), dactolisib (107), idelalisib (107), panulisib (109), pictilisib (107), pilaralisib (108), recilisib (108)	
-listat	**see -stat**	
		USAN
-lubant	**leukotriene B_4 receptor antagonists**	
U.3.0.0	(USAN: leukotriene receptor antagonists (treatment of inflammatory skin disorders))	
(a)	amelubant (85), moxilubant (78), ticolubant (76)	
-lukast	**leukotriene receptor antagonists, see -ast**	
		USAN
-lutamide Q.2.3.1	**non-steroid antiandrogens**	
(a)	bicalutamide (70), enzalutamide (107), flutamide (33), nilutamide (56), topilutamide (91)	
(b)	aceglutamide (15)	
-lutril	**see -tril**	

BAN, USAN

-mab **monoclonal antibodies** (see also Annex 3)

S.7.0.0

-amab rat origin

-emab hamster origin

-imab primate origin

-omab **mouse origin:**

b(a) bacterial: edobacomab (69)

co(l) colon: edrecolomab (74), nacolomab tafenatox (71)

go(v) ovary (tumours): abagovomab (95), igovomab (74), oregovomab (86)

l(i) lymphocyte: afelimomab (72), dorlimomab aritox (66), elsilimomab (89), enlimomab (70), enlimomab pegol (77), faralimomab (76), gavilimomab (84), inolimomab (71), maslimomab (66), nerelimomab (76), odulimomab (73), telimomab aritox (66), vepalimomab (80), zolimomab aritox (69)

c(i) cardiovascular: biciromab (66), imciromab (66)

le(s) inflammatory lesions: besilesomab (92), lemalesomab (84), sulesomab (75), technetium (^{99m}Tc) fanolesomab (86)

pr(o) tumour (prostate): capromab (70)

t(u) tumour (miscellaneous): altumomab (68), anatumomab mafenatox (79), arcitumomab (74), bectumomab (75), blinatumomab (100), detumomab (70), epitumomab (82), epitumomab cituxetan (89), ibritumomab tiuxetan (81), minretumomab (80), mitumomab (82), moxetumomab pasudotox (102), naptumomab estafenatox (96), racotumomab (100), satumomab (67), solitomab (106), taplitumomab paptox (84), technetium (^{99m}Tc) nofetumomab merpentan (76), technetium (^{99m}Tc) pintumomab (75), tenatumomab (98), tositumomab (80)

Others: catomaxomab (92), ertumaxomab (92)

-umab **human origin:**

b(a) bacterial: nebacumab (66), raxibacumab (92)

c(i) cardiovascular: alirocumab (107), enoticumab (107), evolocumab (108), icrucumab (104), inclacumab(106), nesvacumab (108), orticumab (107), ramucirumab (100), vesencumab (104)

f(u) fungal: efungumab (95)

k(i) interleukin: briakinumab (101), canakinumab (97), fezakinumab (101), guselkumab (109), secukinumab (102), sirukumab (105), tralokinumab (102), ustekinumab (99)

l(i) immunomodulator: adalimumab (82), anifrolumab (109), atorolimumab (80), belimumab (89), bertilimumab (88), brodalumab (105), carlumab (104), dupilumab (108), eldelumab (109), foralumab (103), fresolimumab (101), golimumab (91), ipilimumab (94), lerdelimumab (83), lirilumab (107), mavrilimumab (102), metelimumab (86), morolimumab (79), namilumab (104), nivolumab (107), oxelumab (103), placulumab (107), sarilumab (106), sifalimumab (101), tabalumab (105), tremelimumab (97), urelumab (104), zanolimumab (90), ziralimumab (84)

n(e) neural: atinumab (104), fasinumab (107), fulranumab (104), gantenerumab (108)

s(o) bone: denosumab (94)

tox(a) toxin as target: actoxumab (107), bezlotoxumab (107), tosatoxumab (109)

t(u) tumour: adecatumumab (90), anetumab ravtansine (109), cixutumumab (100), conatumumab (99), daratumumab (101), drozitumab (103), duligotumab (107), dusigitumab (108), enfortumab vedotin (109), figitumumab (100), flanvotumab (106), ganitumab (103), glembatumumab (102), intetumumab (101), iratumumab (94), lexatumumab (95), lucatumumab (98), mapatumumab (93), narnatumab (105), necitumumab (100), ofatumumab (93), olaratumab (103), patritumab (106), panitumumab (96), pritumumab (89), radretumab (104), rilotumumab (101), robatumumab (100), seribantumab (108), tarextumab (109), teprotumumab (108), tovetumab (109), vantictumab (109), votumumab (70), zalutumumab (93), yttrium (^{90}Y) clivatuzumab tetraxetan (102)

v(i) viral: exbivirumab (91), foravirumab (99), libivirumab (91), rafivirumab (99), regavirumab (71), sevirumab (66), suvizumab (102), tuvirumab (66)

Other: bimagrumab (108), stamulumab (94), roledumab (103)

-ximab **chimeric origin**

b(a) bacterial: pagibaximab (93)

c(i) cardiovascular: abciximab (70), volociximab (93)

l(i) immunomodulator: basiliximab (76), clenoliximab (77), galiximab (89), infliximab (77), keliximab (76), lumiliximab (90), priliximab (72), teneliximab (87), vapaliximab (87)

me(l) melanoma: ecromeximab (87)

t(u) tumor: amatuximab (104), bavituximab (95), brentuximab vedotin (103), cetuximab (82), coltuximab ravtansine (109), dinutuximab (109), ensituximab (103), futuximab (107), girentuximab (101), indatuximab ravtansine (105), iodine (^{124}I) girentuximab (101), margetuximab (109), pritoxaximab (108), rituximab (77), setoxaximab (108), siltuximab (100), ublituximab (104), zatuximab (107)

-xizumab **chimeric/humanized**: otelixizumab (98), ontuxizumab (109)

-zumab **humanized origin**

anib angiogenesis inhibitor: ranibizumab (90)

b(a) bacterial: tefibazumab (92)

c(i) cardiovascular: alacizumab pegol (98), bevacizumab (83), caplacizumab (106), concizumab (108), demcizumab (107), etaracizumab (99), idarucizumab (109), lodelcizumab (108), tadocizumab (94)

k(i) interleukin: anrukinzumab (98), clazakizumab (107), enokizumab (104), gevokizumab (104), ixekizumab (105), lebrikizumab (101), olokizumab (103), perakizumab (108), tildrakizumab (108)

l(i) lymphocyte: apolizumab (87), aselizumab (88), benralizumab (102), cedelizumab (77), certolizumab pegol (90), daclizumab (78) (previously: dacliximab), eculizumab (87), efalizumab (85), erlizumab (84), etrolizumab (104), fontolizumab (87), ibalizumab (97), itolizumab (103), lambrolizumab (109), lampalizumab (107), ligelizumab (107), mepolizumab (81), mogamulizumab (104), natalizumab (79), ocrelizumab (94), omalizumab (84), ozoralizumab (105), palivizumab (79), pascolizumab (87), pateclizumab (105), pexelizumab (85), pidilizumab (108), quilizumab (106), reslizumab (85), rontalizumab (101), rovelizumab (81), ruplizumab (83), samalizumab (103), siplizumab (87), talizumab (89), teplizumab (97), tocilizumab (90), toralizumab (87), tregalizumab (104), vatelizumab (105), vedolizumab (100), visilizumab (84)

n(e) neural: bapineuzumab (93), crenezumab (105), ozanezumab (108), ponezumab (104), solanezumab (107), tanezumab (99)

s(o) bone: blosozumab (105), romosozumab (106)

tox(a) toxin as target: urtoxazumab (90)

t(u) tumor: (miscellaneous): abituzumab (109), alemtuzumab (83), bivatuzumab (83), cantuzumab mertansine (105), cantuzumab ravtansine (105), citatuzumab bogatox (99), codrituzumab (109), dacetuzumab (98), dalotuzumab (107), elotuzumab (100), enavatuzumab (104), epratuzumab (82), farletuzumab (100), ficlatuzumab (105), gemtuzumab (83), imgatuzumab (107), inotuzumab ozogamicin (92), labetuzumab (85), lintuzumab (76), lorvotuzumab mertansine

(103), matuzumab (88), milatuzumab (98), nimotuzumab (94), obinutuzumab (109), ocaratuzumab (107), onartuzumab (104), oportuzumab monatox (100), parsatuzumab (107), pertuzumab (89), pinatuzumab vedotin (108), polatuzumab vedotin (108), sibrotuzumab (81), simtuzumab (107), sontuzumab (94), tigatuzumab (98), trastuzumab (78), trastuzumab emtansine (103), tucotuzumab celmoleukin (94), veltuzumab (98), vorsetuzumab (107), vorsetuzumab mafodotin (107), yttrium (^{90}Y) tacatuzumab tetraxetan (93)

v(i) viral: felvizumab (77), motavizumab (95)

(c) muromonab CD3 (59)

USAN

-mantadine
-mantine
-mantone **adamantane derivatives**

(USAN: -mantadine or -mantine: antivirals/antiparkinsonians (adamantane derivatives))

(a) antiviral: S.5.3.0: amantadine (15), rimantadine (17), somantadine (51), tromantadine (28)

antiparkinsonian: E.2.0.0: carmantadine (31), dopamantine (31), memantine (35)

immunostimulant: S.7.0.0: idramantone (71)

(b) anthelminthic: S.3.l.0: dimantine (14)

(c) adafenoxate (48) (nootropic agent), adamexine (36) (mucolytic), adapalene (64) (antiacne agent), adaprolol (63) (ß-adrenoreceptor antagonist), adatanserin (70) (serotonin receptor antagonist), amantanium bromide (39) (disinfectant), amantocillin (17) (antibiotic), arterolane (97) (antimalarial), bolmantalate (16) (anabolic), meclinertant (88) (neurotensin antagonist), mantabegron (88) (β_3-adrenoreceptor agonist), saxagliptin (92) (antidiabetic), vildagliptin (90) (antidiabetic)

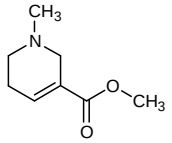
-mapimod **see -imod**

-mastat **see -stat**

USAN

-meline **cholinergic agents (muscarine receptor agonists/partial antagonists used in the treatment of Alzheimer's disease)**

E.1.0.0 (USAN: cholinergic agonists (arecoline derivatives used in the treatment of Alzheimer's disease))



alvameline (79), cevimeline (76), itameline (77), milameline (74), sabcomeline (76), tazomeline (77), xanomeline (70)

mer- or -mer- (d)	**[1]mercury-containing drugs, antimicrobial or diuretic**
(a)	S.2.2.0 antimicrobial: meralein sodium (13), merbromin (1), mercurobutol (1), otimerate sodium (51), phenylmercuric borate (4), sodium timerfonate (13), thiomersal (1)
	[1]*mer-* and *-mer-* can be used for any type of substances and are no longer restricted to use in INNs for mercury-containing drugs
	N.1.3.0 diuretic: chlormerodrin (4), chlormerodrin (^{l97}Hg) (24), meralluride (1), mercaptomerin (1), mercuderamide (1), mercumatilin sodium (4), mercurophylline (1), merisoprol (^{l97}Hg) (24) (diagnostic), mersalyl (4)
(b)	difemerine (17) (spasmolytic), dimercaprol (1) (antidote, -SH group), lomerizine (68), (cerebral vasodilator), mercaptopurine (6) (cytostatic, -SH group), nifurmerone (16), pemerid (25), suxemerid (25) (antitussive)
(c)	hydrargaphen (10)

	USAN
-mer	**polymers**
(a)	amilomer (33), azoximer bromide (97), bixalomer (103), cadexomer (60), carbetimer (50), carbomer (21), crilanomer (53), dextranomer (33), eldexomer (60), exatecan alideximer (89), firtecan peglumer (108), hemoglobin glutamer (80), hemoglobin raffimer (89), leuciglumer (68), maletamer (14), ompinamer (108), patiromer calcium (106), poloxamer (34), porfimer sodium (64), sevelamer (77), surfomer (44), tolevamer (88), zinostatin stimalamer (74)
(b)	succimer (42)

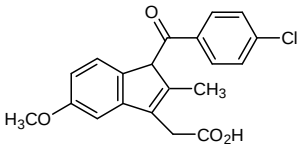
	USAN
-mesine	**sigma receptor ligands**
	cutamesine (100), igmesine (68), panamesine (73), siramesine (81)

	USAN
-mestane	**aromatase inhibitors**
L.0.0.0 /Q.2.1.0	(USAN: antineoplastics, aromatase inhibitors)
	atamestane (54), exemestane (65), formestane (66), minamestane (64), plomestane (66)

BAN; USAN

-metacin (x) **anti-inflammatory, indometacin derivatives**

A.4.2.0 (BAN: anti-inflammatory substances of the indomethacin group)
(USAN: -metacin: anti-inflammatory substances (indomethacin type))



(a) acemetacin (32), cinmetacin (24), clometacin (27), delmetacin (48) (originally demetacin (42)), duometacin (27), glucametacin (32), indometacin (13), niometacin (33), oxametacin (37), pimetacin (47), proglumetacin (35), sermetacin (36), talmetacin (46), zidometacin (39)

other anti-inflammatory, indole derivatives: etoprindole (22), indopine (12), indoxole (17), nictindole (28)

-met(h)asone **see pred**

USAN

-micin **aminoglycosides, antibiotics obtained from various *Micromonospora***

(S.6.5.0) (USAN: antibiotics (*Micromonospora* strains))

astromicin (44), betamicin (38), etisomicin (47), evernimicin (82), fidaxomicin (109), gentamicin (22), isepamicin (54), maduramicin (52), megalomicin (37), micronomicin (45), mirosamicin (58), netilmicin (36), ozogamicin (83), pentisomicin (41), plazomicin (106), repromicin (37), rosaramicin (41) (prev. rosamicin), semduramicin (60), sisomicin (25)

-mifene **see -ifene**

-milast **see -ast**

mito- (d) **antineoplastics, nucleotoxic agents**
L.0.0.0

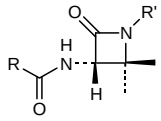
(a) mitobronitol (20), mitocarcin (25), mitoclomine (18), mitoflaxone (60), mitogillin (17), mitoguazone (20), mitolactol (26), mitomalcin (19), mitomycin (26), mitonafide (40), mitopodozide (17), mitoquidone (54), mitosper (24), mitotane (21), mitotenamine (17), mitoxantrone (44), mitozolomide (51)

(c) mitindomide (48)

USAN

-monam **monobactam antibiotics**

S.6.0.0



(a) carumonam (51), gloximonam (54), oximonam (54), pirazmonam (58), tigemonam (57)

(c) aztreonam (48)

-morelin **see -relin**

-mostat **see -stat**

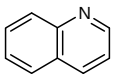
USAN

-mostim **see -stim**

USAN

-motine **antivirals, quinoline derivatives**

S.5.3.0



(a) famotine (23), memotine (22)

USAN

-moxin (d) **monoamine oxidase inhibitors, hydrazine derivatives**

C.3.l.0

(a) benmoxin (20), cimemoxin (17), domoxin (14), octamoxin (15)

(c) carbenzide (11), etryptamine (12), fenoxypropazine (12), iproclozide (13), iproniazid (1), isocarboxazid (11), mebanazine (15), nialamide (10), pargyline (13), phenelzine (10), pheniprazine (11), tranylcypromine (11)

USAN

-mulin **antibacterials, pleuromulin derivatives**

S.6.0.0

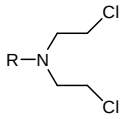
(a) azamulin (54), pleuromulin (35), retapamulin (91), tiamulin (35), valnemulin (74)

(b) nonathymulin (56), thymostimulin (45)

USAN

-mustine **antineoplastic, alkylating agents, (β-chloroethyl)amine derivatives**

L.2.0.0 (USAN: antineoplastic agents (chlorethylamine derivatives))



(a) alestramustine (68), ambamustine (60), atrimustine (61), bendamustine (48), bofumustine (44), carmustine (24), ditiomustine (49), ecomustine (61), elmustine (49), estramustine (24), fotemustine (57), galamustine (61), laromustine (98), lomustine (27), mannomustine (8), neptamustine (48) (originally pentamustine (45)), nimustine (37), prednimustine (31), ranimustine (55), semustine (27), spiromustine (47), tallimustine (68), tauromustine (50), uramustine (13)

(c) canfosfamide (92), chlorambucil (6), chlormethine (1), chlornaphazine (1), cyclophosphamide (10), defosfamide (12), glufosfamide (77), ifosfamide (23), mafosfamide (51), melphalan (8), melphalan flufenamide (105), metamelfalan (41), mitoclomine (18), mitotenamine (17), palifosfamide (99), perfosfamide (66), sarcolysin (17), sufosfamide (36), trichlormethine (11), trofosfamide (23)

BAN, USAN

-mycin (x) **antibiotics, produced by *Streptomyces* strains (see also -kacin)**

S.6.0.0 (USAN: antibiotics, *Streptomyces* strains)

(a) alvespimycin (96), amfomycin (12), antelmycin (15), apramycin (31), avilamycin (46), azalomycin (26), azithromycin (58), bambermycin (21), bekanamycin (24), berythromycin (26), bicozamycin (38), biniramycin (23), bluensomycin (14), capreomycin (12), carbomycin (1), cethromycin (87), clarithromycin (59), clindamycin (21), coumamycin (15), daptomycin (58), dihydrostreptomycin (1), diproleandomycin (33), dirithromycin (53), efrotomycin (53), endomycin (6), enramycin (23), enviomycin (31), erythromycin (4), estomycin (14 - deleted in List 28), flurithromycin (51), fosfomycin (25), fosmidomycin (46), gamithromycin (95), ganefromycin (68), hachimycin (23), heliomycin (25), hydroxymycin (8 - deleted in List 28), josamycin (23), kanamycin (10), kitasamycin (13), laidlomycin (61), lexithromycin (65), lincomycin (13), lividomycin (32), maridomycin (32), midecamycin (30), mikamycin (17), mirincamycin (31), mocimycin (28), modithromycin (101), natamycin (15), nebramycin (19), neomycin (1), neutramycin (15), oleandomycin (6), paldimycin (55), paromomycin (10), paulomycin (47), pirlimycin (47), primycin (38), pristinamycin (12), ranimycin (20), relomycin (15), retaspimycin (99), ribostamycin (27), rifamycin (13), rokitamycin (53), roxithromycin (54), salinomycin (37), sedecamycin (55), solithromycin (104), spectinomycin (13), spiramycin (6), stallimycin (30), steffimycin (20), streptomycin (1), surotomycin (107), tanespimycin (96), telithromycin (80), terdecamycin (65), tobramycin (28), troleandomycin (24), trospectomycin (53), tulathromycin (87) (vet.), vancomycin (6), viomycin (4), virginiamycin (l8)

antibiotics, antineoplastics:
ambomycin (13), antramycin (17), azotomycin (13), bleomycin (23), cactinomycin (15), dactinomycin (18), duazomycin (13), lucimycin (13), mitomycin (26), nogalamycin (16),

olivomycin (18), peliomycin (15), peplomycin (44), plicamycin (50) (previously mithramycin (16)), porfiromycin (15), puromycin (15), rufocromomycin (12), sparsomycin (13), talisomycin (41)

antibiotics, antineoplastics, antibacterial:
cirolemycin (21)

antibiotic, antifungal:
hamycin (17), lidimycin (20), rutamycin (14)

(c) antibiotic, antibacterial:
aspartocin (11), azidamfenicol (14), cetofenicol (14), chloramphenicol (1), cloramfenicol pantotenate complex (14), cycloserine (6), novobiocin (6), ostreogrycin (6), rifamide (15), rifampicin (17), streptoniazid (13), streptovarycin (6), thiamphenicol (10), tylosin (16)

antibiotic, antifungal:
amphotericin B (10), candicidin (17), filipin (20), kalafungin (20), nystatin (6), viridofulvin (16)

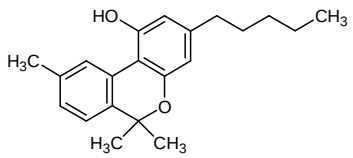
antibiotic, antineoplastic:
daunorubicin (20), mitomalcin (19), streptonigrin (14) (deleted in List 33)

see also -rubicin

USAN

nab **cannabinoid receptors agonists**

(USAN: -nab; or -nab-: cannabinol derivatives)



(a) cannabinol (23), dronabinol (51), menabitan (49), nabazenil (49), nabilone (49), nabitan (42), naboctate (45), nonabine (47), pirnabin (41), tedalinab (103), tinabinol (49)

(b) fenabutene (26), guanabenz (26), muromonab-CD3 (59), nabumetone (44), prinaberel (95)

USAN

-nabant **cannabinoid receptors antagonists**

E.0.0.0

(a) drinabant (99), giminabant (107), ibipinabant (99), otenabant (99), rimonabant (83), rosonabant (97), surinabant (93), taranabant (97)

-nacept **see -cept**

-nakin **see -kin**

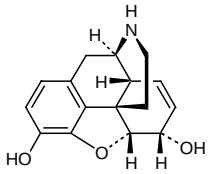
-nakinra **see -kinra**

USAN

nal- **opioid receptor antagonists/agonists related to normorphine**

A.4.1.0
B.2.0.0

(USAN: narcotic agonists/antagonists (normorphine type))



a) methylnaltrexone bromide (96), nalbuphine (21), naldemedine (105), nalfurafine (87), nalmefene (49) (originally nalmetrene (47)), nalmexone (19), nalorphine (1), naloxegol (105), naloxone (13), naltalimide (107), naltrexone (29)

(b) nalidixic acid (13), naluzotan (101)

-naritide **see -tide**

-navir **see vir**

-nermin **see -ermin**

-nercept **see -cept**

-nertant **see -tant**

-netant **see -tant**

-nicate **see nico-**

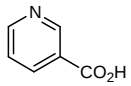
USAN

-nicline **nicotinic acetylcholine receptor partial agonists / agonists**

E.1.1.2

(a) altinicline (82), dianicline (93), facinicline (105), ispronicline (93), pozanicline (100), rivanicline (93), sofinicline (100), tebanicline (86), varenicline (89)

nico- or nic- or ni- **nicotinic acid or nicotinoyl alcohol derivatives**



P.7.0.0

nico-: nicoboxil (43), nicoclonate (29), nicocodine (12), nicocortonide (40), nicodicodine (15), nicofibrate (31), nicofuranose (14), nicofurate (28), nicomol (23), nicomorphine (7), nicopholine (1), nicorandil (44), nicothiazone (10), nicotinamide (4), nicotinic acid (4), nicotredole (72), nicoxamat (44), nikethamide (4)

inositol nicotinate (16), xantinol nicotinate (16)

nic-: nicafenine (40), nicainoprol (46), nicametate (15), nicardipine (42), nicanartine (72), nicergoline (26), niceritrol (23), niceverine (15), nictindole (28), nizofenone (44)
ni-: nialamide (10), niaprazine (24), nifenazone (15), niometacin (33), niprofazone (29), nixylic acid (17)

-nicate: **antihypercholesterolaemic and/or vasodilating nicotinic acid esters**
H.4.0.0
F.2.2.0

(a) ciclonicate (33), derpanicate (58), estrapronicate (34), glunicate (51), hepronicate (22), micinicate (44), pantenicate (56), sorbinicate (33)

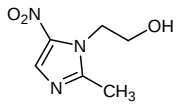
(b) nitrile derivative: nimazone (21)
other: nifungin (24), nimidane (34), nisbuterol (38)

(c) **NO_2 - derivatives**: acenocoumarol (6) (anticoag.), azathioprine (12) and tiamiprine (15) (antimetabolites), bronopol (14) (antiseptic), chloramphenicol (1) (antibiotic), clonazepam (22) (sed.), flurantel (25) (anthelmintic), flutamide (33) (nonsteroid anti-androgen)

BAN, USAN

-nidazole (x) **antiprotozoals and radiosensitizers, metronidazole derivatives**

S.3.3.0 (USAN: antiprotozoal substances (metronidazole type))
Y.0.0.0



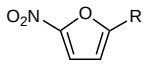
(a) abunidazole (52), azanidazole (38), bamnidazole (37), benznidazole (31), carnidazole (32), doranidazole (90), etanidazole (57), fexinidazole (37), flortanidazole (^{18}F) (108), flunidazole (21), ipronidazole (21), metronidazole (11), misonidazole (38), moxnidazole (33), ornidazole (28), panidazole (24), pimonidazole (57), pirinidazole (32), propenidazole (45), ronidazole (18), satranidazole (48), secnidazole (30), sulnidazole (33), ternidazole (34), tinidazole (21), tivanidazole (48)

(c) dimetridazole (17), nimorazole (22), stirimazole (25)

-nidine **see -onidine**

USAN

nifur- (d) **5-nitrofuran derivatives**

S.2.1.0 

(a) nifuradene (16), nifuraldezone (17), nifuralide (34), nifuratel (17), nifuratrone (24), nifurdazil (16), nifurethazone (10), nifurfoline (20), nifurimide (18), nifurizone (22), nifurmazole (22), nifurmerone (16), nifuroquine (36), nifuroxazide (14), nifuroxime (11), nifurpipone (20), nifurpirinol (22), nifurprazine (16), nifurquinazol (18), nifursemizone (16), nifursol (20), nifurthiazole (14), nifurtimox (21), nifurtoinol (36), nifurvidine (17), nifurzide (37)

(c) furalazine (13), furaltadone (17), furazolidone (13), furazolium chloride (15), furmethoxadone (8), levofuraltadone (17), nidroxyzone (6), nihydrazone (10), nitrofural (1), nitrofurantoin (11), thiofuradene (11)

-nil **see -azenil, also for -carnil, -quinil**

nitro- or nitr- or nit- or ni- or -ni- **NO_2 - derivatives**

nifur- all INN of this series (see under nifur-)

nitro-: nitroclofene (41), nitrocycline (14), nitrodan (15), nitrofural (1), nitrofurantoin (11), nitromifene (33), nitroscanate (33), nitrosulfathiazole (1), nitroxinil (19), nitroxoline (15)

nitr-: nitracrine (35), nitrafudam (40), nitramisole (33), nitraquazone (53), nitrazepam (16), nitrefazole (46), nitricholine perchlorate (6)

nit- and -nit-: nitarsone (17), ranitidine (41)

ni-: nibroxane (35), niclofolan (20), niclosamide (13), nidroxyzone (6), nifenalol (22), nihydrazone (10), nimesulide (44), nimorazole (22), niridazole (17)

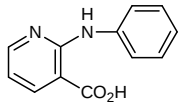
ni-dipine: nicardipine (42), nifedipine (27), niludipine (38), nisoldipine (42), nitrendipine (42), vatamidipine (77)

-nidazole: for INNs of this series see under –nidazole

USAN

-nixin **anti-inflammatory, anilinonicotinic acid derivatives**

A.4.2.0



(a) butanixin (32), clonixin (22), diclonixin (31), flunixin (31), isonixin (34), metanixin (31)

(c) clonixeril (22), niflumic acid (17), nixylic acid (17)

(-)nonacog **see -cog**

-octakin **see -kin**

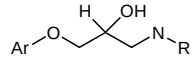
(-)octocog **see -cog**

-ol (d) **for alcohols and phenols**

BAN; USAN

-olol (x) **β-adrenoreceptor antagonists**

E.5.2.0 (BAN: beta-adrenoreceptor antagonists)
(USAN: beta-blockers (propranolol type))



aromat. ring -O-CH_2-CHOH-CH_2-NH-R

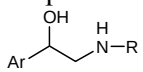
(a) acebutolol (28), adaprolol (63), adimolol (50), afurolol (40), alprenolol (19), ancarolol (47), arnolol (56), arotinolol (48), atenolol (33), befunolol (39), betaxolol (40), bevantolol (36), bisoprolol (48), bometolol (42), bopindolol (42), bornaprolol (46), bucindolol (43), bucumolol (35), bufetolol (30), bunitrolol (28), bunolol (22), bupranolol (27), butocrolol (38), butofilolol (40), carazolol (36), carpindolol (42), carteolol (35), celiprolol (35), cetamolol (47), cicloprolol (48), cinamolol (44), cloranolol (41), crinolol (41) (replaced by pacrinolol (44)), dexnebivolol (98), dexpropranolol (21), diacetolol (41), draquinolol (54), ecastolol (56), epanolol (52), ericolol (50), esatenolol (76), esmolol (50), exaprolol (32), falintolol (53), flestolol (53), flusoxolol (50), idropranolol (31), imidolol (49) (replaced by adimolol (50)), indenolol (37), indopanolol (48), iprocrolol (39), isoxaprolol (45), landiolol (75), levobetaxolol (61), levobunolol (42), levomoprolol (58), levonebivolol (98), mepindolol (36), metipranolol (38), metoprolol (30), moprolol (36), nadolol (34), nadoxolol (28), nafetolol (39), nebivolol (56), nipradilol (50) (previously nipradolol (49)), oxprenolol (20), pacrinolol (44), pafenolol (46), pamatolol (36), pargolol (36), penbutolol (25), penirolol (36), pindolol (23), pirepolol (48), practolol (23), primidolol (42), procinolol (25), propranolol (15), ridazolol (51), ronactolol (57), soquinolol (43), spirendolol (46), talinolol (28), tazolol (31), teoprolol (43), tertatolol (48), tienoxolol (56), tilisolol (57), timolol (29),

tiprenolol (23), tolamolol (29), toliprolol (28), trigevolol (56), xibenolol (48), xipranolol (22), zoleprodolol (102)

(b) Q.2.3.0: stanozolol (18) (anabolic steroid)

-alol **aromatic ring -CH-CH_2-NH-R related to -ols**
OH

E.5.2.0 (USAN: combined alpha and beta blockers)



(a) amosulalol (50), bendacalol (59), brefonalol (56), bufuralol (31), dexsotalol (74), dilevalol (50), labetalol (35), medroxalol (43), nifenalol (22), pronetalol (14), sotalol (18), sulfinalol (41)

(c) butidrine (16)

USAN

-olone **see pred**

-onakin **see -kin**

-one (d) **ketones**

(a) 638 (approx. 7.3 %) INNs ending in *-one* in Lists 1-109 of proposed INNs

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BAN, USAN

-onide **steroids for topical use, acetal derivatives**

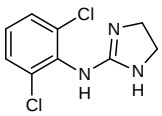
Q.3.0.0

(a) acrocinonide (27), amcinonide (33), budesonide (37), ciclesonide (62), cicortonide (28), ciprocinonide (38), desonide (24), dexbudesonide (80), drocinonide (29), fluclorolone acetonide (22), fluocinolone acetonide (11), flumoxonide (38), fluocinonide (25), halcinonide (29), itrocinonide (62), nicocortonide (40), procinonide (38), rofleponide (72), tralonide (27), triamcinolone benetonide (36), triamcinolone furetonide (36), triamcinolone hexacetonide (15), triclonide (30)

(c) amcinafal (25), amcinafide (25)

-onidine **antihypertensives, clonidine derivatives**

H.3.0.0



(a) apraclonidine (59) (control of intraocular pressure), benclonidine (42), brimonidine (66), clonidine (40), flutonidine (31), moxonidine (48), piclonidine (44), tolonidine (28)
related: alinidine (40) (analgesic)

-nidine
H.3.0.0

(a) related antihypertensives: betanidine (13), indanidine (50), rilmenidine (57), tiamenidine (28)

(b) muscle relaxant: tizanidine (43)
topical anti-infective: octenidine (43), pirtenidine (57)
antibacterial: sulfaguanidine (4)
vetirinary coccidiostatic: robenidine (25)

(c) dexlofexidine (48), levlofexidine (48), lofexidine (33)

-onium **see -ium**

-opamine **see -dopa**

BAN; USAN

-orex **anorexics**

M.1.0.0 (BAN: anorexic agents, phenethylamine derivatives)
(USAN: anorexiants)

(a) acridorex (21), amfepentorex (16), aminorex (14), benfluorex (25), clobenzorex (18), cloforex (16), clominorex (14), difemetorex (41), etolorex (20), fenisorex (29), fenproporex (17), flucetorex (30), fludorex (19), fluminorex (14), formetorex (14), furfenorex (16), indanorex (30), mefenorex (19), morforex (26), oxifentorex (20), pentorex (16), picilorex (40), tiflorex (34)

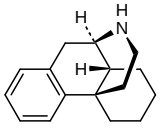
(b) almorexant (98), filorexant (108), suvorexant (105)

(c) bupropion (84) (replaces amfebutamone (31)), amfecloral (12), amfepramone (13), amfetamine (55), amfetaminil (40), benzfetamine (55), brolamfetamine (55), chlorphentermine (11), clortermine (22), dexamfetamine (55), dexfenfluramine (54), dimetamfetamine (38), etilamfetamine (40), fenbutrazate (12), fenfluramine (14), hexapradol (12), levamfetamine (12), levmetamfetamine (83), levofenfluramine (57), lisdexamfetamine (94), mephentermine (6), ortetamine (13), phendimetrazine (11), phenmetrazine (6), phentermine (11)

USAN

orphan **opioid receptor antagonists/agonists, morphinan derivates**

A.4.l.0
B.2.0.0 (USAN: -orphan, -orphan-: narcotic antagonists/agonists (morphinan derivatives))



(a) A.4.1.0: butorphanol (31), dextromethorphan (1), dextrorphan (1), dimemorfan (30), ketorfanol (49), levomethorphan (1), levophenacylmorphan (9), levorphanol (4),

methylsamidorphan chloride (109), norlevorphanol (9), oxilorphan (31), phenomorphan (5), proxorphan (43), racemethorphan (1), racemorphan (1), samidorphan (107), xorphanol (48)

B.2.0.0: levallorphan (2)

-orph- **-orphine**: acetorphine (17), alletorphine (25), buprenorphine (29), cyprenorphine (17), desomorphine (5), diprenorphine (21), etorphine (17), homprenorphine (25), methyldesorphine (5), methyldihydromorphine (5), morphine glucuronide (92), nalorphine (1), nicomorphine (7), normorphine (7)

-orphinol: hydromorphinol (11)

-orphone: conorfone (46), hydromorphone (1), oxymorphone (5), pentamorphone (60), semorphone (67)

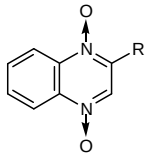
(b) emorfazone (44), morforex (26), morpheridine (6), orphenadrine (8)

-otermin **see -ermin**

-ox **antacids, aluminium derivatives** (see also -aldrate)
-alox

(a) glucalox (13), sucralox (13)

(b) *-dox* antibacterials, quinazoline dioxide derivatives:
(USAN: -adox: antibacterials (quinoline dioxide derivatives))

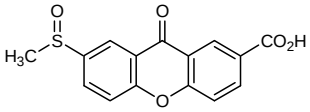


carbadox (19), ciadox (44), cinoquidox (40), drazidox (24), mequidox (19), olaquindox (31), temodox (27)

-pirox antimycotics, pyridone derivatives: USAN

ciclopirox (26), metipirox (26), rilopirox (56)

-xanox antiallergics, tixanox group:
(USAN: antiallergic respiratory tract drugs (xanoxic acid derivatives))



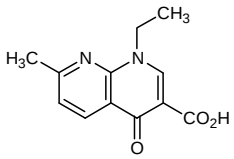
amlexanox (55), mepixanox (49), sudexanox (44), tixanox (37), traxanox (44)

others: acipimox (33) (antihyperlipidaemic), bifeprunox (87) (antipsychotic), cefminox (53) (antibiotic), deferasirox (86) (chelating agent), etofenprox (57) (insecticide), nifurtimox (21) (antiprotozoal), pardoprunox (96) (antiparkinsonian), sulbenox (37) (animal growth regulator), xanoxic acid (33) (bronchodilator)

BAN, USAN

-oxacin (x) **antibacterials, nalidixic acid derivatives**

S.5.5.0 (BAN: antibacterial agents of the cinoxacin group)
(USAN: antibacterial (quinolone derivatives))



(a) cinoxacin (32), droxacin (36), fleroxacin (56), enoxacin (49), garenoxacin (87), irloxacin (53), miloxacin (40), nemonoxacin (96), ozenoxacin (96), rosoxacin (36), tioxacin (34)
-floxacin: alatrofloxacin (75), amifloxacin (51), avarofloxacin (109), balofloxacin (71), besifloxacin (98), binfloxacin (60), cadrofloxacin (81), cetefloxacin (68), ciprofloxacin (50), clinafloxacin (67), danofloxacin (61), delafloxacin (100), difloxacin (55), ecenofloxacin (78), enrofloxacin (56), esafloxacin (60), fandofloxacin (78), finafloxacin (85), gatifloxacin (74), gemifloxacin (81), grepafloxacin (68), ibafloxacin (60), levofloxacin (64), levonadifloxacin (95), lomefloxacin (58), marbofloxacin (65), merafloxacin (69), moxifloxacin (78), nadifloxacin (64), norfloxacin (46), ofloxacin (49), olamufloxacin (79), orbifloxacin (68), pazufloxacin (71), pefloxacin (45), pradofloxacin (84), premafloxacin (72), prulifloxacin (72), rufloxacin (57), sarafloxacin (62), sitafloxacin (75), sparfloxacin (63), temafloxacin (58), tosufloxacin (60), trovafloxacin (73), ulifloxacin (89), vebufloxacin (69), zabofloxacin (93)

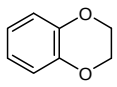
(b) itarnafloxin (103)

(c) flumequine (34), nalidixic acid (13), oxolinic acid (15), pipemidic acid (32), piromidic acid (27), metioxate (34)

USAN

-oxan(e) **benzodioxane derivatives**

E.5.1.0 (USAN: -oxan or -oxane: α-adrenoreceptor antagonists; benzodioxane derivatives)



(a) **α-adrenoreceptor antagonists:** azaloxan (52) (antidepressant), fluparoxan (58) (antidepressant), idazoxan (49) (α_2), imiloxan (52) (α_2) (antidepressant), piperoxan (1) (sympatholytic), proroxan (39)
antihypertensives: flesinoxan (55), guabenxan (32), guanoxan (15)
tranquillizers: butamoxane (12), ethomoxane (12), pentamoxane (12)
muscle relaxant: ambenoxan (21)

oxa, axa, ox: acoxatrine (14) (cardiovascular analeptic), axamozide (53) (neuroleptic), cinepaxadil (50) (coronary vasodilator), dioxadilol (53) (slight ß-adrenoreceptor antagonist), domoxin (14), doxazosin (47), enoxamast (52) (antiallergic), spiroxatrine (14) (analgesic)
related: dexefaroxan (76) (β-adrenoreceptor antagonist), efaroxan (59) (α_2)

(b) amoproxan (22), nibroxane (35), razoxane (40), dexrazoxane (62), sobuzoxane (62), tolboxane (12)

(c) aplindore (92), bendacalol (59), binospirone (65), capeserod (94), eltoprazine (57), lecozotan (93), lurtotecan (50), osemozotan (87), quincarbate (31), silibinin (38), sulamserod (82)

USAN

-oxanide **see -anide**

USAN

-oxef **see cef-**

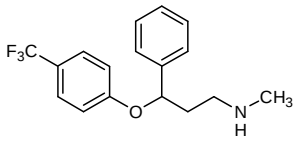
-oxepin **see -pine**

USAN

-oxetine **serotonin and/or norepinephrine reuptake inhibitors, fluoxetine derivatives**

(USAN: antidepressants (fluoxetine type))

C.3.0.0



(a) atomoxetine (86), ansoxetine (58), dapoxetine (65), duloxetine (68), edivoxetine (104), esreboxetine (99), femoxetine (36), fluoxetine (34), ifoxetine (54), litoxetine (64), nisoxetine (34), omiloxetine (76), paroxetine (38), reboxetine (54), seproxetine (66), tedatioxetine (107), vortioxetine (107)

-oxicam **see -icam**

-oxifene **see -ifene**

-oxopine **see -pine**

BAN; USAN

-pafant **platelet-activating factor antagonists**

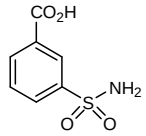
I.2.1.0

(a) apafant (60), bepafant (60), dacopafant (63), foropafant (75), israpafant (76), lexipafant (70), minopafant (80), modipafant (65), nupafant (70), rocepafant (71), setipafant (72), tulopafant (64)

USAN

-pamide **diuretics, sulfamoylbenzoic acid derivatives (could be sulfamoylbenzamide)**

N.1.2.0 (USAN: diuretics (sulfamoylbenzoic acid derivatives))



(a) alipamide (18), besulpamide (52), clopamide (13), indapamide (29), tripamide (44), xipamide (22), zidapamide (50) (previously isodapamide (47))

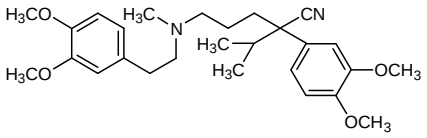
(b) chlorpropamide (8) (hypoglycemic), isopropamide iodide (8) (anticholinergic)

(c) bumetanide (24), chlortalidone (12), clorexolone (15), furosemide (14), sulclamide (15), tiamizide (16)

USAN

-pamil **calcium channel blockers, verapamil derivatives**

F.2.1.0 (USAN: coronary vasodilators (verapamil type))



(a) anipamil (49), dagapamil (52), devapamil (53), dexverapamil (65), emopamil (52), falipamil (48), gallopamil (38), levemopamil (62), nexopamil (67), ronipamil (51), tiapamil (43), verapamil (16)

related: bertosamil (64), bisaramil (60)

USAN

-parcin **glycopeptide antibiotics**

S.6.0.0

(a) avoparcin (29), orientiparcin (72)

USAN

-parib **poly-ADP-ribose polymerase inhibitors**

L.0.0.0 iniparib (103), niraparib (107), olaparib (94), rucaparib (105), veliparib (102)

USAN

-parin **heparin derivatives including low molecular mass heparins**

I.2.0.0 (USAN: heparin derivatives and low molecular weight (or depolymerized) heparins)

(a) adomiparin sodium (104), ardeparin sodium (68), bemiparin sodium (75), certoparin sodium (70), dalteparin sodium (64), deligoparin sodium (89), enoxaparin sodium (52), heparin sodium (54), livaraparin calcium (85), minolteparin sodium (73), nadroparin calcium (65), parnaparin sodium (65), reviparin sodium (65), semuloparin sodium (99), sevuparin sodium (107), tafoxiparin sodium (102), tinzaparin sodium (65)

-parinux **synthetic heparinoids**

(USAN: antithrombotic indirect selective synthetic factor Xa inhibitors)

(a) fondaparinux sodium (83) (replaces fondaparin sodium (79)), idrabiotaparinux sodium (97), idraparinux sodium (84)

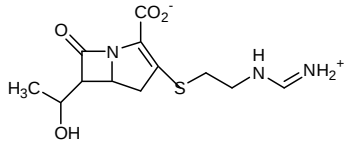
-patril/-patrilat **see -tril/-trilat**

-pendyl **see -dil**

USAN

-penem **analogues of penicillanic acid antibiotics modified in the five-membered ring**

S.6.0.0 (USAN: antibacterials, antibiotics (carbapenem derivatives))



(a) biapenem (69), doripenem (83), ertapenem (84), faropenem (69), imipenem (50), lenapenem (73), meropenem (60), panipenem (64), razupenem (101), ritipenem (67), sulopenem (68), tacapenem (87), tebipenem pivoxil (82), tomopenem (95)

USAN

perfl(u)- **perfluorinated compounds used as blood substitutes and/or diagnostic agents**

(USAN: blood substitutes and/or diagnostics (perfluorochemicals))

(a) perflenapent (78), perflexane (82), perflisobutane (92), perflisopent (78), perfluamine (45), perflubrodec (87), perflubron (66), perflubutane (91) perflunafene (45), perflutren (82)

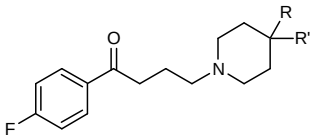
-peridol **see -perone**

-peridone **see -perone**

USAN

-perone **tranquillizers, neuroleptics, 4'-fluoro-4-piperidinobutyrophenone derivatives**

C.1.0.0
C.2.0.0 (USAN: antianxiety agents/neuroleptics ; 4'-fluoro-4-piperidinobutyrophenone derivatives)



(a) aceperone (14), amiperone (14), biriperone (51), carperone (24), cicarperone (28), cinuperone (53), cloroperone (38), declenperone (42), duoperone (54), fenaperone (28), fluspiperone (34), lenperone (27), melperone (34), metrenperone (56), milenperone (37), mindoperone (38), moperone (14), nonaperone (44), pipamperone (17), pirenperone (46), prideperone (54), primaperone (17), propyperone (16), roxoperone (17), setoperone (51), spiperone (17), timiperone (40)

closely related: azabuperone (34), azaperone (18), lodiperone (44), zoloperone (39)

USAN

-peridol **antipsychotics, haloperidol derivatives**

benperidol (14), bromperidol (33), [clofluperol (18)], droperidol (14), [fluanisone (13)], haloperidol (10), trifluperidol (16)

USAN

-peridone **antipsychotics, risperidone derivatives**

abaperidone (80), belaperidone (78), cloperidone (17), iloperidone (69), lusaperidone (82), ocaperidone (64), paliperidone (83), risperidone (57), tioperidone (37)

(c) domperidone (36), etoperidone (36) (antiemetic)

USAN

-pidem **hypnotics/sedatives, zolpidem derivatives**

C.1.0.0

alpidem (53), necopidem (66), saripidem (67), zolpidem (53)

USAN

-pin(e) **see also Pharm S/Nom 970 (tricyclic compounds)**

-dipine see *-dipine*

(a) dosulepin (15)

-zepine antidepressant/neuroleptic: C.3.2.0: dibenzepin (14), elanzepine (35), enprazepine (30), erizepine (54), mezepine (22), nuvenzepine (59), prazepine (15), propizepine (19), tilozepine (40)

	tricyclic antiulcer: J.0.0.0: darenzepine (52), pirenzepine (30), siltenzepine (63), telenzepine (50), zolenzepine (48)
	tricyclic anticonvulsant: A.3.1.0: carbamazepine (15), eslicarbazepine (91), etazepine (51), licarbazepine (81), oxcarbazepine (41), rispenzepine (63)
	hyperthermia: amezepine (42)
-apine	psychoactive: C.0.0.0: amoxapine (25), asenapine (87), batelapine (64), clotiapine (16), clozapine (22), esmirtazapine (93), flumezapine (47), fluperlapine (46), loxapine (22), metiapine (22), mirtazapine (61), olanzapine (67), pentiapine (56), perlapine (23), quetiapine (74), rilapine (52), serazapine (63), tenilapine (52), zicronapine (100)
-cilpine	antiepileptic: A.3.1.0: dizocilpine (60)
-oxepin	beloxepin (75), cidoxepin (17), doxepin (15), maroxepin (54), metoxepin (33), pinoxepin (18), savoxepin (56), spiroxepin (32)
-oxopine	traboxopine (58)
-sopine	adosopine (63)
-tepine	citatepine (54), clorotepine (29), damotepine (27), metitepine (27), tropatepine (28)
(b)	atromepine (15), noscapine (7), prozapine (14)
(c)	clobenzepam (25), homopipramol (20), opipramol (15)

USAN

-piprant	**prostaglandin receptors antagonists, non-prostanoids** (USAN: prostaglandin receptors antagonists, non prostinoid structure)
K.0.0.0	asapiprant (109), fevipiprant (109), laropiprant (97), setipiprant (104), vidupiprant (104)

-piprazole	**see -prazole**

-pirone	**see -spirone**

USAN

-pirox	**see -ox/-alox**

-pitant	**see -tant**

USAN

-plact	**platelet factor 4 analogues and derivatives**
	iroplact (74)

USAN

-pladib	**phospholipase A_2 inhibitors**
W.0.0.0	darapladib (94), ecopladib (90), efipladib (92), giripladib (96), goxalapladib (94), rilapladib (94), varespladib (87)

		USAN
-planin	glycopeptide **antibacterials (*Actinoplanes* strains)**	
S.5.0.0	(USAN: antibacterials (*Actinoplanes* strains))	
	actaplanin (34), mideplanin (66), ramoplanin (57), teicoplanin (48)	
-plase	**see -teplase, -uplase under -ase**	
-plasmid	**see -gene** for gene therapy products (See also Annex4)	
		USAN
-platin (x)	**antineoplastic agents, platinum derivatives**	
L.0.0.0	(USAN: antineoplastics (platinum derivatives))	
(a)	carboplatin (48), cisplatin (39), dexormaplatin (64), enloplatin (64), eptaplatin (83), iproplatin (51), lobaplatin (65), miboplatin (66), miriplatin (85), nedaplatin (67), ormaplatin (63), oxaliplatin (56), picoplatin (87), satraplatin (80), sebriplatin (68), spiroplatin (48), triplatin tetranitrate (87), zeniplatin (63)	
-plermin	**see -ermin**	
-plestim	**see -stim and -kin**	
		USAN
-plon	**imidazopyrimidine or pyrazolopyrimidine derivatives, used as anxiolytics, sedatives, hypnotics**	
A.2.2.0 C.1.0.0	(USAN: non-benzodiazepine anxiolytics, sedatives, hypnotics)	
	adipiplon (98), divaplon (61), fasiplon (61), indiplon (86), lorediplon (105), ocinaplon (72), panadiplon (65), taniplon (61), zaleplon (72)	
		BAN, USAN
-poetin (x)	**erythropoietin type blood factors**	
I.3.0.0	(USAN: erythropoietins)	
(a)	darbepoetin alfa (85), epoetin alfa (62), epoetin beta (62), epoetin delta (85), epoetin gamma (67), epoetin epsilon (72), epoetin kappa (97), epoetin omega (73), epoetin theta (95), epoetin zeta (92)	

USAN

-porfin **benzoporphyrin derivatives**

(a) exeporfinium chloride (105), lemuteporfin (91), padeliporfin (96), padoporfin (93), rostaporfin (83), stannsoporfin (79), talaporfin (84), temoporfin (70), verteporfin (71)

-poride **Na^+/H^+ antiport inhibitor**

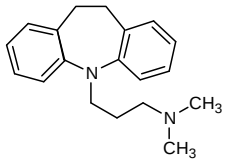
H.3.0.0

amiloride (18), cariporide (74), eniporide (79), rimeporide (92), sabiporide (84), zoniporide (85)

BAN, USAN

-pramine **substances of the imipramine group**

C.3.2.0 (USAN: antidepressants (imipramine type))



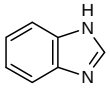
(a) <u>saturated dibenzazepine</u>:
azipramine (36), carpipramine (16), cianopramine (47), ciclopramine (29), clocapramine (28), clomipramine (17), depramine (31), desipramine (13), imipramine (8), ketimipramine (17), lofepramine (24), lopramine (24) (replaced by lofepramine (34)), metapramine (34), mosapramine (64), quinupramine (32), tampramine (54), tienopramine (38), trimipramine (13), imipraminoxide (36)

(c) <u>unsaturated dibenzazepine</u>:
carbamazepine (15), homopipramol (20), opipramol (15)

USAN

-prazole **antiulcer, benzimidazole derivatives**

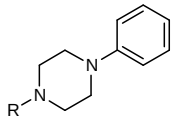
J.0.0.0 (USAN: antiulcer agents (benzimidazole derivatives))



(a) cinprazole (34), dexlansoprazole (93), disuprazole (56), esaprazole (45), esomeprazole (79), fuprazole (39), ilaprazole (86), lansoprazole (60), leminoprazole (68), levolansoprazole (93), nepaprazole (74), nilprazole (37), omeprazole (46), pantoprazole (62), picoprazole (46), pumaprazole (76), rabeprazole (69), saviprazole (62), tenatoprazole (80), timoprazole (35), ufiprazole (58)

-piprazole **psychotropics, phenylpiperazine derivatives** *(Future use is discouraged due to conflict with the stem –prazole)*

C.0.0.0

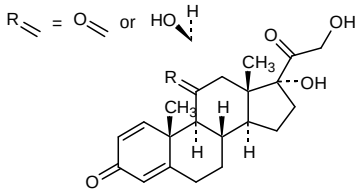


(a) aripiprazole (75), brexpiprazole (107), dapiprazole (45), elopiprazole (70), enpiprazole (24), lorpiprazole (60), mepiprazole (24), sonepiprazole (80), tolpiprazole (25)

USAN

pred **prednisone and prednisolone derivatives**

Q.3.3.0 (USAN: pred-; -pred- or -pred: prednisone and prednisolone derivatives)



(a) chloroprednisone (12), cloprednol (31), difluprednate (21), domoprednate (47), etiprednol dicloacetate (88), fluprednidene (19), fluprednisolone (13), halopredone (36), isoflupredone (36), isoprednidene (24), loteprednol (64), mazipredone (32), meprednisone (15), methylprednisolone (8), methylprednisolone aceponate (52), methylprednisolone suleptanate (56), oxisopred (29), prednazate (16), prednazoline (22), prednicarbate (44), prednimustine (31), prednisolamate (13), prednisolone (6), prednisolone steaglate (16), prednisone (6), prednylidene (13), tipredane (54)

(b) <u>various non-steroidal compounds</u>
citiolone (23) (hepatobil. troubles), clorexolone (15) (diuretic), fenozolone (14) (psychotonic), tioxolone (16) (keratolytic), vistatolon (25) (antiviral)

(c) **-betasol**: clobetasol (26), doxibetasol (26), ulobetasol (54)

(c) **-methasone or -metasone**: alclometasone (41), amelometasone (74), beclometasone (17), betamethasone (11), betamethasone acibutate (26), cormetasone (29), desoximetasone (20), dexamethasone (8), dexamethasone acefurate (57), dexamethasone cipecilate (94), flumetasone (13), halometasone (41), icometasone enbutate (70), mometasone (56), paramethasone (12)

(c) **-olone**: <u>steroids not used as glucocorticosteroids</u>
(USAN: steroids (*not* prednisolone derivatives))
bardoxolone (101), clocortolone (16), descinolone (17), diflucortolone (18), fluclorolone acetonide (22), fluocinolone acetonide (11), fluocortolone (15), fluorometholone (8), fluperolone (13), halocortolone (31), rimexolone (38), triamcinolone (8), triamcinolone benetonide (36), triamcinolone furetonide (36), triamcinolone hexacetonide (15)

(c) clobetasone (26), cloticasone (52), deprodone (20), dichlorisone (10), diflorasone (30), flunisolide (11), fluticasone (52), fluticasone furoate (96), meclorisone (40), timobesone (51)

-olone

A.1.2.0 general anesthetics, pregnanes: alfadolone (27), alfaxalone (27), eltanolone (65), ganaxolone (76), minaxolone (39), renanolone (8), sepranolone (107)

H.2.0.0 antiarrhythmic: amafolone (40), edifolone (56)

H.4.0.0 antihyperlipidaemic: colestolone (59)

J.0.0.0 glycyrrhetic acid derivatives: carbenoxolone (15), cicloxolone (33), cinoxolone (33), deloxolone (51), enoxolone (15), roxolonium metilsulfate (33)

L.6.0.0 cytostatics - sex hormones: drostanolone (13), trestolone (25)

Q.2.3.0 androgens: androstanolone (4), drostanolone (13), mestanolone (10), metenolone (12), nandrolone (22), norethandrolone (6), oxandrolone (12), oxymetholone (11)

Q.2.3.1 oxendolone (42), mesterolone (15), rosterolone (59)

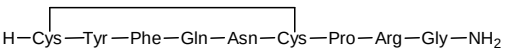
M.4.1.0 bolone (see bol, anabolic steroids): formebolone (31), mesabolone (29), metribolone (17), oxabolone cipionate (14), quinbolone (14), roxibolone (40), stenbolone (17), tibolone (22), trenbolone (24)

-prenaline **see –terol**

USAN

-pressin **vasoconstrictors, vasopressin derivatives**

Q.1.2.0



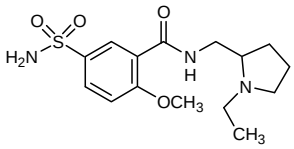
(a) argipressin (13), desmopressin (33), felypressin (13), lypressin (13), ornipressin (22), selepressin (105), terlipressin (46), vasopressin injection (16)

-previr **see vir**

BAN; USAN

-pride **sulpiride derivatives**

C.0.0.0
J.1.0.0



(a) C.0.0.0: alizapride (43), alpiropride (49), amisulpride (44), batanopride (61), broclepride (43), cisapride (49), dazopride (50), denipride (58), etacepride (52), eticlopride (52), flubepride (35), nemonapride (63) (previously emonapride (61)), peralopride (43), prosulpride (43), prucalopride (78), sulmepride (43), sultopride (26), sulverapride (44), veralipride (43)

J.1.0.0: alepride (40), bromopride (27), cinitapride (41), cipropride (41), clebopride (32), dobupride (57), irolapride (55), isosulpride (36), itopride (66), lintopride (65), lirexapride (74), lorapride (44), mezacopride (56), mosapride (66), naronapride (104), pancopride (62), raclopride (52), remoxipride (49), renzapride (60), revexepride (108), tiapride (28), ticalopride (83), tinisulpride (44), trazolopride (51), tropapride (48), zacopride (55)

K.0.0.0: cloxacepride (42)

U.1.1.0/C.0.0.0: iolopride (^{123}I) (73)

(b) glimepride (66)

(c) C.0.0.0: levosulpiride (63), sulpiride (18)

J.1.0.0: metoclopramide (17)

BAN, USAN

-pril (x) **angiotensin-converting enzyme inhibitors**

H.3.0.0 (BAN: inhibitors of angiotensin-converting enzyme)
(USAN: antihypertensive (ACE inhibitors))

(a) alacepril (50), benazepril (58), captopril (39), ceronapril (64), cilazapril (53), delapril (54), enalapril (46), fosinopril (56), idrapril (66), imidapril (60), indolapril (50), libenzapril (58), lisinopril (50), moexipril (60), moveltipril (58), orbutopril (57), pentopril (53), perindopril (53), pivopril (52), quinapril (54), ramipril (52), rentiapril (55), spirapril (56), temocapril (64), trandolapril (53), utibapril (63), zabicipril (58), zofenopril (51)

-prilat (x) USAN

(USAN: antihypertensives (ACE inhibitors) (diacid analogs of the -pril entity))

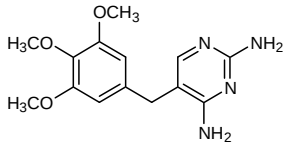
(a) benazeprilat (58), cilazaprilat (54), enalaprilat (50), fosinoprilat (62), imidaprilat (71), moexiprilat (67), perindoprilat (56), quinaprilat (60), ramiprilat (53), spiraprilat (60), temocaprilat (78), trandolaprilat (60), utibaprilat (65), zabiciprilat (64), zofenoprilat (63)

USAN

-prim **antibacterials, dihydrofolate reductase (DHFR) inhibitors, trimethoprim derivatives**

(USAN: antibacterials (trimethoprim type))

S.5.5.0



(a) aditoprim (49), baquiloprim (56), brodimoprim (44), epiroprim (44), iclaprim (88), metioprim (42), ormetoprim (21), talmetoprim (41), tetroxoprim (33), trimethoprim (11), vaneprim (48)

(c) diaveridine (18)

USAN

-pris- **steroidal compounds acting on progesterone receptors (excluding *-gest-* compounds)**

Q.2.0.0 (USAN: -prisnil: selective progesterone receptor modulators (SPRM); -pristone: progesterone receptor antagonists)

(a) aglepristone (70), asoprisnil (88), asoprisnil ecamate (89), lilopristone (54), lonaprisan (97), mifepristone (54), onapristone (58), telapristone (103), toripristone (61), ulipristal (107), vilaprisan (109)

(c) epristeride (69), saprisartan (72), and the stem *-pristin* selected for antibacterials, streptogramins, protein-synthesis inhibitors, pristinamycin derivatives

USAN

-pristin **antibacterials, streptogramins, protein-synthesis inhibitors, pristinamycin derivatives**

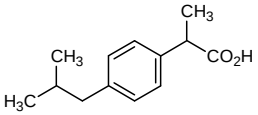
S.6.0.0 (USAN: antibacterials, pristinamycin derivatives)

(a) dalfopristin (67), efepristin (75), flopristin (98), quinupristin (65), linopristin (98), volpristin (80)

BAN; USAN

-profen (x) **anti-inflammatory agents, ibuprofen derivatives**

A.4.2.0 (USAN: anti-inflammatory/analgesic agents (ibuprofen type))



(a) alminoprofen (40), araprofen (65), atliprofen (74), bakeprofen (61), benoxaprofen (34), bermoprofen (57), bifeprofen (57), carprofen (35), cicloprofen (32), cliprofen (32), dexibuprofen (61), dexindoprofen (49), dexketoprofen (70), esflurbiprofen (56), fenoprofen (26), flunoxaprofen (44), fluprofen (18), flurbiprofen (28), frabuprofen (51), furaprofen (42), furcloprofen (44), hexaprofen (30), ibuprofen (16), indoprofen (32), isoprofen (40), ketoprofen (28), lobuprofen (53), lonaprofen (44), losmiprofen (61), loxoprofen (50), mabuprofen (64), mexoprofen (33), miroprofen (44), odalprofen (66), pelubiprofen (76), piketoprofen (40), pirprofen (32), pranoprofen (38), suprofen (31), tazeprofen (50), tetriprofen (29), tilnoprofen arbamel (74), tioxaprofen (39), vedaprofen (72), ximoprofen (37), zaltoprofen (64), zoliprofen (55)

(b) aprofene (12) (antispasm. coron. vasodil.), diprofene (12) (antispasm. blood vessels)

(c) brofezil (31), protizinic acid (27), tiaprofenic acid (30)

BAN, USAN

prost (x) **prostaglandins**

Q.0.0.0 (USAN: -prost- or -prost: prostaglandins)

(a) alfaprostol (45), alprostadil (39), ataprost (62), beraprost (106), bimatoprost (85), butaprost (55), carboprost (36), cicaprost (54), ciprostene (51), clinprost (68), cloprostenol (33), cobiprostone (98), delprostenate (42), dimoxaprost (52), dinoprost (26), dinoprostone (26), doxaprost (34), ecraprost (83), eganoprost (84), enisoprost (50), epoprostenol (44), eptaloprost (56), etiproston (46), fenprostalene (42), flunoprost (53), fluprostenol (33), froxiprost (55), gemeprost (42), iloprost (48) (originally ciloprost (46)), lanproston (72), latanoprost (67), latanoprostene bunod (107), limaprost (56), lubiprostone (89), luprostiol (44), meteneprost (45), misoprostol (47), naxaprostene (58), nileprost (45), nobiprostolan (109), nocloprost (51), oxoprostol (44), penprostene (37), pimilprost (71), piriprost (51), posaraprost (97), prostalene (34), remiprostol (65), rivenprost (93), rosaprostol (48), sulprostone (37), taprostene (58), tiaprost (41), tafluprost (89), tilsuprost (51), tiprostanide (48), travoprost (80), treprostinil (87), unoprostone (66), vapiprost (58), viprostol (53)

-prostil **prostaglandins, anti-ulcer**

(a) arbaprostil (35), deprostil (32), enprostil (50), mexiprostil (52), ornoprostil (56), rioprostil (49), spiriprostil (63), trimoprostil (49)

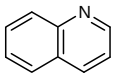
USAN

-quidar **drugs used in multidrug resistance; quinoline derivatives**

L.0.0.0 (USAN: multidrug resistance inhibitors (quinoline derivatives))

dofequidar (88), laniquidar (85), tariquidar (86), zosuquidar (86)

-quine (d) **quinoline derivatives**



(a) antimalarial: amodiaquine (1), amopyroquine (8), bulaquine (82), chloroquine (4), ferroquine (95), hydroxychloroquine (8), mefloquine (33), moxipraquine (26), pamaquine (4), pentaquine (4), primaquine (1), quinocide (34), tafenoquine (80), tebuquine (49)

acequinoline (22), actinoquinol (15), aminoquinol (22), amquinate (21), amiquinsin (17), aminoquinuride (45), benzoxiquine (18), broquinaldol (17), buquineran (40), buquinolate (16), clamoxyquine (16), cletoquine (20), chlorquinaldol (1), cinoquidox (40), ciproquinate (22), clioquinol (16), cloquinate (11), cloxiquine (30), debrisoquine (15), decoquinate (20), diiodohydroxyquinoline (1), esproquine (3l), flumequine (34), guanisoquine (l5), hedaquinium chloride (8), intiquinatine (99), iquindamine (34), isotiquimide (49), leniquinsin (18), mebiquine (29), nequinate (22), nifuroquine (36), olaquindox (31), oxamniquine (28), peraquinsin (29), pirquinozol (43), proquinolate (17), quinaldine blue (17), quincarbate (31), quindecamine (15), quindoxin (26), quinetalate (16), quinfamide (40), quinisocaine (4), quinprenaline (17), quinuclium bromide (40), quipazine (17), sitamaquine (80), tilbroquinol (45), tiliquinol (45), tiquinamide (35), tiquizium bromide (47), toquizine (17), tretoquinol (21), viquidil (25)

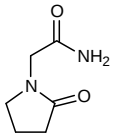
(c) broxaldine (12), cinchocaine (1), cinchophen (l), climiqualine (33), dehydroemetine (15), dequalinium chloride (8), dimethyltubocurarinium chloride (1), dimoxyline (1), drotaverine (17), ethaverine (4), euprocin (22), famotine (23), flucarbril (14), glafenine (15), laudexium metilsulfate (4), laurolinium acetate (12), memotine (22), metofoline (12), neocinchophen (l), niceverine (15), nitroxoline (15), noscapine (7), octaverine (18), oxolinic acid (15), oxycinchophen (6), pyrvinium chloride (6), trethinium tosilate (14), tritoqualine (14), tubocurarine chloride (1)

-quinil **see -azenil**

BAN; USAN

-racetam **amide type nootrope agents, piracetam derivatives**

B.1.0.0 (BAN: substances of the piracetam group)
(USAN: nootropics (learning, cognitive enhancers) piracetam type)



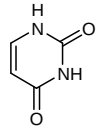
(a) aloracetam (62), aniracetam (44), brivaracetam (93), cebaracetam (66), coluracetam (86), dimiracetam (68), doliracetam (53), dupracetam (38), etiracetam (40), fasoracetam (79), fonturacetam (104), imuracetam (42), levetiracetam (62), molracetam (55), nebracetam (62), nefiracetam (64), nicoracetam (63), oxiracetam (43), piracetam (22), pramiracetam (46), rolziracetam (54), seletracetam (93)

related: tenilsetam (51)

USAN

-racil **uracil type antineoplastics**

L.0.0.0



(a) eniluracil (77), fluorouracil (13), gimeracil (80), oteracil (80)

-thiouracil **uracil derivatives used as thyroid antagonists**

M.7.3.0 (USAN: -uracil: uracil derivatives used as thyroid antagonists and as antineoplastics)

(a) iodothiouracil (01), methylthiouracil (01), propylthiouracil (01)

BAN; USAN

-relin (x) **pituitary hormone-release stimulating peptides**

Q.0.0.0 (BAN: hypophyseal hormone release-stimulating peptides)
(USAN: prehormones or hormone-release stimulating peptides)

(a) LHRH-release-stimulating peptides: avorelin (74), buserelin (36), deslorelin (61), gonadorelin (32), goserelin (55), histrelin (53), leuprorelin (47), lutrelin (51), nafarelin (50), peforelin (93), triptorelin (56), zoptarelin doxorubicin (107)

-morelin growth hormone release-stimulating peptides: USAN

(a) anamorelin (97), capromorelin (83), dumorelin (59), examorelin (72), ipamorelin (78), lenomorelin (106), macimorelin (100), pralmorelin (77), rismorelin (74), sermorelin (56), tabimorelin (80), tesamorelin (96), ulimorelin (103)

(c) somatorelin (57)

-tirelin thyrotropin releasing hormone analogues: USAN

(a) azetirelin (60), fertirelin (42), montirelin (58), orotirelin (58), posatirelin (60), protirelin (31), rovatirelin (107), taltirelin (75)

other: corticorelin (64) (diagnostic agent)

(c) thyrotropin alfa (78) (thyrotropin releasing hormone (TRH) analog)

USAN

-relix **gonadotropin-releasing-hormone (GnRH) inhibitors, peptides**

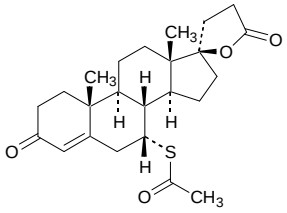
Q.0.0.0 (USAN: -relix: hormone-release inhibiting peptides)

(a) abarelix (78), cetrorelix (66), degarelix (86), detirelix (56), ganirelix (65), iturelix (79), ozarelix (94), prazarelix (81), ramorelix (69), teverelix (78)

USAN

-renone **aldosterone antagonists, spironolactone derivates**

N.1.8.0 (USAN: aldosterone antagonists (spironolactone type))



(a) canrenoic acid (20) and potassium canrenoate (20), canrenone (20), dicirenone (50), drospirenone (63), finerenone (108), eplerenone (77), mespirenone (51), spirorenone (45)

(b) bromchlorenone (12) (antifungal), menatetrenone (28) (antihemorrhagic), teprenone (50), ubidecarenone (48) (in congestive heart failure)

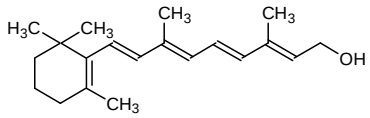
(c) oxprenoate potassium (53), prorenoate potassium (32), spironolactone (11), spiroxasone (14)

-restat **see -stat**

USAN

retin **retinol derivatives**

P.1.0.0 (USAN: -retin- or -retin: retinol derivatives)



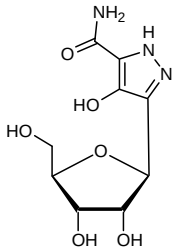
(a) acitretin (56) (previously etretin (51)), alitretinoin (80), doretinel (60), etretinate (41), fenretinide (51), isotretinoin (41), motretinide (38), pelretin (60), peretinoin (98), retinol (18), tretinoin (25), tretinoin tocoferil (66)

(b) noretynodrel (13), secretin (1), trethinium tosilate (14)

USAN

-ribine **ribofuranyl-derivatives of the "pyrazofurin" type**

L.0.0.0/
S.5.3.0



(a) azaribine (19), cladribine (68), isatoribine (83), loxoribine (64), mizoribine (46), triciribine (46)

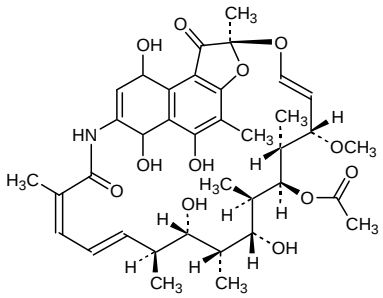
(c) pirazofurin (31), ribavirin (31), riboprine (20), tiazofurine (48)

related: benaxibine (50)

USAN

rifa- **antibiotics, rifamycin derivatives**

S.6.4.0

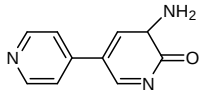


(a) rifabutin (52), rifalazil (78), rifametane (61), rifamexil (67), rifamide (15), rifampicin (17), rifamycin (13), rifapentine (43), rifaximin (49) (previously rifaxidine (48))

USAN

-rinone **cardiac stimulants, amrinone derivatives**

H.1.0.0 (USAN: cardiotonics (amrinone type))



(a) amrinone (38), bemarinone (57), medorinone (54), milrinone (50), nanterinone (60), olprinone (70), pelrinone (53), saterinone (56), toborinone (72), vesnarinone (57)

(b) gestrinone (39), indacrinone (51), taziprinone (48)

USAN

-rixin **chemokine CXCR receptors antagonists**

S.7.0.0 (USAN: Chemokine (C-X-C motif) receptor 2 (CXCR2) modulators)

dazirixin (107), elubrixin (107), ladarixin (105), navarixin (105), reparixin (91)

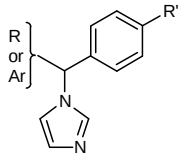
-rizine **see -izine**

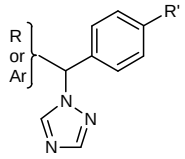
-rolimus **see -imus**

USAN

-rozole **aromatase inhibitors, imidazole-triazole derivatives**

L.0.0.0





anastrozole (72), fadrozole (64), finrozole (81), letrozole (70), liarozole (64), talarozole (99), vorozole (64)

(b) aminitrozole (4), sulfatrozole (24), tenonitrozole (47)

USAN

-rsen **antisense oligonucleotides**

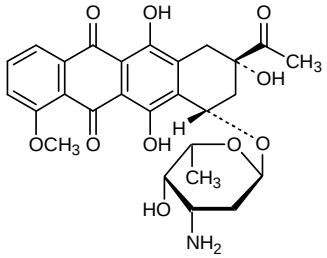
aganirsen (101), alicaforsen (85), anivamersen (105), aprinocarsen (89), beclanorsen (01), cenersen (97), custirsen (99), drisapersen (106), gataparsen (103), eteplirsen (103), mipomersen (99), oblimersen (87), trabedersen (97)

-virsen (antivirals): afovirsen (71), fomivirsen (75), miravirsen (101), radavirsen (106), trecovirsen (77)

USAN

-rubicin **antineoplastics, daunorubicin derivatives**

L.5.0.0 (USAN: antineoplastic antibiotics (daunorubicin type))

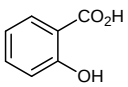


(a) aclarubicin (44), aldoxorubicin (108), amrubicin (65), berubicin (98), carubicin (40), daunorubicin (20), detorubicin (41), doxorubicin (25), epirubicin (48) (originally pidorubicin (47)), esorubicin (47), galarubicin (80), idarubicin (47), ladirubicin (83), leurubicin (64), medorubicin (47), nemorubicin (71), pirarubicin (55), rodorubicin (54), sabarubicin (90), valrubicin (79), zorubicin (39), zoptarelin doxorubicin (107)

USAN

sal **salicylic acid derivatives**

(USAN: -sal-; -sal; or sal-: anti-inflammatory agents (salicylic acid derivatives))



(a) **sal-** analgesic anti-inflammatory A.4.2.0
choline salicylate (15), imidazole salicylate (51), salacetamide (1), salcolex (23), saletamide (20), salfluverine (29), salicylamide (1), salnacedin (73), salprotoside (31), salsalate (28), salverine (15)

various
salafibrate (41) (antihyperlipidaemic), salantel (29) (anthelmintic), salcaprozic acid (88) (absorption promotor), salclobuzic acid (92) (pharmaceutical aid), salinazid (8) (antituberculosis agent), salirasib (97) (antineoplastic)

-sal analgesic anti-inflammatory A.4.2.0
detanosal (23), diflunisal (33), fendosal (35), flufenisal (22), fosfosal (37), guacetisal (40), guaimesal (50), parcetasal (65), pranosal (24), sulprosal (36), tenosal (63)

antithrombotic
flufosal (42)

various: antituberc.
fenamisal (15), thiomersal (1) (disinfect.), triflusal (37) (antithrombotic)

-sal- analgesic anti-inflammatory A.4.2.0
acetaminosalol (1), carbasalate calcium (27), carsalam (13), etersalate (50), etosalamide (14), isalmadol (92), parsalmide (32), talosalate (43)

various
amotosalen (85), calcium benzamidosalicylate (10), homosalate (28) (sunscreen agent), isalsteine (63) (mucolytic), lasalocid (30) (antibiotic (veterinary)), mersalyl (4) (mercurial diuretic), octisalate (83) (sunscreen), osalmid (15) (choleretic), susalimod (73) (immunomodulator), xenysalate (12) (antiseborrheic)

salazo- phenylazosalicylic acid derivatives antibacterial S.5.l.0
salazodine (22), salazosulfadimidine (11), salazosulfamide (1), salazosulfathiazole (1)

-salazine/-salazide
dersalazine (86), mesalazine (52), olsalazine (52), sulfasalazine (55), balsalazide (48), ipsalazide (48)

-salan brominated salicylamide derivatives disinfectant S.2.l.0
bensalan (18), dibromsalan (14), flusalan (16), fursalan (18), metabromsalan (16), tiosalan (18), tribromsalan (14)

(b) non-salicylic acid derivatives
fosalvudine tidoxil (95), macrosalb (^{99m}Tc) (33), rusalatide (96), trioxysalen (l6) (pigmenting agent)

bronchodilators
levosalbutamol (78), salbutamol (20), salmefamol (23)

(c) analgesic, anti-inflammatory A.4.2.0
aloxiprin (13), anilamate (13), benorilate (21), brosotamide (29), cresotamide (28), dibusadol (24), dipyrocetyl (6), ethenzamide (10), fenamifuril (16), gentisic acid (01), hydroxytoluic acid (17), sodium gentisate (1), sodium glucaspaldrate (17)

various
4-aminosalicylates of the -*caine* series D.1.0.0: ambucaine (6), hydroxyprocaine (1), hydroxytetracaine (1), propoxycaine (4)

antihypertensives H.3.0.0: labetalol (35)

antitussives K.1.0.0: alloclamide (l6), flualamide (20)

saluretics N.l.2.0: xipamide (22) (sulfamoyl derivative),

mercurial diuretics N.l.3.0: mercuderamide (1)

anthelmintics S.3.l.0: bromoxanide (31), clioxanide (19), niclosamide (13), rafoxanide (24) closantel (36), flurantel (25), resorantel (23)

antifungals S.4.0.0: buclosamide (16), exalamide (37), pentalamide (13)

See also Pharm S/Nom 557

USAN

-sartan (x) **angiotensin II receptor antagonists, antihypertensive (non-peptidic)**

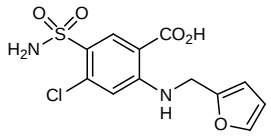
H.3.0.0 (USAN: -sartan: angiotensin II receptor antagonists)

abitesartan (73), azilsartan (95), azilsartan medoxomil (97), candesartan (71), elisartan (72), embusartan (78), eprosartan (71), fimasartan (94), forasartan (74), irbesartan (71), losartan (66), milfasartan (76), olmesartan (93), olmesartan medoxomil (86), pomisartan (73), pratosartan (85), ripisartan (73), saprisartan (72), tasosartan (72), telmisartan (70), valsartan (68), zolasartan (70)

USAN

-semide **diuretics, furosemide derivatives**

N.1.1.0



(a) azosemide (35), furosemide (14), galosemide (33), sulosemide (49), torasemide (35)

-sermin **see -ermin**

USAN

-serod **serotonin receptor antagonists and partial agonists**

J.0.0.0

(a) capeserod (94), piboserod (79), sulamserod (82), tegaserod (79)

USAN

-serpine (d) **derivatives of *Rauwolfia* alkaloids**

E.5.4.0

(a) bietaserpine (14), mefeserpine (15), reserpine (4)

(c) chloroserpidine (11), deserpidine (6), methoserpidine (11), metoserpate (20), rescimetol (44), rescinnamine (6), syrosingopine (10)

USAN

-sertib **serine/threonine kinase inhibitors**

L.0.0.0

afuresertib (108), alisertib (104), barasertib (102), cenisertib (104), danusertib (99), delcasertib (105), galunisertib (109), ilorasertib (108), ipatasertib (108), pimasertib (105), rabusertib (107), rigosertib (106), silmitasertib (103), tanzisertib (106), tozasertib (100), volasertib (102)

BAN, USAN

-setron **serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists**

C.7.0.0

(BAN: serotonin receptor antagonists ($5HT_3$) used as antihypertensives)
(USAN: serotonin 5-HT_3 receptors antagonists)

(a) alosetron (66), azasetron (68), bemesetron (64), cilansetron (68), dolasetron (65), fabesetron (74), galdansetron (72), granisetron (59), indisetron (76), itasetron (68), lerisetron (69), lurosetron (69), mirisetron (72), ondansetron (59), palonosetron (74), ramosetron (70), ricasetron (70), tropisetron (62), zatosetron (64)

USAN

som- **growth hormone derivatives**

Q.0.0.0 (USAN: growth hormone derivatives)
(USAN: som- -bove: bovine somatotropin derivatives)
(USAN: som- -por: porcine sonatotropin derivatives)

(a) -bove: bovine type substances: somagrebove (63), somavubove (63), sometribove (74), somidobove (58)

-por: porcine-type substances: somalapor (62), somenopor (62), somfasepor (66), sometripor (55)
-salm: salmon-type substances: somatosalm (69)
Others: somatrem (54), somatropin (56), somatropin pegol (103)

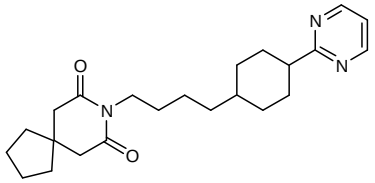
(b) somatorelin (57), somantadine (51), somatostatin (46)

-sopine **see -pine**

USAN

-spirone **anxiolytics, buspirone derivatives**

C.1.0.0



(a) alnespirone (70), binospirone (65), buspirone (30), enilospirone (52), perospirone (71), revospirone (61), tandospirone (60), tiospirone (57), umespirone (60), zalospirone (64)

(c) eptapirone (82), gepirone (54), ipsapirone (54)

BAN; USAN

-stat- or -stat **enzyme inhibitors**

-castat dopamine β-hydroxylase inhibitors
(a) etamicastat (101), nepicastat (78), zamicastat (108)

-elestat elastase inhibitors
(a) alvelestat (104), depelestat (91), freselestat (89), sivelestat (78), tiprelestat (103)

-inostat histone deacetylase inhibitors
(a) abexinostat (105), belinostat (97), dacinostat (89), entinostat (99), givinostat (101), mocetinostat (101), panobinostat (96), pracinostat (104), quisinostat (107), resminostat (102), tefinostat (105), vorinostat (94)

-listat gastrointestinal lipase inhibitors
(a) cetilistat (91), orlistat (66)

-mastat matrix metalloproteinase inhibitors
(a) batimastat (70), cipemastat (81), ilomastat (73), marimastat (75), prinomastat (82), rebimastat (89), ricolinostat (109), solimastat (80), tanomastat (82)

-mostat proteolytic enzyme inhibitors:

(a) camostat (46), nafamostat (53), patamostat (69), sepimostat (68), upamostat (105)

(c) aloxistatin (57), ulinastatin (56)

-restat or *-restat-* aldose reductase inhibitors

M.5.0.0

(a) alrestatin (37), epalrestat (55), fidarestat (78), imirestat (59), lidorestat (87), minalrestat (76), ponalrestat (58), ranirestat (91), risarestat (82), tolrestat (51), zenarestat (64), zopolrestat (64)

various:

afegostat (101) β-glucocerebrosidase inhibitor
apratastat (93): inhibition of TNF-α converting enzyme
avagacestat (104): gamma secretase inhibitor
azalanstat (73): lanosterol 14α-demethylase inhibitor
begacestat (97) gamma secretase inhibitor
benurestat (31): urease inhibitor
cilastatin (50): renal dehydropeptidase inhibitor
cindinustat (107): nitric oxide synthase inhibitor
cobicistat (103) cytochrome P450 3A4 (CYP3A4) inhibitor
conestat alfa (98) human plasma protease C1 inhibitor
duvoglustat (102) Pompe's disease therapy
eliglustat (103) glucosylceramide synthase inhibitor
emixustat (108): retinol isomerase inhibitor
ezatiostat (98) glutathione-S-transferase inhibitor
febuxostat (85): xanthine oxydase and xanthine dehydrogenase inhibitor
imetelstat (101) antineoplastic, telomerase inhibitor
iofolastat (^{123}I) (105) radiopharmaceutical
irosustat (104) antineoplastic
lapaquistat (96) squalene synthase inhibitor
lucerastat (106): ceramide glucosyltransferase inhibitor
migalastat (95): alpha-galactosidase A enzyme inhibitor
miglustat (85): glucosyltransferase inhibitor
niraxostat (99): xanthine oxydase inhibitor
molidustat (108): HIF (hypoxia induced factor)-prolyl hydroxylases inhibitor
pentostatin (38): vidarabin activity potentiator; inhibitor of enzymatic deaminative metabolism
pepstatin (28): pepsin inhibitor
pevonedistat (109): antineoplastic
pradigastat (106): acyl CoA:diacylglycerol acyltransferase inhibitor
roxadustat (108): HIF (hypoxia induced factor)-prolyl hydroxylases inhibitor
selisistat (106): inhibitor of sirtuin enzymes
semgacestat (99): gamma secretase inhibitor
somatostatin (43): growth hormone release inhibiting factor
talabostat (92): antineoplastic
technetium (^{99m}Tc) trofolastat chloride (109): radiolabelled diagnostic agent
telotristat (104) tryptophan hydroxylase inhibitor
tendamistat (44): amylase inhibitor

topiroxostat (102) xanthine oxidase and xanthine dehydrogenase inhibitor
tosedostat (99) antineoplastic, aminopeptidase inhibitor
vistatolon (25): antiviral antibiotic
zinostatin (40): antineoplastic
zinostatin stimalamer (74)

(b) nystatin (6)

-vastatin **antihyperlipidaemic substances, HMG CoA reductase inhibitors** USAN

H.4.0.0 (USAN: -statin: antihyperlipidaemic substances, HMG CoA reductase inhibitors)

(a) atorvastatin (71), bervastatin (72), cerivastatin (74), crilvastatin (63), dalvastatin (64), fluvastatin (62), glenvastatin (70), lovastatin (57), mevastatin (44), pitavastatin (86) (replaces itavastatin (80)), pravastatin (57), rosuvastatin (94), simvastatin (58), tenivastatin (85)

BAN

-steine **mucolytics, other than bromhexine derivatives**

K.0.0.0 (BAN: substances of the acetylcysteine group)

(a) acetylcysteine (13), bencisteine (30), carbocisteine (34), cartasteine (72), dacisteine (49), danosteine (53), erdosteine (56), fudosteine (77), guaisteine (57), isalsteine (63), letosteine (38), mecysteine (13), midesteine (63), moguisteine (61), nesosteine (52), omonasteine (40), prenisteine (42), salmisteine (58), taurosteine (63), telmesteine (63)

USAN

-ster- **androgens/anabolic steroids**

Q.2.3.1

(a) **-testosterone**: cloxotestosterone (12), methyltestosterone (4), testosterone (4), testosterone ketolaurate (16)

-sterone: bolasterone (13), fluoxymesterone (6), oxymesterone (12), prasterone (23), tiomesterone (14)

-ster-: mesterolone (15), penmesterol (14), rosterolone (59)

(b) progestational steroids

-gesterone: dydrogesterone (12), haloprogesterone (11), hydroxyprogesterone (8), medroxyprogesterone (10), norgesterone (14), progesterone (4), segesterone (89)

-sterone: dimethisterone (8), ethisterone (4), norethisterone (6), norvinisterone (10)

various: **-sterone**: aldosterone (6) (corticosteroid), calusterone (23) (antineoplastic)

-sterol: azacosterol (16) (hypocholesterolemic), dihydrotachysterol (1) (antihypoparathyroid), iodocholesterol (^{131}I) (39)

ster: nisterime (38) (contraceptive agent), stercuronium iodide (21) (neuromuscular blocking agent)

-steride **testosterone reductase inhibitors** USAN

bexlosteride (81), dutasteride (78), epristeride (69), finasteride (62), izonsteride (81), lapisteride (85), turosteride (67)

USAN

-stigmine (d) **acetylcholinesterase inhibitors**

E.1.2.0 (USAN: cholinesterase inhibitors (physostigmine type))

(a) distigmine bromide (16), eptastigmine (62), ganstigmine (81), neostigmine bromide (4), pyridostigmine bromide (6), quilostigmine (76), rivastigmine (77), terestigmine (77)

(c) eseridine (53)

USAN

-stim **colony stimulating factors**

I.5.0.0

(a) ancestim (79) (cell growth factor), garnocestim (85) (immunomodulator), pegacaristim (80) (megakaryocyte growth factor), romiplostim (97) (platelet stimulating factor)

-distim **combination of two different types of colony stimulating factors**
(USAN: conjugates of two different types of colony-stimulating factors)

(a) leridistim (80), milodistim (74)

-gramostim **granulocyte macrophage colony stimulating factor (GM-CSF) types substances**

(a) ecogramostim (62), molgramostim (64), regramostim (64), sargramostim (66)

-grastim **granulocyte colony stimulating factor (G-CSF) type substances**

(a) balugrastim (107), empegfilsgrastim (107), filgrastim (64), lenograstim (64), lipegfilgrastim (105), nartograstim (66), pegbovigrastim (109), pegfilgrastim (85), pegnartograstim (80), pegteograstim (109)

-mostim **macrophage stimulating factors (M-CSF) type substances**

(a) cilmostim (71), lanimostim (91), mirimostim (65)

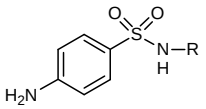
-plestim **interleukin-3 analogues and derivatives**
(USAN: interleukin-3 derivatives, pleiotropic colony-stimulating factors)

(a) daniplestim (76), muplestim (72)

BAN, USAN

sulfa- **anti-infectives, sulfonamides**

S.5.1.0 (BAN: sulpha-)
(USAN: antimicrobials (sulfonamides derivatives))



(a) sulfabenz (17), sulfabenzamide (27), sulfacarbamide (12), sulfacecole (30), sulfacetamide (1), sulfachlorpyridazine (10), sulfachrysoidine (1), sulfacitine (23), sulfaclomide (17), sulfaclorazole (25), sulfaclozine (25), sulfadiasulfone sodium (1), sulfadiazine (4), sulfadiazine sodium (4), sulfadicramide (4), sulfadimethoxine (10), sulfadimidine (1), sulfadoxine (20), sulfaethidole (8), sulfafurazole (1), sulfaguanidine (4), sulfaguanole (23), sulfalene (12), sulfaloxic acid (15), sulfamazone (40), sulfamerazine (4), sulfamerazine sodium (4), sulfamethizole (1), sulfamethoxazole (14), sulfamethoxypyridazine (8), sulfametomidine (12), sulfametoxydiazine (17), sulfametrole (31), sulfamonomethoxine (11), sulfamoxole (12), sulfanilamide (4), sulfanitran (15), sulfaperin (14), sulfaphenazole (10), sulfaproxyline (4), sulfapyrazole (18), sulfapyridine (1), sulfaquinoxaline (46), sulfasalazine (55), sulfasomizole (10), sulfasuccinamide (41), sulfasymazine (12), sulfathiazole (4), sulfathiourea (l), sulfatolamide (10), sulfatroxazole (29), sulfatrozole (24)

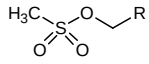
(b) galsulfase (92), idursulfase (90), sulfarsphenamine (4)

(c) benzylsulfamide (1), glucosulfamide (1), maleylsulfathiazole (1), mesulfamide (41), nitrosulfathiazole (1), phthalylsulfamethizole (6), phthalylsulfathiazole (1), salazodine (22), salazosulfadimidine (11), salazosulfamide (1), salazosulfathiazole (1), stearylsulfamide (1), succinylsulfathiazole (4), sulfisomidine (1), vanyldisulfamide (1), mafenide (1) (sulfonamide, but not sulfanilamide)

USAN

-sulfan **antineoplastic, alkylating agents, methanesulfonates**

L.2.0.0



(a) busulfan (6), improsulfan (35), mannosulfan (24), piposulfan (15), ritrosulfan (33), treosulfan (26)

-tacept **see -cept**

-tadekin **see -kin**

		USAN
-tadine	**histamine-H_1 receptor antagonists, tricyclic compounds**	
G.2.1.0	(USAN: -(a)tadine: tricyclic histaminic-H_1 receptor antagonists, loratadine derivative (formerly -tadine))	
(a)	alcaftadine (94), azatadine (18), cyproheptadine (10), desloratadine (80), loratadine (54), napactadine (46), olopatadine (72), rupatadine (74), vapitadine (95)	
(b)	amantadine (15), carmantadine (31), rimantadine (17), somantadine (51), tromantadine (28) (see -mantadine)	

		USAN
-tant	**neurokinin (tachykinin) receptor antagonists**	
-pitant	neurokinin NK_1 (substance P) receptor antagonist	
(a)	aprepitant (84), befetupitant (91), burapitant (101), casopitant (94), dapitant (74), ezlopitant (82), figopitant (82), fosaprepitant (94), lanepitant (77), maropitant (90), netupitant (90), nolpitantium besilate (75), orvepitant (94), rolapitant (97), serlopitant (100), telmapitant (108), vestipitant (91), vofopitant (82)	
-dutant	neurokinin NK_2 receptor antagonist	
(a)	ibodutant (98), nepadutant (78), saredutant (75)	
-nertant	neurotensin receptor antagonist	
(a)	meclinertant (88) (replaces reminertant (85))	
-netant	neurokinin NK_3 receptor antagonist	
(a)	osanetant (74), talnetant (81)	

		USAN
-tapide	**microsomal triglyceride transfer protein (MTP) inhibitors**	
H.4.0.0	dirlotapide (91), granotapide (104), implitapide (82), mitratapide (90), lomitapide (101), usistapide (104)	

		USAN
-taxel	**antineoplastics, taxane derivatives**	
L.0.0.0		
	cabazitaxel (98), docetaxel (71), larotaxel (94), milataxel (91), ortataxel (87), paclitaxel (68), paclitaxel ceribate (91), paclitaxel poliglumex (90), paclitaxel trevatide (109), simotaxel (94), tesetaxel (93)	

USAN

-tecan **antineoplastics, topoisomerase I inhibitors**

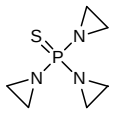
L.0.0.0 (USAN: antineoplastics (camptothecin derivatives))

afeletecan (85), atiratecan (101), belotecan (91),ositecan (100), delimotecan (97), diflomotecan (84), elemotecan (92), etirinotecan pegol (107), exatecan (81), exatecan alideximer (89), firtecan peglumer (108), firtecan pegol (107), gimatecan (86), irinotecan (64), lurtotecan (74), mureletecan (85), namitecan (100), pegamotecan (91), rubitecan (82), tenifatecan (102), topotecan (65)

USAN

-tepa **antineoplastics, thiotepa derivatives**

L.2.0.0



(a) azatepa (12), pumitepa (48), thiotepa (10)

-tepine **see -pine**

USAN

-teplase **tissue type plasminogen activators, see -ase item VI**

USAN

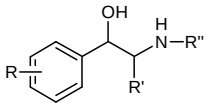
-termin **see -ermin**

BAN, USAN

-terol **bronchodilators, phenethylamine derivatives**

(previously -prenaline
or -terenol unofficial)

E.4.0.0



(a) abediterol (104), amiterol (26), arformoterol (90), bitolterol (34), broxaterol (51), carmoterol (91), cimaterol (54), colterol (36), difeterol (36), etanterol (53), fenoterol (26), formoterol (44), imoxiterol (52), indacaterol (91), milveterol (97), naminterol (53), nardeterol (62), olodaterol (106), picumeterol (64), procaterol (37), reproterol (30), rimiterol (26), salmeterol (55), sulfonterol (3l), vilanterol (103), zilpaterol (60), zinterol (38)

-buterol: bambuterol (49), carbuterol (29), clenbuterol (28), divabuterol (51), flerobuterol (59), ibuterol (31), mabuterol (46), nisbuterol (38), pirbuterol (30), tobuterol (45), tulobuterol (40)

cardiac stimulants: metaterol (43), prenalterol (38), xamoterol (48)

previously -prenaline or -terenol: clorprenaline (17), hexoprenaline (21), isoprenaline (1), levisoprenaline (10), metiprenaline (24), orciprenaline (14), quinprenaline (17) deterenol (25), soterenol (20)

(b) azacosterol (16), dihydrotachysterol (1), penmesterol (14)

(c) dioxethedrine (6), isoetarine (13), methoxyphenamine (1), pseudoephedrine (11), salbutamol (20), salmefamol (23), terbutaline (22)

-terone **antiandrogens**

(Q.2.3.1)

(a) abiraterone (74), benorterone (15), cyproterone (16), delanterone (42), galeterone (105), inocoterone (54), osaterone (68), topterone (39), zanoterone (67)

(b) clometerone (15) (antiestrogen)

(c) cioteronel (62), orteronel (104), oxendolone (42), rosterolone (60),

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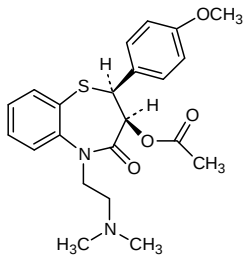
USAN

-tiazem **calcium channel blockers, diltiazem derivatives**

F.2.1.0



clentiazem (61), diltiazem (30), iprotiazem (56), nictiazem (54), siratiazem (68)

USAN

-tibant **bradykinin receptors antagonists**
(USAN : antiasthmatics (bradykinin antagonists))

H.0.0.0

anatibant (88), deltibant (75), fasitibant chloride (103), icatibant (67), safotibant (105)

USAN

-tide **peptides and glycopeptides (for special groups of peptides see -actide, -pressin, -relin, -tocin)**

analgesic: leconotide (86), ziconotide (78)

angiogenesis inhibitor: cilengitide (81)

angiotensin convers. inhibitor: teprotide (36)

anti-inflammatory: icrocaptide (89)

antianaemic: peginesatide (108)

antiarrhythmic: danegaptide (101), rotigaptide (94)

antidepressant: nemifitide (87)

antidiabetic: amlintide (76), davalintide (101), exenatide (89), langlenatide (109), lixisenatide (99), pramlintide (74), seglitide (57)

antidiarrhoeal: lagatide (75)

antithrombotic: eptifibatide (78)

antiviral: enfuvirtide (85), tifuvirtide (91)

autoimmune disorders: dirucotide (100)

atrial natriuretic factor type substances: anaritide (57), carperitide (65), cenderitide (105), neseritide (80), ularitide (69)

calcium sensing receptor agonist: velcalcetide (109)

cicatrisation promoter: ensereptide (107)

diagnostic: betiatide (58), bibapcitide (78), ceruletide (34), depreotide (80), flotegatide (^{18}F) (108), fluciclatide (^{18}F) (103), maraciclatide (103), mertiatide (60), pendetide (70), technetium (^{99m}Tc) apcitide (78), technetium (^{99m}Tc) etarfolatide (107), teriparatide (50)

expectorant (in cystic fibrosis): lancovutide (99)

gastro-intestinal bleeding/antineoplastic: edotreotide (84), ilatreotide (66), lanreotide (64), octreotide (52), pentetreotide (66), vapreotide (62)

gastrointestinal functions normalizing agent: linaclotide (96), plecanatide (104)

growth stimulant-veterinary: nosiheptide (35)

gut motility increasing: ociltide (52)

hormone analogues: abaloparatide (109), semparatide (80), teriparatide (50) (see also diagnostic)

immunological agents - antineoplastic: almurtide (74), delmitide (92), edratide (89), goralatide (72), mifamurtide (95), murabutide (49), paclitaxel trevatide (109), pentigetide (60), pimelautide (53), prezatide copper acetate (67), rolipoltide (94), romurtide (61), tabilautide (60), temurtide (60), tigapotide (95),

inhibition of growth hormone release: pasireotide (90)

kallicrein inhibitor: ecallantide (93)

melanocortin receptor agonist: afamelanotide (100), bremelanotide (95)

neuromodulator: davunetide (100), ebiratide (56), obinepitide (96)

peptic ulcer: sulglicotide (29), triletide (50)

pulmonary surfactant: lusupultide (80), sinapultide (78)

sedative: emideltide (70)

thrombin fragment: rusalatide (96)

transforming growth factor inhibitor: disitertide (99)

treatment of Alzheimer's disease: vanutide cridificar (100)

treatment of Parkinson's disease: doreptide (58), pareptide (38)

treatment of coeliac disease: larazotide (99)

-glutide **Glucagon-like Peptide (GLP) analogues** USAN
albiglutide (97), dulaglutide (103), elsiglutide (104), liraglutide (87), semaglutide (101), taspoglutide (99), teduglutide (90)

-motide **immunological agents for active immunization**
abecomotide (109), alicdamotide (109), amilomotide (105), asudemotide (107), disomotide (94), elpamotide (103), latromotide (107), ovemotide (94), pradimotide (107), tanurmotide (109), tecemotide (108), tertomotide (98), tiplimotide (82), trempamotide (107)

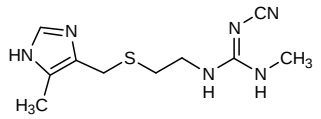
(b) defibrotide (44) (nucleotide), diamfenetide (28) (fasciolicide), diclometide (19) (behaviour modificator), fludroxycortide (12), glisentide (58)

(c) angiotensin II (65), angiotensinamide (12)

BAN, USAN

-tidine **histamine-H_2-receptor antagonists, cimetidine derivatives**

G.2.2.0 (BAN: H_2-receptor antagonists of the cimetidine group)
(USAN: H_2-receptor antagonists (cimetidine type))



(a) bisfentidine (57), cimetidine (33), dalcotidine (76), donetidine (56), ebrotidine (57), etintidine (44), famotidine (48), lafutidine (70), lamtidine (48), lavoltidine (61) (previously loxtidine (48)), lupitidine (53), mifentidine (50), niperotidine (54), nizatidine (48), osutidine (76), oxmetidine (44), pibutidine (78), quisultidine (47) (replaced by quisultazine (51)), ramixotidine (55), ranitidine (41), roxatidine (54), sufotidine (54), tiotidine (44), tuvatidine (54), venritidine (67), zaltidine (54)

(b) azacitidine (40) (antineoplastic), benzethidine (9), furethidine (9), guanethidine (11), hexetidine (6), hydroxypethidine (5), pethidine (4), propinetidine (12)

(c) metiamide (30)

-tiline **see -triptyline**

USAN

-tinib **tyrosine kinase inhibitors**

L.0.0.0

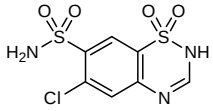
(a) adelatinib (108), afatinib (104), alectinib (108), amuvatinib (103), axitinib (94), bafetinib (101), baricitinib (107), binimetinib (109), bosutinib (94), cabozantinib (105), canertinib (87), ceritinib (109), cobimetinib (107), crizotinib (103), dacomitinib (103), dasatinib (94), dovitinib (97), erlotinib (85), fedratinib (108), filgotinib (108), foretinib (102), fostamatinib (100), gandotinib (108), gefitinib (85), golvatinib (107), ibrutinib (107), imatinib (86), lapatinib (89), lenvatinib (104), lestaurtinib (91), linsitinib (104), masitinib (96), momelotinib (107), mubritinib (90), neratinib (97), nilotinib (95), oclacitinib (105), orantinib (103), pacritinib (104), pelitinib (93), ponatinib (104), poziotinib (108), quizartinib (104), radotinib (104), ralimetinib (109), rebastinib (107), refametinib (106), ruxolitinib (103), sapitinib (106), saracatinib (99), selumetinib (100), sunitinib (93), tandutinib (91), telatinib (96), tivantinib (103), tofacitinib (105), trametinib (105), varlitinib (102)

-tirelin **see -relin**

USAN

-tizide **diuretics, chlorothiazide derivatives**

N.1.2.1 (USAN: thiazide: diuretics (thiazide derivatives))



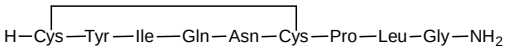
(a) altizide (13), bemetizide (27), butizide (13), carmetizide (30), epitizide (13), hydrobentizide (14), mebutizide (15), paraflutizide (16), penflutizide (29), sumetizide (20)

(c) bendroflumethiazide (11), benzthiazide (10), chlorothiazide (8), cyclopenthiazide (12), cyclothiazide (12), disulfamide (11), ethiazide (14), flumethiazide (10), hydrochlorothiazide (10), hydroflumethiazide (10), methyclothiazide (11), polythiazide (12), teclothiazide (12), trichlormethiazide (11)

USAN

-tocin **oxytocin derivatives**

Q.1.2.0

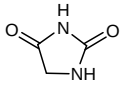


(a) argiprestocin (13), aspartocin (11), carbetocin (45), cargutocin (35), demoxytocin (22), nacartocin (49), oxytocin (13)

USAN

-toin (d) **antiepileptics, hydantoin derivatives**

A.3.1.1



(a) albutoin (13), doxenitoin (3l), ethotoin (6), fosphenytoin (62), imepitoin (96), mephenytoin (1), metetoin (12), phenytoin (4)

ropitoin (40) (H.2.0.0.)

(b) clodantoin (13) (antifungal), nitrofurantoin (11) (antibacterial)

-trakin **see -kin**

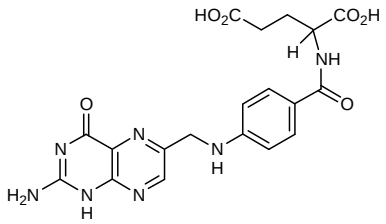
-trakinra **see -kinra**

-tredekin **see -kin**

USAN

-trexate **folic acid analogues**

L.4.0.0 (USAN: antimetabolites (folic acid analogues))



(a) edatrexate (61), ketotrexate (50), methotrexate (10), pralatrexate (92), trimetrexate (46)

(c) aminopterin sodium (04)

USAN

-trexed **antineoplastics; thymidylate synthetase inhibitors**

L.0.0.0

nolatrexed (78), pemetrexed (78), plevitrexed (89), raltitrexed (94)

USAN

-tricin **antibiotics, polyene derivatives**

S.6.2.0

(a) mepartricin (34), partricin (27)

(b) tyrothricin (1)

(c) amphotericin B (10), candicidin (17), filipin (20), hachimycin (23), hamycin (17), levorin (15), mocimycin (28), natamycin (15), nystatin (6), pecilocin (16)

USAN

tril/trilat **endopeptidase inhibitors**

H.3.0.0

candoxatril (62), candoxatrilat (62), sacubitril (109)

-dotril dexecadotril (73), ecadotril (68), fasidotril (74), racecadotril (73)
-lutril daglutril (90)
-patril/-patrilat gemopatrilat (84), ilepatril (95), omapatrilat (78), sampatrilat (74)

USAN

-triptan **serotonin (5-HT_1) receptor agonists, sumatriptan derivatives**

C.0.0.0

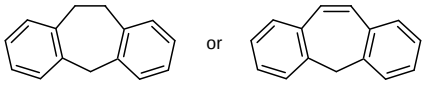
(a) almotriptan (76), avitriptan (76), donitriptan (82), eletriptan (74), frovatriptan (78), naratriptan (69), oxitriptan (39), rizatriptan (75), sumatriptan (59), zolmitriptan (74)

(c) alniditan (72)

USAN

-triptyline **antidepressants, dibenzo[*a,d*]cycloheptane or cyclopheptene derivatives**

C.3.2.0 (USAN: antidepressants (dibenzo[*a,d*]cycloheptane derivatives))



(a) amitriptyline (11), butriptyline (16), cotriptyline (26), intriptyline (26), nortriptyline (12), octriptyline (33), protriptyline (14), amitriptylinoxide (36), demexiptiline (43), levoprotiline (56), noxiptiline (20), oxaprotiline (45), setiptiline (56)

(b) oxitriptyline (21) (anticonvulsant)

(c) hepzidine (15)

see also Pharm S/Nom 970

USAN

-troban **thromboxane A_2-receptor antagonists; antithrombotic agents**

I.2.1.0 (USAN: antithrombotics (thromboxane A_2 receptor antagonists)

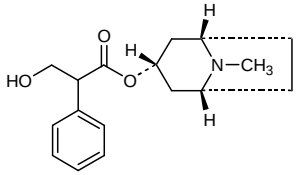
argatroban (57), daltroban (57), domitroban (73), ifetroban (71), linotroban (69), mipitroban (73), ramatroban (73), sulotroban (55), terutroban (93)

-trodast **see -ast**

USAN

trop **atropine derivatives**

E.2.0.0 (USAN: trop- ; –trop- or -trop)



(a) <u>parasympatholytic/anticholinergic: E.2.2.0</u>:
<u>tertiary amines</u>: atropine oxyde (12), benzatropine (4), decitropine (18), etybenzatropine (12), eucatropine (1), tropatepine (28), tropicamide (11), tropigline (8), tropodifene (18)

closely related:
esbatropate (65)

quaternary ammonium salts:
atropine methonitrate (4), butropium bromide (30), ciclotropium bromide (50), cimetropium bromide (51), darotropium bromide (99), flutropium bromide (50), homatropine methylbromide (1), ipratropium bromide (28), octatropine methylbromide (10), oxitropium bromide (36), phenactropinium chloride (8), ritropirronium bromide (33), sevitropium mesilate (56), sintropium bromide (47), sultroponium (18), tematropium metilsulfate (64), tiotropium bromide (67), tipetropium bromide (42), tropenziline bromide (11), xenytropium bromide (15)

various:
clobenztropine (13) (antihistaminic), cyheptropine (15) (antiarrhythmic), deptropine (12) (antiasthmatic), revatropate (74) (bronchodilator), tropabazate (41) (tranquillizer), tropanserin (55) (serotonin receptor antagonist), tropapride (48) (antipsychotic), tropirine (20) (respiratory disorders), tropantiol (97) (chelating agent), tropisetron (62) (serotonin antagonist)

(b) dextropropoxyphene (7), somatropin (56), somatropin pegol (103), varfollitropin alfa (101)

(c) parasympatholytic/anticholinergic, tertiary amines:
poskine (8), prampine (11), tigloidin (14)

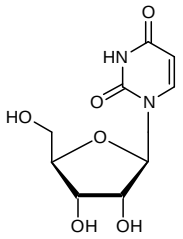
various:
zepastine (26) (antihistaminic)

-uplase **urokinase type plasminogen activator, see -ase item VII**

USAN

-uridine **uridine derivatives used as antiviral agents and as antineoplastics**
(USAN: antivirals; antineoplastics (uridine derivatives))

S.5.3.0
L.4.0.0



L.4.0.0: broxuridine (30), doxifluridine (44)

related: carmofur (45), clanfenur (58), tegafur (41)

S.5.3.0: fialuridine (68), floxuridine (16), fosfluridine tidoxil (93), idoxuridine (17), navuridine (84), ropidoxuridine (97), trifluridine (37), uridine triacetate (103)

-vudine (USAN: -vudine: antineoplastics; antivirals (zidovudine type))

(a) alovudine (68), brivudine (59), clevudine (78), epervudine (61), fosalvudine tidoxil (95), fozivudine tidoxil (73), lamivudine (66), netivudine (72), sorivudine (64), stavudine (65), telbivudine (88), zidovudine (56)

(c) edoxudine (52)

USAN

-vaptan (x) vasopressin receptor antagonists

H.0.0.0

(a) conivaptan (82), lixivaptan (83), mozavaptan (87), nelivaptan (98), relcovaptan (82), satavaptan (93), tolvaptan (83)

-vastatin **see -stat**

-vec **see -gene** for gene therapy products

BAN, USAN

-verine spasmolytics with a papaverine-like action

F.1.0.0 (USAN: spasmolytic agents (papaverine type))

(a) alverine (16), amifloverine (28), bietamiverine (6), butaverine (13), camiverine (29), caroverine (28), clofeverine (31), demelverine (17), denaverine (25), dexsecoverine (53), dicycloverine (6), dihexyverine (4), dipiproverine (10), diproteverine (51), drotaverine (17), elziverine (57), ethaverine (4), febuverine (27), fenoverine (28), floverine (28), heptaverine (16), ibuverine (21), idaverine (55), mebeverine (14), milverine (52), mofloverine (28), moxaverine (36), nafiverine (16), niceverine (15), octaverine (18), pargeverine (38), pentoxyverine (6), pramiverine (21), prenoverine (41), propiverine (45), rociverine (33), salfluverine (29), salverine (15), secoverine (38), temiverine (76), zardaverine (59)
Related:
fenpiverinium bromide (26), pinaverium bromide (32)

(b) cinnamaverine (10) (anticholinergic, tert. amine), diaveridine (18)

(c) spasmolytics chemically related to some of the above INN ending in *-verine*

butetamate (17), butinoline (14), camylofin (12), cinnamedrine (19), cyclandelate (8), difemerine (17), diisopromin (11), dimoxylin (1), fenpiprane (17), fenyramidol (12), metindizate (16), oxybutynin (13), papaveroline (29), pentapiperide (10), prozapine (14), triclazate (10), tropenziline bromide (11)

USAN

vin- and -vin- (x)	**vinca alkaloids**
	(USAN: vin-; or -vin-)
(a)	B.l.0.0 stimulation of cerebrovascular circulation apovincamine (48), brovincamine (42), vinburnine (45), vincamine (22), vincanol (37), vincantril (51), vinconate (47), vindeburnol (49), vinmegallate (59), vinpocetine (36), vinpoline (35), vintoperol (61)
	L.5.0.0 cytostatic vinblastine (12), vincristine (13), vindesine (35), vinepidine (50), vinflunine (75), vinformide (38), vinfosiltine (64), vinglycinate (16), vinleucinol (64), vinleurosine (13), vinorelbine (57), vinrosidine (13), vintafolide (107), vintriptol (51), vinzolidine (46)
(b)	barbiturates vinbarbital (l), vinylbital (12) others: vincofos (28) (phosphate, anthelmintic), vintiamol (16) (vitamin B derivative, antineuralgic)

BAN; USAN

vir	**antivirals (undefined group)**
S.5.3.0	(USAN: -vir; -vir; or vir-: antivirals)
(a)	alisporivir (100), alvircept sudotox (69), amdoxovir (85), amenamevir (100), amitivir (67), atevirdine (69), balapiravir (100), bevirimat (96), daclatasvir (107), delavirdine (71), denotivir (70), dolutegravir (105), efavirenz (78), elvitegravir (97), enfuvirtide (85), enviradene (49), enviroxime (44), favipiravir (98), ledipasvir (109), letermovir (104), litomeglovir (84), loviride (70), maribavir (80), nevirapine (66), opaviraline (83), pirodavir (63), pocapavir (107), pritelivir (106), raltegravir (97), ribavirin (31), rupintrivir (88), taribavirin (95), talviraline (75), tecovirimat (99), tifuvirtide (91), tivirapine (74), tomeglovir (84), trovirdine (73), umifenovir (103), vapendavir (106), viroxime (49), zinviroxime (44)
-amivir	neuraminidase inhibitors: laninamivir (100), oseltamivir (80), peramivir (86), zanamivir (72)
-buvir	RNA polymerase (NS5B) inhibitors: dasabuvir (109), deleobuvir (108), filibuvir (101), lomibuvir (107), nesbuvir (98), setrobuvir (106), sofosbuvir (108), tegobuvir (103)
-cavir	carbocyclic nucleosides: abacavir (76), entecavir (82), lobucavir (72)
-ciclovir	bicyclic heterocycle compounds: aciclovir (42), buciclovir (52), desciclovir (55), detiviciclovir (86), famciclovir (61), ganciclovir (56), lagociclovir (101), lagociclovir valactate (101), omaciclovir (84), penciclovir (61), rociclovir (62), tiviciclovir (86), valaciclovir (69), valganciclovir (78), valomaciclovir (84)

-fovir phosphonic acid derivatives: adefovir (72), alamifovir (89), besifovir (105), cidofovir (72), pradefovir (93), tenofovir (82)

-gosivir glucoside inhibitors: celgosivir (77)

-navir HIV protease inhibitors: amprenavir (79), atazanavir (88), brecanavir (94), darunavir (88), droxinavir (74), fosamprenavir (83), indinavir (74), lasinavir (76), lopinavir (80), mozenavir (84), nelfinavir (76), palinavir (74), ritonavir (74), saquinavir (69), telinavir (73), tipranavir (80)

-previr Hepatitis Virus C (HVC) protease inhibitors: asunaprevir (105), boceprevir (97), ciluprevir (90), danoprevir (102), faldaprevir (106), narlaprevir (102), neceprevir (107), simaprevir (105), sovaprevir (106), telaprevir (94), vaniprevir (103), vedroprevir (109)

-virine Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI): capravirine (83), dapivirine (86), doravirine (109), emivirine (82), etravirine (88), fosdevirine (103), lersivirine (101), rilpivirine (82)

-viroc CCR5 (Chemokine CC motif receptor 5) receptor antagonists: ancriviroc (92), aplaviroc (94), cenicriviroc (103), maraviroc (94), vicriviroc (94)

-virsen see *-rsen*

-virumab see *mab*

(b) virginiamycin (18), viridofulvin (16)

(c) aranotin (21), arildone (38), avridine (50), didanosine (64), disoxaril (55), dimepranol (42), foscarnet sodium (42), fosfonet sodium (35), ketoxal (22), impacarzine (36), inosine (42), lodenosine (75), metisazone (14), moroxydine (22), pleconaril (77), tilorone (24), xenazoic acid (11)

-vircept **see -cept**

-virine **see -vir**

-viroc **see -vir**

-virsen **see -rsen**

-virumab **see -mab**

-vos **see -fos**

-vudine **see -uridine**

USAN

-xaban **blood coagulation factor X_A inhibitors, antithrombotics**

I.2.0.0

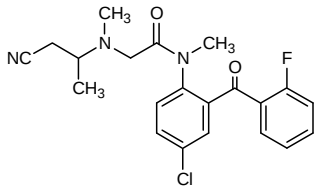
(a) apixaban (93), betrixaban (98), darexaban (104), edoxaban (99), eribaxaban (98), fidexaban (91), letaxaban (104), otamixaban (86), razaxaban (90), rivaroxaban (90)

-xanox **see -ox/-alox**

-yzine **see -izine**

-zafone **alozafone derivatives**

C.1.0.0



(a) alozafone (40), avizafone (64), ciprazafone (50), dinazafone (46), dulozafone (56), lorzafone (48), oxazafone (45), rilmazafone (55)

-zepine **see -pine**

-zolast see -ast

USAN

-zomib **proteasome inhibitors**

L.0.0.0 (USAN: proteozome inhibitors)

bortezomib (88), carfilzomib (97), delanzomib (105), ixazomib (104), marizomib (102), oprozomib (107)

-zone	**see -buzone**

	USAN
-zotan	**serotonin 5-HT_{1A} receptor agonists/antagonists acting primarly as neuroprotectors**
C.0.0.0	ebalzotan (72), lecozotan (93), naluzotan (101), osemozotan (87), piclozotan (92), robalzotan (90), sarizotan (94)

ANNEX 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES[1]

The following procedure shall be followed by the World Health Organization (hereinafter also referred to as "WHO") in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with resolution WHA3.11 of the World Health Assembly, and in the substitution of such names.

Article 1

Proposals for recommended international nonproprietary names and proposals for substitution of such names shall be submitted to WHO on the form provided therefor. The consideration of such proposals shall be subject to the payment of an administrative fee designed only to cover the corresponding costs of the Secretariat of WHO ("the Secretariat"). The amount of this fee shall be determined by the Secretariat and may, from time to time, be adjusted.

Article 2

Such proposals shall be submitted by the Secretariat to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, such designated members hereinafter referred to as "the INN Expert Group", for consideration in accordance with the "General principles for guidance in devising International Nonproprietary Names for Pharmaceutical Substances", annexed to this procedure.[2] The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

Article 3

Subsequent to the examination provided for in article 2, the Secretariat shall give notice that a proposed international nonproprietary name is being considered.

(a) Such notice shall be given by publication in *WHO Drug Information*[3] and by letter to Member States and to national and regional pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice shall also be sent to the person who submitted the proposal ("the original applicant") and other persons known to be concerned with a name under consideration.

(b) Such notice shall:
(i) set forth the name under consideration;
(ii) identify the person who submitted the proposal for naming the substance, if so requested by such person;
(iii) identify the substance for which a name is being considered;
(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;
(v) state the authority under which WHO is acting and refer to these rules of procedure.

[1] See Annex 1 in WHO Technical Report Series, No. 581, 1975. The original text was adopted by the Executive Board in resolution EB15.R7 and amended in resolution EB43.R9.
[2] See Annex 2
[3] Before 1987, lists of international nonproprietary names were published in the *Chronicle of the World Health Organization*.

(c) In forwarding the notice, the Secretariat shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by WHO.

Article 4

Comments on the proposed name may be forwarded by any person to WHO within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.

Article 5

A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in *WHO Drug Information*.
Such objection shall:

(i) identify the person objecting;
(ii) state his or her interest in the name;
(iii) set forth the reasons for his or her objection to the name proposed.

Article 6

Where there is a formal objection under article 5, WHO may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by WHO of a substitute name or names, a name shall not be selected by WHO as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

Article 7

Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Secretariat shall give notice in accordance with subsection (a) of article 3 that the name has been selected by WHO as a recommended international nonproprietary name.

Article 8

In forwarding a recommended international nonproprietary name to Member States under article 7, the Secretariat shall:
(a) request that it be recognized as the nonproprietary name for the substance; and
(b) request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name and to prohibit registration of the name as a trademark or trade name.

Article 9

(a) In the extraordinary circumstance that a previously recommended international nonproprietary name gives rise to errors in medication, prescription or distribution, or a demonstrable risk thereof, because of similarity with another name in pharmaceutical and/or prescription practices, and it appears that such errors or potential errors cannot readily be resolved through other interventions than a possible substitution of a previously recommended international nonproprietary name, or in the event that a previously recommended international nonproprietary name differs substantially from the nonproprietary name approved in a significant number of Member States, or in other such extraordinary circumstances that justify a substitution of a recommended international nonproprietary name, proposals to that effect may be filed by any interested person. Such proposals shall be submitted on the form provided therefore and shall:

(i) identify the person making the proposal;

(ii) state his or her interest in the proposed substitution; and

(iii) set forth the reasons for the proposal; and

(iv) describe, and provide documentary evidence regarding, the other interventions undertaken in an effort to resolve the situation, and the reasons why these other interventions were inadequate.

Such proposals may include a proposal for a new substitute international nonproprietary name, devised in accordance with the General principles, which takes into account the pharmaceutical substance for which the new substitute international nonproprietary name is being proposed.

The Secretariat shall forward a copy of the proposal, for consideration in accordance with the procedure described in subsection (b) below, to the INN Expert Group and the original applicant or its successor (if different from the person bringing the proposal for substitution and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations).

In addition, the Secretariat shall request comments on the proposal from:

(i) Member States and national and regional pharmacopoeia commissions or other bodies designated by Member States (by including a notice to that effect in the letter referred to in article 3(a), and

(ii) any other persons known to be concerned by the proposed substitution.

The request for comments shall:

(i) state the recommended international nonproprietary name that is being proposed for substitution (and the proposed substitute name, if provided);

(ii) identify the person who submitted the proposal for substitution (if so requested by such person);

(iii) identify the substance to which the proposed substitution relates and reasons put forward for substitution;

(iv) set forth the time within which comments will be received and the person and place to whom they should be directed; and

(v) state the authority under which WHO is acting and refer to these rules of procedure.

Comments on the proposed substitution may be forwarded by any person to WHO within four months of the date of the request for comments.

(b) After the time period for comments referred to above has elapsed, the Secretariat shall forward any comments received to the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution. If, after consideration of the proposal for substitution and the comments received, the INN Expert Group, the person bringing the proposal for substitution and the original applicant or its successor all agree that there is a need to substitute the previously recommended international nonproprietary name, the Secretariat shall submit the proposal for substitution to the INN Expert Group for further processing.

Notwithstanding the foregoing, the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed for substitution.

In the event that a proposal for substitution shall be submitted to the INN Expert Group for further processing, the INN Expert Group will select a new international nonproprietary name in accordance with the General principles referred to in article 2 and the procedure set forth in articles 3 to 8 inclusive. The notices to be given by the Secretariat under article 3 and article 7, respectively, including to the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), shall in such event indicate that the new name is a substitute for a previously recommended international nonproprietary name and that Member States may wish to make transitional arrangements in order to accommodate existing products that use the previously recommended international nonproprietary name on their label in accordance with national legislation.

If, after consideration of the proposal for substitution and the comments received in accordance with the procedure described above, the INN Expert Group, the original applicant or its successor and the person bringing the proposal for substitution do not agree that there are compelling reasons for substitution of a previously recommended international nonproprietary name, this name shall be retained (provided always that the original applicant or its successor shall not be entitled to withhold agreement to a proposal for substitution in the event that the original applicant or its successor has no demonstrable continuing interest in the recommended international nonproprietary name proposed to be substituted). In such an event, the Secretariat shall advise the person having proposed the substitution, as well as the original applicant or its successor (if not the same as the person proposing the substitution, and provided that the original applicant or its successor is known or can be found through diligent effort, including contacts with industry associations), Member States, national and regional pharmacopoeia commissions, other bodies designated by Member States, and any other persons known to be concerned by the proposed substitution that, despite a proposal for substitution, it has been decided to retain the previously recommended international nonproprietary name (with a description of the reason(s) why the proposal for substitution was not considered sufficiently compelling).

ANNEX 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. ”oxacillin” and “oxacillin sodium”, “ibufenac” and “ibufenac sodium”.

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.* Where a stem is shown without any hyphens it may be used anywhere in the name.

Latin	*English*	
-acum	*-ac*	anti-inflammatory agents, ibufenac derivatives
-adolum	*-adol)*	analgesics
-adol-	*-adol-)*	
-astum	*-ast*	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	*-astine*	antihistaminics
-azepamum	*-azepam*	diazepam derivatives
bol	*bol*	anabolic steroids
-cain-	*-cain-*	class I antiarrhythmics, procainamide and lidocaine derivatives
-cainum	*-caine*	local anaesthetics
cef-	*cef-*	antibiotics, cefalosporanic acid derivatives
-cillinum	*-cillin*	antibiotics, 6-aminopenicillanic acid derivatives
-conazolum	*-conazole*	systemic antifungal agents, miconazole derivatives
cort	*cort*	corticosteroids, except prednisolone derivatives
-coxibum	*-coxib*	selective cyclo-oxygenase inhibitors
-entanum	*-entan*	endothelin receptor antagonists
gab	*gab*	gabamimetic agents
gado-	*gado-*	diagnostic agents, gadolinium derivatives
-gatranum	*-gatran*	thrombin inhibitors, antithrombotic agents
gest	*gest*	steroids, progestogens
gli	*gli*	antihyperglycaemics
io-	*io-*	iodine-containing contrast media
-metacinum	*-metacin*	anti-inflammatory, indometacin derivatives
-mycinum	*-mycin*	antibiotics, produced by *Streptomyces* strains
-nidazolum	*-nidazole*	antiprotozoals and radiosensitizers, metronidazole derivatives
-ololum	*-olol*	β-adrenoreceptor antagonists
-oxacinum	*-oxacin*	antibacterials, nalidixic acid derivatives
-platinum	*-platin*	antineoplastic agents, platinum derivatives
-poetinum	*-poetin*	erythropoietin type blood factors
-pril(at)um	*-pril(at)*	angiotensin-converting enzyme inhibitors
-profenum	*-profen*	anti-inflammatory agents, ibuprofen derivatives
prost	*prost*	prostaglandins
-relinum	*-relin*	pituitary hormone release-stimulating peptides
-sartanum	*-sartan*	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-vaptanum	*-vaptan*	vasopressin receptor antagonists
vin-	*vin-)*	vinca alkaloids
-vin-	*-vin-)*	

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* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic “stem” indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.

ANNEX 3

General policies for monoclonal antibodies

· INN for monoclonal antibodies (mAbs) are composed of a prefix, a substem A, a substem B and a suffix.

· The common stem for mAbs is *-mab,* placed as a suffix.

· The stem *-mab* is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

· Substem B indicates the species on which the immunoglobulin sequence of the mAb is based:

a	rat
axo (pre-sub-stem)	rat/mouse
e	hamster
i	primate
o	mouse
u	human
xi	chimeric
xizu	chimeric/humanized
zu	humanized

The distinction between chimeric and humanized antibodies is as follows:

Chimeric: A chimeric antibody is one of which both chain types are chimeric as a result of antibody engineering. A chimeric chain is a chain that contains a foreign variable domain (V-D-J-REGION) (originating from one species other than human, or synthetic) linked to a constant region (C-REGION) of human origin.

Humanized: A humanized antibody is one of which both chain types are humanized as a result of antibody engineering. A humanized chain is a chain in which the complementarity determining regions (CDR) of the variable domains are foreign (originating from one species other than human, or synthetic) whereas the remaining chain is of human origin. By extension an antibody is described as humanized if more recent protocoles were used for the humanization.

The *–xizu-* infix is used for an antibody having both chimeric and humanized chains.
The *-axo-* infix is used for an antibody having both rat and mouse chains.

· Substem A indicates the target (molecule, cell, organ) class:

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion)	neural
-s(o)-	bone
-tox(a)	toxin
-t(u)-	tumour
-v(i)-	viral

In principle, a single letter, e.g. *-b-* for bacterial is used as substem A. Whenever substem B starts with a consonant (e.g. x or z), to avoid problems in pronunciation, an additional vowel indicated in the table, e.g. *-ba-* is inserted.

Prefix

The prefix should be random, e.g. the only requirement is to contribute to an euphonious and distinctive name.

Second word

If the product is radiolabelled or conjugated to another chemical, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For instance, for mAbs conjugated to a toxin, the suffix *-tox* can be used in the second word.

If the monoclonal antibody is used as a carrier for a radioisotope, the latter will be listed first in the INN, e.g. *technetium (^{99m}Tc) nofetumomab merpentan (81)(42)*.

The prefix *peg-* can be used for pegylated mAbs, but this should be avoided if it leads to over-long INN. In most cases, it is best to adopt two-word INN for pegylated mAbs, with the first word describing the mAb and the second being pegol or a related designation.

References

1. World Health Organization. International Nonproprietary Names (INN) Working Group Meeting on Nomenclature for Monoclonal Antibodies (mAb), Geneva, October 2008, Meeting report, INN Working Document 08.242 *
2. World Health Organization. International Nonproprietary Names (INN) for biological and biotechnological substances (a review), INN Working Document 05.179, update November 2009*
3. World Health Organization. The use of stems in the selection of International Nonproprietary Names (INN) for pharmaceutical substances, 2009, *WHO/PSM/QSM/2009.3**

* *These documents are available on the INN Programme Website at:*

http://www.who.int/medicines/services/inn/en/index.html

ANNEX 4

INNs FOR GENE THERAPY PRODUCTS

The following nomenclature scheme was adopted by the members of the INN Expert Group designated to deal with the selection of nonproprietary names in December 2005 after a broad consultative process. These tables show the latest developments.
A two-word name approach has been selected:

Word 1 *gene component*

prefix	infix	suffix
random to contribute to euphonious and distinctive name	to identify the gene using, when available, existing infixes for biological products or using similar infix as for the protein for which the gene codes. e.g. *-cima-*: cytosine deaminase *-ermin-*: growth factor *-kin-*: interleukin *-lim-*: immunomodulator *-lip-*: human lipoprotein lipase *-mul-*: multiple gene *-stim-*: colony stimulating factor *-tima-*: thymidine kinase *-tusu-*: tumour suppression	*-(*a vowel*)gene* e.g. *-(o)gene*

Word 2 *vector component*

prefix	infix	suffix
random to contribute to euphonious and distinctive name	e.g. *-adeno-*: adenovirus *-cana-*: canarypox virus *-foli-*: fowlpox virus *-herpa-*: herpes virus *-lenti-*: lentivirus *-morbilli-*: paramyxoviridae morbillivirus *-parvo-*: adeno-associated virus (parvoviridae dependovirus) *-retro-*: other retrovirus *-vaci-*: vaccinia virus	*-vec (*nonreplicating viral vector*)* *-repvec* (replicating viral vector)
		-plasmid (plasmid vector)

In the case of non-plasmid naked DNA products, there is no need for a second word in the name.
In case of antisense oligonucleotides, please refer to the aéready existing stem *–rsen*.

ANNEX 5

Reference to publications containing proposed lists of INNs

List no.	and reference
1	*Chron. Wld Hlth Org.* **7**: 299 (1953)
2	*Chron. Wld Hlth Org.* **8**: 216 (1954)
3	*Chron. Wld Hlth Org.* **9**: 313 (1954)
4	*Chron. Wld Hlth Org.* **10**: 28 (1956)
5	*Chron. Wld Hlth Org.* **11**: 231 (1957)
6	*Chron. Wld Hlth Org.* **12**: 102 (1958)
7	*WHO Chronicle* **13**: 105 (1959)
8	*WHO Chronicle* **13**: 152 (1959)
9	*WHO Chronicle* **14**: 168 (1960)
10	*WHO Chronicle* **14**: 244 (1960)
11	*WHO Chronicle* **15**: 314 (1961)
12	*WHO Chronicle* **16**: 385 (1962)
13	*WHO Chronicle* **17**: 389 (1963)
14	*WHO Chronicle* **18**: 433 (1964)
15	*WHO Chronicle* **19**: 446 (1965)
16	*WHO Chronicle* **20**: 216 (1966)
17	*WHO Chronicle* **21**: 70 (1967)
18	*WHO Chronicle* **21**: 478 (1967)
19	*WHO Chronicle* **22**: 112 (1968)
20	*WHO Chronicle* **22**: 407 (1968)
21	*WHO Chronicle* **23**: 183 (1969)
22	*WHO Chronicle* **23**: 418 (1969)
23	*WHO Chronicle* **24**: 119 (1970)
24	*WHO Chronicle* **24**: 413 (1970)
25	*WHO Chronicle* **25**: 123 (1971)
26	*WHO Chronicle* **25**: 415 (1971)
27	*WHO Chronicle* **26**: 121 (1972)
28	*WHO Chronicle* **26**: 414 (1972)
29	*WHO Chronicle* **27**: 120 (1973)
30	*WHO Chronicle* **27**: 380 (1973)
31	*WHO Chronicle* **28**: 133 (1974)
32	*WHO Chronicle* **28**: No. 9, suppl. (1974)
33	*WHO Chronicle* **29**: No. 3, suppl. (1975)
34	*WHO Chronicle* **29**: No. 9, suppl. (1975)
35	*WHO Chronicle* **30**: No. 3, suppl. (1976)
36	*WHO Chronicle* **30**: No. 9, suppl. (1976)
37	*WHO Chronicle* **31**: No. 3, suppl. (1977)
38	*WHO Chronicle* **31**: No. 9, suppl. (1977)
39	*WHO Chronicle* **32**: No. 3, suppl. (1978)
40	*WHO Chronicle* **32**: No. 9, suppl. (1978)
41	*WHO Chronicle* **33**: No. 3, suppl. (1979)
42	*WHO Chronicle* **33**: No. 9, suppl. (1979)
43	*WHO Chronicle* **34**: No. 3, suppl. (1980)
44	*WHO Chronicle* **34**: No. 9, suppl. (1980)
45	*WHO Chronicle* **35**: No. 3, suppl. (1981)
46	*WHO Chronicle* **35**: No. 5, suppl. (1981)
47	*WHO Chronicle* **36**: No. 2, suppl. (1982)
48	*WHO Chronicle* **36**: No. 5, suppl. (1982)
49	*WHO Chronicle* **37**: No. 2, suppl. (1983)
50	*WHO Chronicle* **37**: No. 5, suppl. (1983)
51	*WHO Chronicle* **38**: No. 2, suppl. (1984)
52	*WHO Chronicle* **38**: No. 4, suppl. (1984)
53	*WHO Chronicle* **39**: No. 1, suppl. (1985)
54	*WHO Chronicle* **39**: No. 4, suppl. (1985)
55	*WHO Chronicle* **40**: No. 1, suppl. (1986)
56	*WHO Chronicle* **40**: No. 5, suppl. (1986)

List no.	and reference
57	*WHO Drug Information* **1**: No. 2 (1987)
58	*WHO Drug Information* **1**: No. 3 (1987)
59	*WHO Drug Information* **2**: No. 2 (1988)
60	*WHO Drug Information* **2**: No. 4 (1988)
61	*WHO Drug Information* **3**: No. 2 (1989)
62	*WHO Drug Information* **3**: No. 4 (1989)
63	*WHO Drug Information* **4**: No. 2 (1990)
64	*WHO Drug Information* **4**: No. 4 (1990)
65	*WHO Drug Information* **5**: No. 2 (1991)
66	*WHO Drug Information* **5**: No. 4 (1991)
67	*WHO Drug Information* **6**: No. 2 (1992)
68	*WHO Drug Information* **6**: No. 4 (1992)
69	*WHO Drug Information* **7**: No. 2 (1993)
70	*WHO Drug Information* **7**: No. 4 (1993)
71	*WHO Drug Information* **8**: No. 2 (1994)
72	*WHO Drug Information* **8**: No. 4 (1994)
73	*WHO Drug Information* **9**: No. 2 (1995)
74	*WHO Drug Information* **9**: No. 4 (1995)
75	*WHO Drug Information* **10**: No. 2 (1996)
76	*WHO Drug Information* **10**: No. 4 (1996)
77	*WHO Drug Information* **11**: No. 2 (1997)
78	*WHO Drug Information* **11**: No. 4 (1997)
79	*WHO Drug Information* **12**: No. 2 (1998)
80	*WHO Drug Information* **12**: No. 4 (1998)
81	*WHO Drug Information* **13**: No. 2 (1999)
82	*WHO Drug Information* **13**: No. 4 (2000)
83	*WHO Drug Information* **14**: No. 2 (2000)
84	*WHO Drug Information* **14**: No. 4 (2000)
85	*WHO Drug Information* **15**: No. 2 (2001)
86	*WHO Drug Information* **16**: No. 1 (2002)
87	*WHO Drug Information* **16**: No. 2 (2002)
88	*WHO Drug Information* **17**: No. 1 (2003)
89	*WHO Drug Information* **17**: No. 3 (2003)
90	*WHO Drug Information* **18**: No. 1 (2004)
91	*WHO Drug Information* **18**: No. 2 (2004)
92	*WHO Drug Information* **18**: No. 4 (2004)
93	*WHO Drug Information* **19**: No. 2 (2005)
94	*WHO Drug Information* **19**: No. 4 (2005)
95	*WHO Drug Information* **20**: No. 2 (2006)
96	*WHO Drug Information* **20**: No. 4 (2006)
97	*WHO Drug Information* **21**: No. 2 (2007)
98	*WHO Drug Information* **21**: No. 4 (2007)
99	*WHO Drug Information* **22**: No. 2 (2008)
100	*WHO Drug Information* **22**: No. 4 (2008)
101	*WHO Drug Information* **23**: No. 2 (2009)
102	*WHO Drug Information* **23**: No. 4 (2009)
103	*WHO Drug Information* **24**: No. 2 (2010)
104	*WHO Drug Information* **24**: No. 4 (2010)
105	*WHO Drug Information* **25**: No. 2 (2011)
106	*WHO Drug Information* **25**: No. 4 (2011)
107	*WHO Drug Information* **26**: No. 2 (2012)
108	*WHO Drug Information* **26**: No. 4 (2012)
109	*WHO Drug Information* **27**: No. 2 (2013)

Lists 1-105 of proposed INN are included in *Cumulative List* No. 14, WHO, Geneva, 2011 (available in CD-ROM only)

ANNEX 6

WHY INNs?

Since the number of drug substances being registered during the last decades is constantly increasing, there is a strong need to ensure the identification of each pharmaceutical compound by a unique, universally available and accepted name. The existence of an international nomenclature system for pharmaceutical products is crucial for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.

An **International Nonproprietary Name (INN)** identifies a pharmaceutical substance by a **unique name that is globally recognized and is public property**. A nonproprietary name is also known as a generic name. Generic names are intended to be used in pharmacopoeias, labeling, advertising, drug regulation and scientific literature.

WHO has a constitutional mandate to offer recommendations to its Member States on any matter that falls within its competence. This includes setting norms and standards for pharmaceutical products moving in international commerce.

The INN system as it exists today was initiated in 1950 by the *World Health Assembly resolution WHA3.11* and began operating in 1953, when the first list of International Nonproprietary Names for pharmaceutical substances was published.

So far, some 8800 names have been designated as INNs, and this number is growing every year by some 120 – 150 new INNs.

INNs are selected in close collaboration with national nomenclature commissions (e.g. BAN *British Approved name*, JAN *Japanese Accepted Name*, USAN *United States Adopted Name* etc.). Today, the INN Committee assumes the leading role in assigning generic names to drug substances. Instances where a national generic name for a new pharmaceutical substance is different from the INN are rare exceptions.

As unique names, INNs have to be distinctive in sound and spelling, and should not be liable to confusion with other names in common use (e.g. trade marks). To make INNs universally available they are formally placed by WHO in the public domain, hence their designation as “nonproprietary”. They can be used without any restriction whatsoever to identify pharmaceutical substances. The clear depiction of INNs on labels assures that prescribers and users alike can easily identify the nature of the pharmacologically active substance in a brand product. The use of INNs is already common in research and clinical documentation, while the importance of the Programme is growing further due to the expanding use of generic names for pharmaceutical products.

28/10/2013

The Antibody Society maintains a comprehensive table of approved antibody therapeutics and those in regulatory review in the European Union (EU) or United States (US). In the table below, candidates undergoing review are listed first, and approved products are listed in reverse chronological order by year of first approval. Products that were granted approvals but subsequently withdrawn from the market are included in the table. Approved antibody therapeutics that were not granted a first approval (i.e., first approval in any country for any indication) in either the EU or US are listed at the end of the table.

Therapeutic monoclonal antibodies approved or in review in the European Union or the United States

International non-proprietary name	Brand name	Target; Format	Indication first approved or reviewed	First EU approval year	First US approval year
Erenumab	(Pending)	CGRP receptor; Human IgG2	Migraine prevention	In review	In review
Ibalizumab	(Pending)	CD4; Humanized IgG4	HIV infection	NA	In review
Tildrakizumab	(Pending)	IL-23 p19; Humanized IgG1	Plaque psoriasis	In review	In review
Caplacizumab	(Pending)	von Willebrand factor; Humanized Nanobody	Acquired thrombotic thrombocytopenic purpura	In review	NA
Benralizumab	(Pending)	IL-5R α; Humanized IgG1	Asthma	In review	In review
Burosumab	(Pending)	FGF23; Human IgG1	X-linked hypophosphatemia	In review	NA
Sirukumab	(Pending)	IL-6; Human IgG1	Rheumatoid arthritis	In review	In review
Romosozumab	EVENITY	Sclerostin; Humanized IgG2	Osteoporosis in postmenopausal women at increased risk of fracture	NA	In review
(Pending)	Xilonix	IL-1 α; Human IgG1	Advanced colorectal cancer	In review	NA
Guselkumab	TREMFYA	IL-23 p19; Human IgG1	Plaque psoriasis	In review	2017
Inotuzumab ozogamicin	BESPONSA	CD22; Humanized IgG4; ADC	Acute lymphoblastic leukemia	2017	In review
Sarilumab	Kevzara	IL-6R; Human IgG1	Rheumatoid arthritis	2017	2017
Durvalumab	IMFINZI	PD-L1; Human IgG1	Bladder cancer	NA	2017
Dupilumab	Dupixent	IL-4R α; Human IgG4	Atopic dermatitis	In review	2017
Ocrelizumab	OCREVUS	CD20; Humanized IgG1	Multiple sclerosis	In review	2017
Avelumab	Bavencio	PD-L1; Human IgG1	Merkel cell carcinoma	In review	2017
Brodalumab	Siliq, LUMICEF	IL-17R; Human IgG2	Plaque psoriasis	EC decision pending	2017
Atezolizumab	Tecentriq	PD-L1; Humanized IgG1	Bladder cancer	In review	2016
Bezlotoxumab	Zinplava	*Clostridium difficile* enterotoxin B; Human IgG1	Prevention of *Clostridium difficile* infection recurrence	2017	2016
Olaratumab	Lartruvo	PDGFRα; Human IgG1	Soft tissue sarcoma	2016	2016

Reslizumab	Cinqaero, Cinqair	IL-5; Humanized IgG4	Asthma	2016	2016
Obiltoxaximab	Anthim	Protective antigen of B. anthracis exotoxin; Chimeric IgG1	Prevention of inhalational anthrax	NA	2016
Ixekizumab	Taltz	IL-17a; Humanized IgG4	Psoriasis	2016	2016
Daratumumab	Darzalex	CD38; Human IgG1	Multiple myeloma	2016	2015
Elotuzumab	Empliciti	SLAMF7; Humanized IgG1	Multiple myeloma	2016	2015
Necitumumab	Portrazza	EGFR; Human IgG1	Non-small cell lung cancer	2015	2015
Idarucizumab	Praxbind	Dabigatran; Humanized Fab	Reversal of dabigatran-induced anticoagulation	2015	2015
Mepolizumab	Nucala	IL-5; Humanized IgG1	Severe eosinophilic asthma	2015	2015
Alirocumab	Praluent	PCSK9; Human IgG1	High cholesterol	2015	2015
Evolocumab	Repatha	PCSK9; Human IgG2	High cholesterol	2015	2015
Dinutuximab	Unituxin	GD2; Chimeric IgG1	Neuroblastoma	2015	2015
Secukinumab	Cosentyx	IL-17a; Human IgG1	Psoriasis	2015	2015
Nivolumab	Opdivo	PD1; Human IgG4	Melanoma, non-small cell lung cancer	2015	2014
Blinatumomab	Blincyto	CD19, CD3; Murine bispecific tandem scFv	Acute lymphoblastic leukemia	2015	2014
Pembrolizumab	Keytruda	PD1; Humanized IgG4	Melanoma	2015	2014
Ramucirumab	Cyramza	VEGFR2; Human IgG1	Gastric cancer	2014	2014
Vedolizumab	Entyvio	α4β7 integrin; humanized IgG1	Ulcerative colitis, Crohn disease	2014	2014
Siltuximab	Sylvant	IL-6; Chimeric IgG1	Castleman disease	2014	2014
Obinutuzumab	Gazyva, Gazyvaro	CD20; Humanized IgG1; Glycoengineered	Chronic lymphocytic leukemia	2014	2013
Ado-trastuzumab emtansine	Kadcyla	HER2; humanized IgG1; ADC	Breast cancer	2013	2013
Raxibacumab	(Pending)	B. anthrasis PA; Human IgG1	Anthrax infection	NA	2012
Pertuzumab	Perjeta	HER2; humanized IgG1	Breast Cancer	2013	2012
Brentuximab vedotin	Adcetris	CD30; Chimeric IgG1; ADC	Hodgkin lymphoma, systemic anaplastic large cell lymphoma	2012	2011
Belimumab	Benlysta	BLyS; Human IgG1	Systemic lupus erythematosus	2011	2011
Ipilimumab	Yervoy	CTLA-4; Human IgG1	Metastatic melanoma	2011	2011
Denosumab	Prolia	RANK-L; Human IgG2	Bone Loss	2010	2010
Tocilizumab	RoActemra, Actemra	IL-6R; Humanized IgG1	Rheumatoid arthritis	2009	2010
Ofatumumab	Arzerra	CD20; Human IgG1	Chronic lymphocytic leukemia	2010	2009
Canakinumab	Ilaris	IL-1β; Human IgG1	Muckle-Wells syndrome	2009	2009
Golimumab	Simponi	TNF; Human IgG1	Rheumatoid and psoriatic arthritis, ankylosing spondylitis	2009	2009

Ustekinumab	Stelara	IL-12/23; Human IgG1	Psoriasis	2009	2009
Certolizumab pegol	Cimzia	TNF; Humanized Fab, pegylated	Crohn disease	2009	2008
Catumaxomab	Removab	EPCAM/CD3;Rat/mouse bispecific mAb	Malignant ascites	2009#	NA
Eculizumab	Soliris	C5; Humanized IgG2/4	Paroxysmal nocturnal hemoglobinuria	2007	2007
Ranibizumab	Lucentis	VEGF; Humanized IgG1 Fab	Macular degeneration	2007	2006
Panitumumab	Vectibix	EGFR; Human IgG2	Colorectal cancer	2007	2006
Natalizumab	Tysabri	a4 integrin; Humanized IgG4	Multiple sclerosis	2006	2004
Bevacizumab	Avastin	VEGF; Humanized IgG1	Colorectal cancer	2005	2004
Cetuximab	Erbitux	EGFR; Chimeric IgG1	Colorectal cancer	2004	2004
Efalizumab	Raptiva	CD11a; Humanized IgG1	Psoriasis	2004#	2003#
Omalizumab	Xolair	IgE; Humanized IgG1	Asthma	2005	2003
Tositumomab-I131	Bexxar	CD20; Murine IgG2a	Non-Hodgkin lymphoma	NA	2003#
Ibritumomab tiuxetan	Zevalin	CD20; Murine IgG1	Non-Hodgkin lymphoma	2004	2002
Adalimumab	Humira	TNF; Human IgG1	Rheumatoid arthritis	2003	2002
Alemtuzumab	Lemtrada; MabCampath, Campath-1H	CD52; Humanized IgG1	Multiple sclerosis; chronic myeloid leukemia#	2013; 2001#	2014; 2001#
Gemtuzumab ozogamicin	Mylotarg	CD33; Humanized IgG4; ADC	Acute myeloid leukemia	In review	In review; 2000#
Trastuzumab	Herceptin	HER2; Humanized IgG1	Breast cancer	2000	1998
Infliximab	Remicade	TNF; Chimeric IgG1	Crohn disease	1999	1998
Palivizumab	Synagis	RSV; Humanized IgG1	Prevention of respiratory syncytial virus infection	1999	1998
Basiliximab	Simulect	IL-2R; Chimeric IgG1	Prevention of kidney transplant rejection	1998	1998
Daclizumab	Zinbryta; Zenapax	IL-2R; Humanized IgG1	Multiple sclerosis; prevention of kidney transplant rejection#	2016; 1999#	2016; 1997#
Rituximab	MabThera, Rituxan	CD20; Chimeric IgG1	Non-Hodgkin lymphoma	1998	1997
Edrecolomab	Panorex	EpCAM; Murine IgG2a	Colon cancer	1995*#	NA
Abciximab	Reopro	GPIIb/IIIa; Chimeric IgG1 Fab	Prevention of blood clots in angioplasty	1995*	1994
Nebacumab	Centoxin	Endotoxin; Human IgM	Gram-negative sepsis	1991*#	NA
Muromonab-CD3	Orthoclone Okt3	CD3; Murine IgG2a	Reversal of kidney transplant rejection	1986*	1986#

Source: Janice M. Reichert, PhD, The Antibody Society; table updated July 13, 2017.

Table notes: *, Country-specific approval. #, Withdrawn or marketing discontinued for the first approved indication. NA, not approved or in review in the EU; not approved or information on review status not available in US.

Additional notes:
1. Of the antibody therapeutics listed in the table, the following products were not first approved in the EU or US:
Sarilumab, first approved in Canada on January 12, 2017;
Brodalumab, first approved in Japan on July 4, 2016;
Secukinumab, first approved in Japan in December 2014;
Cetuximab, first approved in Switzerland December 1, 2003.

2. Several antibody therapeutics are approved for marketing in regions other than the EU or US. These products include:
Nimotuzumab (TheraCIM®, BIOMAB-EGFR®), humanized anti-EGFR IgG1 approved in numerous countries for various forms of solid tumors starting in the 2000s;
Mogamulizumab (POTELIGEO®), humanized anti-CCR4 IgG1 first approved in Japan on March 30, 2012 for relapsed or refractory CCR4-positive adult T-cell leukemia-lymphoma;
Itolizumab (Alzumab), humanized anti-CD6 IgG1 approved in India in January 2013 for psoriasis;
Rmab (RabiShield), human anti-rabies virus G glycoprotein IgG1 approved in India in 2016 for post-exposure prophylaxis of rabies.

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WHO Drug Information

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Contents *(continued)*

International Nonproprietary Names

Nomenclature for monoclonal antibodies

In October 2008, the World Health Organization's (WHO) Programme on International Nonproprietary Names (INN) convened a Working Group meeting to discuss nomenclature for monoclonal antibodies (mAbs). The objective of the meeting was to review the current situation in light of the challenges highlighted during the 46th Consultation on International Nonproprietary Names (INNs) for Pharmaceutical Substances in April 2008 (1, 2). The Working Group focused on drafting recommendations for any necessary modifications to the system to facilitate development of INNs for mAbs. A report from that meeting has now been published and is summarized below.

The first INN for a monoclonal antibody (mAb), muromonab CD3, was adopted twenty years ago. Following this, the stem –mab was proposed and adopted for all new INNs for mAbs. Between 1991 and 1993, the basis of the INN system for mAbs was devised with the first infixes for source and target of antibodies being formulated. Since 1998, 173 mAb INNs have been published and this class of products now represents a significant proportion of the total number of INNs for biologicals. This period also saw a move away from rodent-sequence mAbs to humanized or human mAbs.

Requirements for INNs for mAbs
INNs for mAbs must be unique and unrelated to trade names/trademarks. They must be distinct and transposable into several languages. They need to be convenient for users and it is preferable that they be limited to no more than three or four syllables. INNs are intended to provide information concerning mAbs to scientists, physicians, pharmacists and other interested parties.

The linguistics concerning INNs for mAbs can be very problematic. Many groups of INNs appear "overcrowded" and many have similarities in look or sound. This situation is made more complex by the need to include systems for pegylated mAbs and for radiolabelled mAbs. Additionally, mAb conjugates use a second word for the non-mAb part.

The length and complexity of the words and stems has led to clumsy, long INNs when compared to INNs for other classes of biologicals and chemicals and the need to adopt INNs for an ever increasing number of mAb products is causing INNs to become ever longer. At present 52 names have 4 syllables, 99 have 5 syllables and 5 have 6 syllables and this trend towards very long names is increasing. The clinical success rate for mAbs is relatively low compared with other products, which results in many adopted INNs finally remaining unused, at least as names for approved products.

Usage, stems and sub-stems
The stem -mab is well accepted and recognized as indicating a mAb. However, several antibody products are fragments, such as Fab or F(ab')2 while a range of other types of fragments (e.g., minibodies) are being developed. It would be possible to adopt new stems for these, e.g., -fab, but this would cause confusion since several Fab fragments have already been given an INN with the -mab stem. It is also unclear if -fab would be used for all fragments or whether further stems would also need to be adopted.

Sub-stems (infixes) which indicate species sequence/structure of mAbs are widely understood and used. They may also include some information on how the mAb may have been produced. Four such sub-stems, -zu-,-o-,-u-,-xi- (humanized, mouse, human and chimeric) have been used, but some e.g., -e- and -i- (hamster and primate mAbs), have never been used. Nonetheless, it is possible that this could change in the future: for example, there is current interest in some primate antibodies. It has been proposed to discontinue the use of sub-stems and replace them with syllables indicating the specific targets of the mAbs. However, this would cause discontinuity with existing INNs and ignores any need to consider the species origin of the sequence of mAbs.

Sub-stems for disease/target are less well known. The target sub-stems -li- (immunomodulatory) and -tu- (tumour) have been used mostly: 48 as -li(m)- and 50 as -tu(m)-, followed by -vi(r)-. Others have much lower usage. Specific tumour sub-stems (other than -tu(m)-) have been little used and some have never been used. In many cases it is possible to select more than one sub-stem for a particular mAb. It may be necessary to introduce new target-related sub-stems for some types of antibodies such as bispecific mAbs.

Post-translational modifications and implications for INNs

MAbs undergo post-translational modifications which are dependent on the expression system used for production. Most of these do not significantly affect clinical use but some can influence pharmacokinetics and/or immunobiological functions. In particular, glycosylation can, in some cases, be necessary for optimal clinical activity. Nearly all mAbs are glycosylated and show expression system and production process related glycan structures. Glycosylation sites are present in the Fc region and sometimes also in the Fab part of the mAb. Differences in glycosylation of mAbs can be introduced deliberately (by glycoengineering) or occur unintentionally because of differences in manufacturing processes. Products are ‘mixtures’ containing different glycoforms and are not all of one homogeneous glycoprotein structure. Different batches of a product can vary in microheterogeneity and, in addition, modification to production processes can result in changes in glycosylation pattern (and other post-translational modifications). Significant clinical effects of glycosylation may need to be reflected in INNs.

Although most mAbs are glycosylated, their INNs have not been given terminal Greek letters as has been done for some other glycoproteins (e.g., hormones). The possibility exists that two or more mAbs could be produced which have the same amino acid sequence, but differ in glycosylation. To introduce terminal Greek letters for all new INNs could cause confusion and discontinuity with existing INNs.

At present all existing INNs for mAbs relate to mAbs with different amino acid sequences. If future INN applications are received for mAbs with the same sequence as an existing mAb, but different glycosylation, the INN for the latter application could be the existing INN but with a terminal beta added. Subsequent Greek letters could be used for further INNs for mAbs with this antibody sequence, as for other glycoproteins. Concern was also raised that the use of Greek letters to denote any difference in glycosylation could lead to product specific INNs which would undermine the nonproprietary nature of the INN. Nevertheless, this is consistent with the INN policy for recombinant DNA derived proteins.

Definitions

The INN cannot possibly fully describe all the characteristics of a mAb. The descrip-

tion/definition should be the source of detailed information concerning the mAb. Definitions are very important but some are very complicated and detailed. They should consist of two parts, one general and easy to follow and the other more detailed. The definition is linked to the amino acid sequence.

Applicants will need to be asked to provide the required information for the definition as well as details on glycosylation, etc. The details of the type of information needed are available on the INN application form and the correct amino acid sequence must be stated. The clone name should also be included but not in the general definition. If mAbs contain a glycosylation site, then they will normally be glycosylated. If the mAb is glycoengineered this should be indicated in the definition.

General policies for monoclonal antibodies

- INNs for monoclonal antibodies (mAbs) are composed of a prefix, a substem A, a substem B and a suffix.
- The common stem for mAbs is -mab, placed as a suffix.
- The stem -mab is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

Sub-stem B indicates the species on which the immunoglobulin sequence of the mAb is based:

a		rat
axo	(pre-sub-stem)	rat/mouse
e		hamster
i		primate
o		mouse
u		human
xi		chimeric
-xizu-	(under discussion)	chimeric/humanized
zu		humanized

The distinction between chimeric and humanized antibodies is as follows:

A ***chimeric*** antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable domain of both heavy and light chains linked to heavy and light constant regions of human origin.

A ***humanized*** antibody has segments of foreign-derived amino acids interspersed among variable domain segments of human-derived amino acid residues and the humanized variable heavy and variable light domains are linked to heavy and light constant regions of human origin.

The -xizu- infix is used for an antibody having both chimeric and humanized chains.

The -axo- infix is used for an antibody having both rat and mouse chains.

Continued overleaf ...

General policies for monoclonal antibodies *(continued)*

Sub-stem A indicates the target (molecule, cell, organ) class:

-b(a)-	bacterial
-c(i)-	cardiovascular
-f(u)-	fungal
-k(i)-	interleukin
-l(i)-	immunomodulating
-n(e)- (under discussion)	neural
-s(o)-	bone
-tox(a)	toxin
t(u)	tumour
-v(i)-	viral

In principle, a single letter, e.g., -b- for bacterial, is used as substem A. Whenever substem B starts with a consonant (e.g., x or z), an additional vowel indicated in the table, e.g., -ba-, is inserted to avoid problems in pronunciation.

Prefix
The prefix should be random, e.g., the only requirement is to contribute to a euphonious and distinctive name.

Second word
If the product is radiolabelled or conjugated to another chemical, identification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For instance, for mAbs conjugated to a toxin, the suffix -tox can be used in the second word.

If the monoclonal antibody is used as a carrier for a radio-isotope, the latter will be listed first in the INN, e.g., technetium (99mTc) nofetumomab merpentan (81).

The prefix peg- can be used for pegylated mAbs, but this should be avoided if it leads to over-long INNs. In most cases, it is best to adopt two-word INNs for pegylated mAbs, with the first word describing the mAb and the second being pegol or a related designation.

Other matters
Information relating to details of structure (which must be provided by the manufacturer/applicant) is crucial for deciding on an appropriate INN. It is up to manufacturers to approach WHO for an INN and regulators should request companies to apply for an INN. They are also responsible for checking and validating if an INN is correctly used and corresponds to the substance which is the subject of a Marketing Authorization.

Companies should apply for an INN when clinical evaluation begins. INNs are needed for a product at this stage because an alternative means of identification, e.g., using manufacturer codes, is very confusing.

Many mAbs fail at phase III trials. This is late in the evaluation process when they will almost certainly have received an INN. This accounts for the many INNs which exist for clinically failed mAbs.

Recommendations

The present system needs modification, revision and improvement to deal with specific problems. However, it has been used successfully for twenty years and changes should be carefully considered and implemented only where necessary. The following proposals have been highlighted in particular:

- The stem -mab should be retained. Also -mab is to continue to be used for mAb fragments. The description should clearly indicate if the product is a fragment.

- The system for conjugates and radiolabelled mAbs need not be changed.

- The stem -mab is to be used for all products containing an immunoglobulin variable domain which binds to a defined target.

- The prefix peg- can be used for pegylated mAbs, but this should be avoided if it leads to an over-long INN. In most cases, it is best to adopt two-word INNs for pegylated mAbs, with the first word describing the mAb and the second being pegol. This is consistent with INNs for other pegylated substances.

- The use of sub-stems is valuable but possibly too complicated. The 'source' sub-stem should be kept but redefined as 'the species on which the immunoglobulin sequence of the mAb is based'. The 'tumour group' sub-stem should be simplified to -tu(m)-, the other tumour sub-stems should be discontinued. But -tu(m)- should be truncated to -t- or -tu-. Similarly -li(m)- should be truncated to -m- or discontinued and replaced with more precise sub-stems, which relate to the target. Also the other sub-stems for 'disease or target' should be shortened, e.g., -fung- to -f-.

- The use of Greek terminal letters to indicate differences in glycosylation cannot be introduced retrospectively. However, mAbs which have the same amino acid sequence but different glycosylation may need distinct INNs unless significant differences on post-translational modifications are excluded/misproven. In particular, if the glycosylation has been glycoengineered to produce a different structure, then the glycoengineered mAb should be given a different INN to the parent mAb.

- When the antibody is directed against a toxin, the infix -toxa- can be used in the name. For monoclonals conjugated to a toxin, the suffix -tox can be used in the second word. This will be clarified in the mAb naming rules.

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Safety and Efficacy Issues

Mycophenolate mofetil: pure red cell aplasia

Canada — The manufacturer of mycophenolate mofetil (CellCept®) has provided new safety information on reports of pure red cell aplasia (PRCA). Mycophenolate mofetil is an immunosuppressive agent indicated for the prophylaxis of acute transplant rejection in adults receiving allogeneic renal, cardiac or hepatic transplants, and in children and adolescents (2–18 years) receiving renal transplants. Mycophenolate mofetil should be used concomitantly with cyclosporine and corticosteroids.

The mechanism for mycophenolate mofetil induced PRCA is unknown. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy. In transplant patients, however, reduced immunosuppression may place the graft at risk. PRCA is usually treated by attending to the underlying condition (disease) or discontinuing the drug that causes PRCA.

PRCA is a type of anaemia that develops secondary to failure of erythropoiesis. Erythropoiesis is a process by which red blood cells (RBCs) are produced from immature precursors in the bone marrow. PRCA describes a condition in which RBC precursors in bone marrow are nearly absent, while megakaryocytes and white blood cell precursors are usually present at normal levels. PRCA may be idiopathic or occur as a manifestation of an underlying condition. Approximately 5% of all cases of PRCA are drug induced. Patients with PRCA may present with fatigue, lethargy, and/or abnormal paleness of the skin. Anaemia is the primary clinical concern in PRCA. The degree of anaemia can range from subclinical to severe.

As of 24 February 2008, 41 cases of PRCA have been reported in patients receiving mycophenolate mofetil in combination with other immunosuppressive agents (tacrolimus, cyclosporine, corticosteroids, azathioprine, sirolimus and alemtuzumab).

Reference: Communication dated 3 June 2009 from Hoffmann-La Roche Limited posted on the Health Canada site at http://www.hc-sc.gc.ca

Swine flu ADR portal

United Kingdom — Oseltamivir (Tamiflu®) and zanamivir (Relenza®) have been stockpiled for management of the swine flu pandemic. In order to efficiently monitor the safety of oseltamivir and zanamivir as their use increases, a special web-based system for reporting suspected ADRs to these medicines – the Swine Flu ADR Portal — has been set up.

This is available at www.mhra.gov.uk/swineflu and will remain in operation for the duration of the pandemic. The portal has been designed to make completing a report as quick and easy as possible. When H1N1 swine flu vaccines become available in the Autumn, the portal should also be used to report suspected ADRs to these vaccines.

The Swine Flu ADR Portal will be open to members of the public as well as health care professionals.

Reference: MHRA. Swine flu - Reporting suspected adverse reactions to Tamiflu®, Relenza® and future Swine flu H1N1 vaccines. http://www.mhra.gov.uk/

Propylthiouracil: serious liver injury

United States of America — The Food and Drug Administration (FDA) has warned health care professionals of the risk of serious liver injury associated with the use of propylthiouracil for the treatment of Graves disease.

Propylthiouracil was approved for marketing in 1947. A total of 32 cases of serious liver injury associated with the use of propylthiouracil were reported to the FDA's Adverse Event Reporting System since that system was established in 1969 through October 2008. Of the 22 adult cases, the FDA identified 12 deaths and five liver transplants. Of the 10 paediatric cases, there was one death and six reports of liver transplant.

Propylthiouracil is considered second-line drug therapy except in certain patients who are allergic or intolerant of methimazole. Because a rare birth defect has been reported with methimazole and not with propylthiouracil, propylthiouracil may be more appropriate for patients with Graves disease who are in the first trimester of pregnancy.

Reference: *FDA News Release*, 3 June 2009 at http://www.fda.gov

Fosamprenavir: myocardial infarction

Canada — The manufacturer of fosamprenavir (Telzir®) has informed healthcare professionals of important safety information regarding a potential association between myocardial infarction and exposure to fosamprenavir in HIV-infected patients. Fosamprenavir is a protease inhibitor (PI) used in combination with low-dose ritonavir and other antiretrovirals in the treatment of HIV-1 infection.

A nested case-control study conducted in the French Hospital Database on HIV has reported an association between exposure to fosamprenavir and an increased risk of myocardial infarction. This may be related to the propensity for this drug class to raise blood lipids. Triglyceride and cholesterol levels should therefore be checked prior to initiating therapy with fosamprenavir and at periodic intervals during therapy. Other modifiable risk factors for cardiovascular disease (such as hypertension, diabetes and smoking) should also be monitored in HIV-infected subjects and managed as clinically appropriate.

Recent data presented at the 16th Conference on Retroviruses and Opportunistic Infections suggested a potential association between fosamprenavir and myocardial infarction in HIV infected adults. The nested case-control study reported an increased risk of myocardial infarction in association with cumulative exposure to fosamprenavir. Myocardial infarction has already been identified as being potentially associated with the PI class in the ongoing Data Collection on Adverse Events of Anti-HIV Drugs (DAD).

Suppression of viral replication in HIV disease with antiretroviral therapy is of the utmost importance. Physicians should monitor a patient's cardiovascular risk as part of the follow-up and seek to adjust modifiable risk factors. Combination antiretroviral therapy is associated with redistribution of body fat (lipodystrophy) in HIV-infected patients. Clinical examination should include evaluation for physical signs of fat distribution. HIV infection itself has been associated with lipid disorders and ischaemic heart disease.

Reference: Communication from the manufacturer dated 17 July 2009 at http://www.hc-sc.gc.ca

TNF inhibitors and lupus erythematosus: an emerging association

Australia — Systemic lupus erythematosus (SLE) is considered drug-induced when, in relation to a suspect drug, both of the following apply:

- Idiopathic lupus features or antibodies are absent prior to treatment.
- Recovery occurs within one year of withdrawal of treatment.

Clinically, drug-induced lupus erythematosus (DILE) tends to be similar to and less severe than idiopathic SLE: arthralgia, myalgia and skin rash (not the classic malar rash) are prominent, renal or neurological involvement is rare. Management requires withdrawal of the suspect drug, after which improvement begins, generally within weeks. Arthralgia/arthritis may call for treatment with an NSAID, and severe symptoms may require short courses of corticosteroids (1).

Tumour necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept) are powerful immunosuppressants approved for indications including rheumatoid and psoriatic arthritis, ankylosing spondylitis, and Crohn disease. However, the deficiency of TNF caused by these drugs is known to predispose some patients to TNF inhibitor-induced SLE.

In clinical studies of rheumatoid arthritis, two of 3000 adalimumab-treated patients developed new-onset lupus-like syndrome, remitting on withdrawal of adalimumab (2). There are also case reports of DILE in association with adalimumab, etanercept and infliximab (3, 4).

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Triamcinolone acetonide: serious ocular reactions

Canada —Triamcinolone acetonide is a synthetic corticosteroid primarily used for its marked anti-inflammatory action (1). It was authorized for use in Canada as a 10-mg/mL suspension (Kenalog-10®) in 1966, and as a 40-mg/mL suspension (Kenalog-40®) in 1973. Currently, generic products are also available. In Canada, the 40-mg/mL suspension has been authorized for intramuscular and intra-articular administration or for injection into tendon sheaths or ganglia. It is indicated for systemic corticosteroid therapy in conditions such as dermatoses or rheumatoid arthritis and other connective tissue disorders (1).

Intravitreal or intra-ocular injection of this product is not an authorized route of administration in Canada. Diabetic macular edema, cystoid macular edema and choroidal neovascularization secondary to age-related macular degeneration are among the conditions for which the use of intravitreal injection of triamcinolone has been reported (2, 3). In 2007, a safety notice was published in France regarding the occurrence of serious ocular adverse reactions (ARs) following intravitreal injections of the 40-mg/mL suspension (4).

Topical ophthalmic, oral and intravenous corticosteroids have long been associated with ocular ARs. Local injections of corticosteroids, even at sites far from the eye, have been associated with eye complications such as the development of cataract, glaucoma, and even retinal and choroidal emboli (5).

Intravitreal injection of triamcinolone has several reported complications including retinal detachment and vitreous haemorrhage. Complications developing later include cataract progression, steroid-induced glaucoma and endophthalmitis (2). Triamcinolone persists for long periods. Low concentrations were found in samples of aqueous humor up to 1.5 years after intravitreal injection (6). Cases of increased intraocular pressure requiring medical intervention following intravitreal injection have also been reported. Patients with a history of primary open-angle glaucoma are at a higher risk of increased intra-ocular pressure (2).

A number of ocular ARs following intravitreal injection of triamcinolone in Canada have been reported in the scientific literature (2). They included increased intraocular pressure requiring glaucoma medication (60 cases), cataract progression requiring extraction (12), endophthalmitis (1) and temporary occlusion of the central retinal artery (1).

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Safety updates on insulin glargine

European Union — The European Medicines Agency (EMEA) is looking into four recently published registry studies investigating a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer. The studies were published on the *Diabetologia* website on 26 June 2009.

Insulin glargine is a long-acting insulin analogue, authorized in the European Union (EU) as Lantus® and Optisulin®, for the treatment of adults, adolescents and children aged six years or above with diabetes when treatment with insulin is required.

The results of the four studies were found to be inconsistent. In two studies (Scottish Diabetes Research Network Epidemiology Group and Jonasson et al) an association between breast cancer was found in a group of patients taking insulin glargine as monotherapy, but not in another group of patients using insulin glargine together with other types of insulin. For other cancers, no association was found. In these two studies, dose-dependency was not evaluated. The third study (Hemkens et al) reported a dose-

dependent association between use of insulin glargine and malignancies. However, no information is available on the types of cancer found in this study. In the fourth study (Currie et al), no association between cancer (either breast, colorectal, pancreatic or prostate cancer) and the use of insulin glargine, or any other insulin, was found.

On the basis of currently available data, a relationship between insulin glargine and cancer cannot be confirmed nor excluded. However, concerns raised by the four studies require further in-depth evaluation (1).

The Committee for Medicinal Products for Human Use (CHMP) has since carried out an in-depth review of four studies and their outcomes. Due to methodological limitations the studies were found to be inconclusive and did not allow a relationship between insulin glargine and cancer to be confirmed or excluded. In addition, the Committee noted that the results of the studies were not consistent.

Because of the limitations of the existing evidence, the Committee has requested the marketing authorization holder to develop a strategy for generation of further research in this area. In addition the Committee is exploring possibilities for cooperation with academia to generate further information.

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Fentanyl transdermal patches and accidental child exposure

Canada — The fentanyl transdermal system is indicated in the management of persistent, moderate to severe chronic pain that cannot be managed by other means such as opioid combination products or immediate-release opioids (1). The system has been marketed in Canada under the brand name Duragesic® since 1992. In 2006, the generic products Ratio-Fentanyl® and Ran-Fentanyl® transdermal systems were introduced.

Safety of the fentanyl transdermal system is contingent on its use according to the conditions recommended in the Canadian product monographs. The warnings and precautions section of the monographs have been updated to include accidental exposure. Examples of accidental exposure include the transfer of a fentanyl transdermal patch while hugging, sharing a bed or moving a patient (1–3).

In December 2008, Health Canada received a report of suspected accidental fentanyl exposure in a healthy 19-month-old child. He was sleeping in the same bed as his mother, who was using a fentanyl patch for chronic pain. The patch inadvertently became attached to the child. He was taken to hospital and given naloxone 0.01mg/kg intramuscularly as required. The child was monitored overnight, and his condition improved after treatment (1–4).

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Clopidogrel interactions with proton pump inhibitors

United Kingdom — The European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) has recently considered the available evidence for an interaction between clopidogrel and proton pump inhibitors (PPIs). They concluded that PPIs reduce the effectiveness of clopidogrel in preventing the recurrence of adverse cardiac events such as heart attack and coronary artery restenosis.

Clopidogrel (Plavix®) is used to prevent atherothrombotic events in patients who have previously had one of these events, or in at-risk patients who have peripheral arterial disease. In combination with aspirin, it can also be used to prevent atherothrombotic events in patients with acute coronary syndrome.

PPIs are used to treat gastrointestinal disorders, oesophageal reflux disease , dyspepsia or gastric ulcers. In the United Kingdom, five PPIs are available on prescription: omeprazole, esomeprazole, pantoprazole, rabeprazole, and lansoprazole. Omeprazole is also available over the counter (Losec®).

Clopidogrel can cause side effects on the gastrointestinal system and is therefore frequently prescribed together with a PPI.

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Long-acting beta-agonists in chronic obstructive pulmonary disease

United Kingdom — Chronic obstructive pulmonary disease (COPD) is a slowly progressive, mainly irreversible disease characterized by airflow limitation. It is one of the few diseases associated with an increasing mortality rate and, by 2020, is predicted to be the third most common cause of death.

The National Institute for Health and Clinical Excellence (NICE) and the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines recommend the addition of a long-acting beta-agonist (LABA) to short-acting beta-2 agonists when moderate COPD is diagnosed. The two LABAs currently licensed for treatment of COPD are salmeterol and formoterol (eformoterol). Both are licensed in COPD either as monotherapy or in conjunction with an ICS (fluticasone propionate and budesonide, respectively).

The Medicines and Healthcare Products Regulatory Agency (MHRA) has recently completed a comprehensive review of the use of LABAs, both as monotherapy and in combination with ICS. The review assessed published literature and unpublished trials investigating the efficacy or safety (or both) of LABA or LABA plus ICS against a range of clinical endpoints. The review concluded that:

- A LABA/ICS combination had greater efficacy than either LABA or ICS monotherapy in every study.

- The extent of the additional benefit provided by the LABA/ICS combination versus LABA alone was variable and was not always clinically significant. A convincing additional benefit of combination therapy was however seen in reduction in the rate of exacerbations.

- A significant additional benefit of the LABA/ICS combination has not been proven for milder disease and ICS should not be introduced earlier than guidelines suggest.

- In terms of efficacy, no clear dose-response relation was shown for either LABAs or ICS. To date, no treatment has been shown to influence the accelerated decline in lung function that is characteristic of COPD, highlighting the limited treatment options for this patient population.

A range of side effects have been reported after LABA or LABA/ICS therapy. However their incidence should be considered in the context of systemic inflammation and several co-existing conditions (including cardiovascular disease).

The overall benefits of long-acting beta-agonists (LABAs) both as monotherapy and in combination with inhaled corticosteroids (ICS) in the treatment of chronic obstructive pulmonary disease (COPD) continue to outweigh any risks. However, healthcare professionals are reminded that ICS should not be used alone in COPD. A key issue remains the increased risk of pneumonia associated with the use of ICS in COPD.

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Varenicline and bupropion: serious mental health events

United States of America — The Food and Drug Administration (FDA) has announced that it is requiring manufacturers to put a boxed warning on the prescribing information for the smoking cessation drugs varenicline (Chantix®) and bupropion (Zyban®). The warning will highlight the risk of serious mental health events including changes in behaviour, depressed mood, hostility, and suicidal thoughts when taking these drugs.

Similar information on mental health events will be required for bupropion marketed as the antidepressant Wellbutrin® and for generic versions of bupropion. These drugs already carry a boxed warning for suicidal behaviour in treating psychiatric disorders.

In addition, the FDA also is requesting more information in the Warnings section of the prescribing information and updated information in the Medication Guide for patients that further discuss the risk of mental health events when using these products.

Manufacturers will also be required to conduct a clinical trial to determine how often serious neuropsychiatric symptoms occur in patients using various smoking cessation therapies, including patients who currently have psychiatric disorders. The FDA's review of adverse events for patients using nicotine patches did not identify a clear link between those medications and suicidal events.

Reference: *Public Health Advisory*, 1 July 2009 at http://www.fda.gov

Pain medications containing propoxyphene: overdose

United States of America — The Food and Drug Administration (FDA) has taken action to reduce the risk of overdose in patients using pain medications such as Darvon® and Darvocet® that contain propoxyphene. Action was taken because of data linking propoxyphene and fatal overdoses.

The agency is requiring manufacturers of propoxyphene-containing products to strengthen the label, including the boxed warning, emphasizing the potential for overdose when using these products. Manufacturers will also be required to provide a medication guide to patients stressing the importance of using the drugs as directed.

In addition, the FDA is requiring a new safety study assessing unanswered questions about the effects of propoxyphene on the heart at higher than recommended doses. Findings from this study, as well as other data, could lead to additional regulatory action.

Propoxyphene has been on the market since 1957. It is widely prescribed and is used as a treatment for mild to moderate pain. The most frequent side effects of propoxyphene include lightheadedness, dizziness, sedation, nausea, and vomiting.

Reference: *FDA News Release*, 7 July 2009 at http://www.fda.gov

Latanoprost and rosiglitazone: macular edema

Australia — Macular edema causes blurred or distorted vision due to painless swelling of the macula. The condition is relatively common and is frequently associated with various ocular conditions including cataract surgery, age-related macular degeneration and, rarely, drug toxicity. Chronic macular edema or multiple recurrences may result in macular photoreceptor damage with permanent impairment of central vision (1).

To date, the Therapeutic Goods Administration (TGA) has received 25 adverse reaction reports of drug-associated macular edema. Most have implicated latanoprost (7 reports from a total of 216 for this drug) or rosiglitazone (9 reports from a total of 344), and three each have reported use of an NSAID or a bisphosphonate.

Latanoprost is a prostaglandin F_2-alfa analogue used as eye drops for the treatment of open angle glaucoma or ocular hypertension either alone (Xalatan®) or in combination with the beta-blocker timolol (Xalacom®). It reduces intraocular pressure by decreasing resistance and thereby increasing uveoscleral outflow of aqueous humor. It has not been found to have significant systemic pharmacological effects.

Macular edema is identified in the latanoprost product information as a potential adverse effect, more commonly occurring in patients with aphakia or pseudophakia with anterior chamber lenses and/or torn posterior lens capsule, or in patients with known risk factors for macular edema such as diabetic retinopathy and retinal vein occlusion. An association between the hypoglycaemic agent rosiglitazone and macular edema is also known. There is evidence that withdrawal of rosiglitazone is followed by resolution of macular edema (2, 3).

Macular edema should be suspected with any loss of visual acuity not correctible by pinhole refraction, and requires prompt specialist evaluation for confirmation of diagnosis and further measures as appropriate.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Metformin, dehydration and lactic acidosis

Australia — Lactic acidosis is a rare but extremely serious metabolic complication of metformin usage. The association has featured in two issues of the *Australian Adverse Drug Reaction Bulletin* (1, 2) and the following boxed warning on this serious reaction appears in product information for metformin-containing products:

"Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment; other risk factors include old age associated with reduced renal function and high doses of metformin (> 2g/day).

'Metformin is contraindicated in acute conditions with the potential to compromise renal function, such as dehydration. This highlights the importance of educating patients about how to manage their diabetes, including their medications, when they become acutely unwell."

Since 1985, the Therapeutic Goods Administration (TGA) has received 141 reports of lactic acidosis associated with metformin, 25 of which described a fatal outcome. Many of the reports describe a recent history of diarrhoea, vomiting or gastrointestinal infection prior to the development of acidosis.

Patients should be educated about managing their diabetes and medications, particularly metformin, in the context of acute illness. If a patient on metformin develops vomiting and/or diarrhoea, especially when coupled with poor oral intake, they should see their doctor and consideration should be given to temporarily ceasing metformin until a normal dietary intake can be tolerated. Consideration should also be given to temporarily withholding any concomitant diuretic therapy, as this will exacerbate acute renal impairment in a dehydrated patient.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 3, June 2009 at http://www.tga.gov.au/adr/aadrb/aadr0906.htm#a1

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Montelukast: suicidality and other psychiatric reactions

Canada — Montelukast sodium (Singulair®), a leukotriene-receptor antagonist, is indicated for the prophylaxis and chronic treatment of asthma in patients two years of age and older (1). It is also indicated for the relief of symptoms of seasonal allergic rhinitis in patients 15 years of age and older when other treatments are not effective or not tolerated. Montelukast has been marketed in Canada since 1997.

Between September 2007 and July 2008, updates were made to the Canadian product monograph to include depression, suicidality and anxiety (1, 2). In March 2008, the US Food and Drug Administration (FDA) stated that it was

investigating further the suspected association between montelukast and suicidality (3). Following the FDA communication, there was a sevenfold increase in the number of montelukast-related cases reported to the Adverse Event Reporting System database in the United States (4).

From the date of marketing to 31 January 2009, Health Canada has received 13 adverse reaction (AR) reports related to suicidality or self-injury suspected of being associated with the use of montelukast.

From the date of marketing to 31 January 2009, Health Canada has received 29 other AR reports relating to depression, hostility or psychosis suspected of being associated with the use of montelukast.

Extracted from Canadian Adverse Reactions Newsletter, volume 19, issue 3, july 2009 at http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v19n3-eng.php

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Duloxetine: serotonin syndrome

Australia — Duloxetine (Cymbalta®) is a serotonin and noradrenaline reuptake inhibitor recently approved for the treatment of major depressive disorder. It was included on the Australian reimbursement system in June 2008 and, to up May 2009, over 200 000 prescriptions have been dispensed. Over this same period, 108 reports of suspected adverse drug reactions with duloxetine have been received. The commonly reported reactions include dizziness (10 cases), suicidal ideation (10), tremor (8), agitation (8) and serotonin syndrome (7).

Serotonin syndrome is caused by the accumulation of serotonin in the central nervous system. It is characterized by a triad of autonomic dysfunction, cognitive-behavioural changes and neuromuscular dysfunction. In five of the seven cases of reported serotonin syndrome, there was no evidence of other risk factors normally associated with this condition, such as concomitant use of other serotonergic agents or excessive dosing.

A case report published recently describes a 70 year old female who developed serotonin syndrome within 48 hours of commencing the drug (1). Symptoms rapidly resolved when duloxetine was ceased and re-emerged when duloxetine was re-introduced.

Based on this early post-market information, it appears that serotonin syndrome can occur with duloxetine treatment alone, even at therapeutic doses, as well as in combination with other drugs known to cause this syndrome. The Cymbalta® product information has recently been updated to reflect this new information (2).

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

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Is it leflunomide lung?

Australia — The Australian Adverse Reactions Committee (ADRAC) continues to receive reports of severe pulmonary disease, including interstitial lung disease (ILD) in association with leflunomide (Arava®, Arabloc®). In some cases, the association with leflunomide was not recognized early enough and resulted in a fatal outcome.

Reports of ILD with leflunomide alone or in combination with methotrexate (also unilaterally associated with ILD) were described in two previous *Adverse Drug Reactions Bulletins* (1, 2). In December 2006, 142 of the 699 reports with leflunomide described respiratory symptoms including 22 of ILD. In June 2009, the number of leflunomide reports had increased to 845, 196 of which describe respiratory symptoms including 39 of ILD. Of the 196 reports describing respiratory symptoms, 78% described concomitant use of methotrexate; 23 of the 39 ILD reports involved this combination.

Although clinically variable, manifestations of drug-induced pulmonary toxicity commonly include fever, cough (especially dry and non-productive), dyspnoea, pleurisy, chest pain, hypoxaemia and/or radiological evidence of pulmonary infiltrates (usually diffuse and/or alveolar).

New onset or worsening pulmonary symptoms with or without associated fever in those taking leflunomide with or without methotrexate may indicate development of leflunomide lung and should prompt further investigation.

If ILD develops, discontinuation of these therapies and implementation of a washout with cholestyramine (as recommended in the leflunomide Product Information) may be appropriate (3).

In addition to ILD, leflunomide and methotrexate are both associated with a number of other severe, potentially fatal adverse effects, including liver failure, Stevens-Johnson syndrome and agranulocytosis. It is expected that the risks for ILD and other severe toxicities would be at the least additive when these drugs are used concomitantly.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

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Isotretinoin and acquired hearing impairment

Australia — Isotretinoin is a retinoid therapy indicated for the treatment of severe cystic acne unresponsive to conventional treatments.

Isotretinoin therapy has been associated with acquired hearing impairment in previously well individuals, although the mechanism/s have not been established. This should not be confused with congenital hearing impairment, which is a known potential complication following fetal exposure to isotretinoin in-utero.

The Therapeutic Goods Administration (TGA) has received 609 adverse event reports for isotretinoin dating back to 1982. These include two cases of unilateral hearing loss, one case of hearing loss at low frequencies and two cases of tinnitus. Isotretinoin was the sole suspect in all five cases. The ages ranged from 14

to 46 years of age and, where reported, duration of therapy ranged from 2–8 months. In all cases the outcomes were unknown.

Prescribers are reminded that isotretinoin has been associated with acquired hearing impairment which can be unilateral or bilateral. Symptoms may include tinnitus, impaired hearing at certain frequencies and deafness. It is unknown whether hearing impairment is permanent. If isotretinoin-associated auditory toxicity is suspected, the drug should be ceased and the patient referred for audiology assessment.

Extracted from Australian Adverse Drug Reactions Bulletin, Volume 28, Number 4, August 2009 at http://www.tga.gov.au/adr/adrac-bulletin

Pharmacovigilance Focus

Safety of medicinal products

The World Health Organization's (WHO) Advisory Committee on Safety of Medicinal Products (ACSoMP) meets regularly to provide advice on current pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. The following summary captures much of the discussion and recommendations from the Committee's Sixth Meeting in 2009.

Global awareness of medicines safety
A CD-ROM is being prepared for those interested in pharmacovigilance. A key objective is to highlight the importance of risk-benefit assessment based on information available. It is hoped that the CD-ROM will further convince governments of the cost-effectiveness of implementing a pharmacovigilance system.

Three phases are proposed as a framework for action.

- social marketing.
- identifying a medium for disseminating messages.
- creating social networking through patient participation.

Developing impact indicators specific to pharmacovigilance
Discussion on benchmarking and outcome assessment in pharmacovigilance covered rationale for pharmacovigilance indicators, broad and specific objectives, characteristics, types of indicators, data sources and the process of developing indicators. Structural indicators, process indicators and outcome (impact) indicators were also reviewed and ACSoMP agreed that both core and supplementary indicators should be developed.

A sub-group was assigned to continue developing a set of practical indicators for developing countries. These will be prepared in draft for presentation at the annual meeting of National Pharmacovigilance Centres to be held in Morocco in November 2009 and a final draft will be resubmitted to the next meeting of ACSoMP in 2010.

Guidelines for acute safety issues management
This item dealt with the management of acute safety issues by regulatory authorities. Major considerations focused on:

- evidence for decision-making after signal detection.
- analytical and methodological challenges.
- optimal design and organization of a signal detection system.
- signal detection and public health.
- risk communication.

Several matters were discussed including how people in developing countries react when regulatory decisions are made in developed countries which impact on their work. Also what should constitute the basis for decisions and how to prepare for any potentially embarrassing public health crisis.

Two associated issues were also considered. The first was how and when to take action on an acute drug safety issue and the second was how to communicate and

share information once action has been taken so that others can appreciate the underlying reasons. The need for development of a protocol was identified to help in dealing with acute safety issues in light of limitations in the WHO ICSR (Individual Case Safety Reports) database in providing complete information. While WHO should provide leadership and guidance, national governments and regional agencies need to take on local roles and responsibilities. Confidentiality agreements regarding information exchange should be made by and among all members of the WHO International Drug Monitoring Programme rather than bilaterally or within specific regions.

Members agreed that ACSoMP should design a protocol on how and when to take action on drug safety issues. However, when it comes to information sharing between regulators, the appropriate platform would be the International Conference for Drug Regulatory Authorities (ICDRA). Consequently, a recommendation will be made to the planning committee for the 14th ICDRA to include a session on information sharing between regulators. A guideline for the management of acute safety issues will be prepared accordingly.

International network of safe medication practice centres

The International Medication Safety Network (IMSN) is a growing network of countries that are working together to promote safe medication practices. The IMSN Group made a presentation on why pharmacovigilance centres should be concerned with medication error reports. Medication errors are a system issue and involve different regulatory bodies. Since there may be reluctance to report medication errors for fear of litigation and punitive measures, there is a need to develop strategies to encourage reporting.

It was recommended that a training workshop and/or group activity should be organized in parallel with the next annual meeting of National Pharmacovigilance Centres to share common concerns and objectives, and to facilitate collaboration between IMSN and pharmacovigilance networks.

Collaboration with the Expert Committee on the Selection and Use of Essential Medicines

A comprehensive draft guideline on the safety evaluation of medicines was presented, outlining the information needed to accompany an application for inclusion or deletion of a medicine in the WHO Model List of Essential Medicines (EML).

General issues concerning safety evaluation requirements were discussed including sources of information, advice on the handling of safety information, drug administration, adverse drug reactions and references. Consideration was given to whether every new EML application should be accompanied by a risk management plan for the medicine involved. In which case, risk management plans should cover any adverse drug reaction already known to be associated with use of a medicine. It was also suggested that cohort event monitoring studies should accompany the deployment of any new medicine being proposed for mass administration in order to ensure that potential problems are quickly identified before patients are affected.

Current EML applications do not contain sufficient information to provide an adequate safety evaluation. The safety component of most applications passed to ACSoMP for assessment until now meet neither the proposed guidelines nor the current requirements. Consequently, there is a need for applicable guidelines.

ACSoMP is willing to provide guidance and leadership in the development and

adoption of these guidelines. The principles of the new guideline on safety evaluation of products proposed for inclusion in the EML should be complete, up-to-date, rigorous, and scientifically valid. These principles should be applicable to all safety assessments for the EML. This proposal will be presented to the next meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines.

Public access to signals
A proposal was made to open the WHO ICSR database to the public and provide wider distribution of the signal document. In principle, opening the WHO database to the public and consumers was supported. However, it was agreed that the narrative section should remain hidden in order to protect patient confidentiality. It was also noted that publication in the scientific media was a way of promoting pharmacovigilance activities spearheaded by WHO and the Uppsala Monitoring Centre (UMC).

The Committee therefore agreed that it would be acceptable to provide information without narrative to academia to help with research provided there is a declaration of interest and the usual caveats inserted. The proposal will be revised accordingly and presented at the next annual meeting of National Pharmacovigilance Centres and the subject of making the signal document more available will be discussed further.

Global strategy for best practice in pharmacovigilance
The broad outline of a global strategy for best practice in pharmacovigilance was presented. It is part of the overall WHO strategy for the next five years, with which the UMC four-year plan will be aligned. The principal objectives will be to provide an advocacy tool for stakeholders, to develop a plan for a health systems approach to pharmacovigilance and to build cost-effective pharmacovigilance systems with a broad scope to respond to questions covering several health areas. ACSoMP was requested to discuss specific strategic components and help identify a core group to lead the development. Consequently, a document will be drafted for circulation and comment by other ACSoMP members and presented at the annual meeting of National Pharmacovigilance Centres.

Leishmaniasis
Safety monitoring of medicines used in the leishmaniasis elimination programme in Bangladesh, India and Nepal was described. The presentation included an assessment of the risk of preventable ADRs using surrogate markers, risk minimization through use of checklists of precautions and contra-indications, use of patient cards, training and supervision of healthcare workers, analysis of ADRs, and evaluation of pharmacovigilance activity. There are serious safety concerns concerning miltefosine, a recently developed medicine which is effective in controlling the disease. In this respect, control programmes should work closely with pharmacovigilance personnel to develop risk management and risk minimization plans.

Chagas disease
WHO activities in the area of Chagas disease were presented. In 2007, WHO and Bayer Healthcare agreed on distributing 500 000 tablets of nifurtimox free of charge each year. Chagas disease, which used to be encountered only in Latin America, is now present in other regions of the world including Europe and the Western Pacific. In 2008, for example, around 150 patients were diagnosed in Geneva, Switzerland, with Chagas disease within a period of six months.

Currently, there are two medicines available for Chagas disease: nifurtimox and benznidazole, both developed in the 1960s. In Bolivia, deaths have been

reported in children following incorrect use of nifurtimox. WHO is assisting with the distribution of benznidazole and nifurtimox, both of which are on the WHO Essential Medicines List.

Even though nifurtimox and benznidazole were developed in the 1960s, available information on safety is limited. It is important not only to implement pharmacovigilance but also to consider what kind of operational research needs to be implemented to ensure the collection, analysis and dissemination of safety information on these products to patients and healthcare providers. Further discussion is necessary to determine optimal pharmacovigilance systems in these settings.

Vaccines
A dedicated vaccine safety specialist has been appointed at the WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre) to strengthen the signal detection process and improve tools used for reporting vaccines. Activities are being undertaken to address key safety challenges with new vaccines, such as quality of safety data in individual countries, capacity to respond to crises, quality of data for signal detection and risk assessment at global level. Activities also include routine capacity strengthening, developing a global crisis management plan and strengthening the Global Network for Postmarketing Surveillance of Newly Prequalified Vaccines. The Network will provide data and support to the WHO vaccine prequalification system by generating data in the postmarketing phase.

Other collaboration between the WHO vaccines and medicines safety departments and the UMC includes development of a vaccine dictionary (part of the WHO Drug Dictionary) and an ATC classification for vaccines. The Global Advisory Committee on Vaccine Safety (GACVS) continues to provide support and oversight on all activities related to vaccine safety and acts as an independent advisory committee to WHO. A member of ACSoMP serves on GACVS to ensure collaboration and sharing of information.

Malaria
A presentation was made on the rationale and need for collaboration between malaria and medicines safety programmes in WHO, challenges at country, regional and global levels, and the way forward to improving access to artemisinin combination therapy (ACT). The move to deregulate ACT to over the counter medicines as a way to improve treatment will involve home-based care. The way forward will be to promote risk management plans, empower consumers, and strengthen integration between pharmacovigilance and public health programmes.

The Affordable Medicines Facility for Malaria (AMFm) aims to lower the net cost of ACTs and expand availability for this treatment. The initiative should be accompanied by increased safety monitoring for these medicines in all settings and under all conditions of use. The first phase of the AMFm will be rolled out in eleven countries and will provide a challenge and an opportunity to develop pharmacovigilance systems and strengthen those already existing.

Various initiatives run by different organizations exist in the area of pharmacovigilance of antimalarials and tropical diseases in general. These activities should be coordinated and members suggested that WHO should take a leading role in coordinating these initiatives which involve several different players. ACSoMP should be informed of all the safety studies being undertaken so that it can provide independent scientific and technical advice to WHO and Member States. Future WHO plans in this disease area include a meeting with the Medi-

cines for Malaria Venture (MMV) and other partners to develop a joint protocol and guidelines for the pharmacovigilance of antimalarials. Such joint meetings will ensure harmonization in safety monitoring. An ACSOMP member will assist WHO by coordinating various ongoing initiatives in Africa.

HIV/AIDS
A presentation was made on methods to improve the safety of antiretroviral medicines (ARVs) in public health use, pharmacovigilance for ARVs — including identifying gaps and needs — and a pilot project for improving the safety of ARVs.

Different toxicities are expected of medicines when used for post-exposure prophylaxis of HIV and management of patients with HIV/AIDS. As more and more people stay on treatment, toxicities are becoming an important issue. Gap analysis has identified specific needs in ART programmes such as development of additional definitions and newer methodologies for capturing data relating to toxicity. Towards this, a pilot project that is being funded by the Bill and Melinda Gates Foundation will establish internationally agreed reporting tools, strengthen pharmacovigilance capacity in selected countries, support key studies, and coordinate the analysis of safety data on ARVs.

Switching of patients from a first to second-line regimen has huge cost implications. Safety data on ARVs is very limited regarding a second-line regimen. For example, the pharmacokinetic effects of protease inhibitors in children are little documented. It is particularly important to learn the reasons why patients are switched. Subjective reasons may dominate the switching of patients and this must be determined.

ACSoMP agreed that guidelines on management of adverse events and treatment limiting toxicities should be developed and disseminated to all countries. Given the issues of co-morbidity and drug interactions, collaboration with other programmes is important to ensure the safe use of ARVs.

Review of artesunate+amodiaquine
Based on a draft proposal for action, the safety issues of artesunate+amodiaquine (ASAQ) were discussed. A meeting with DNDi and Sanofi-Aventis had resulted in a risk management plan for ASAQ. Sanofi-Aventis is currently carrying out studies in Cote d'Ivoire on the real-life safety of this fixed dose combination. Weaknesses in the study design were identified and discussed by ACSoMP. Several groups are planning to undertake active ASAQ pharmacovigilance but there are currently delays in engaging key personnel and local associations. Safety and use of concomitant medicines administered with ASAQ should also be studied.

ACSoMP members will review the risk management plans and offer suggestions to WHO. In addition, a consultant, currently reviewing some adverse events reported with ASAQ will be requested to outline the safety profile of ASAQ.

Pharmacovigilance and dependence inducing drugs
Feedback on use of pharmacovigilance data for the assessment of dependence and abuse potential of drugs of dependence has been generated through e-mail consultation. Conclusions point out that pharmacovigilance is useful for evaluating drug dependence liability but that a distinction should be made between ADRs from clinical trials and those made from spontaneous reporting. It was agreed that using defined daily doses (DDDs) provided the best assessment tool. Various drug classes should continue to be dealt with separately.

A presentation on "opioids, safety surveillance and risk management: elaborating key challenges in the review of postmarketing safety information on opioids in the USA" was made. Quantifying known

adverse events including those which indicate abuse is very difficult. While geographic clustering of abuse and abuse potential may occur, reporting practices are variable and many reports focus on the active ingredient rather than the finished product.

Understanding prescribing decisions is very hard in post-approval setting. The number of persons at risk is often unknown and information is not always available in a timely manner. There are also several important factors that are difficult to ascertain in spontaneous reports, including medication theft, overuse of prescribed medication, abuse/dependence/addiction, overdose, nonprescription use, etc. It is also important to understand the abuse potential of new formulations. Thus, definitions related to abuse potential should be broadened to include non-opioids. The legal classification for products is also an important issue which needs attention.

Ethics in observational studies
A wider understanding of the importance of ethical aspects of epidemiological and observational studies must be recognized globally. There are currently few documents discussing ethical review and ethical applications in pharmacovigilance. The Council for International Organizations of Medical Sciences (CIOMS) has recently published *International Guidelines for Ethical Review of Epidemiological Studies*.

Ethical committee approval must be sought in all settings and in particular where there are vulnerable groups and populations. In preparing a study protocol, it is important to comply with national legislation and internationally approved guidelines in order to ensure that studies are scientifically and ethically acceptable.

Internet connectivity in Africa
A WHO initiative Africa Health Infoway has been launched to improve internet connectivity in Africa. Expected deliverables include better access to information, telemedicine, e-Learning, and disease surveillance. Since WHO's mandate does not include establishing internet infrastructure, a collaborative agreement has been entered into with the International Telecommunications Union. Partnerships have also been set up with regional organizations, including the African Union Commission through which funding is being sought.

Several initiatives are aimed at improving Internet infrastructure in Africa. One initiative, the Telemedicine Task Force, involves the European Space Agency, the European Union, African Union, WHO and others. This initiative proposes the use of satellite technology for e-health. ACSoMP has requested updates on progress and has proposed collaborating by communicating the usefulness of this project to management, policy makers, and donors.

The WHO Medicines Safety team has proposed cooperation with Africa Health Infoway in the following ways.

• The pharmacovigilance programme tools VigiFlow and CEMFlow will be incorporated into the AHI plan.

• A priority list of countries will be identified for support by this initiative.

• Promotion of Africa Health Infoway will be made in all workshops.

Review of existing definitions
Support is strong for a review of existing definitions in pharmacovigilance. This topic was also discussed at the annual meeting of National Pharmacovigilance Centres in 2008. Signals and adverse reactions/adverse events are top priorities. During the past year, the CIOMS Working Group on Signal Detections has been moving ahead with new definitions.

ACSoMP was requested to provide guidance on WHO's role in this activity.

ACSoMP agreed that WHO should take this activity forward because it has the mandate and capacity to coordinate activities for developing global norms and standards. Led by ACSoMP, the WHO Programme for International Drug Monitoring should prepare a set of definitions. A concept paper will be drafted for the next annual meeting of National Pharmacoviiglance Centres.

Reference: *WHO Pharmaceuticals Newsletter* No. 3, 2009 at http://www.who.int/medicines

Regulatory Action and News

Withdrawal of dextropropoxyphene

European Union — Finalizing a review of the safety and efficacy of dextropropoxyphene-containing medicines, the European Medicines Agency (EMEA) Committee for Medicinal Products for Human Use (CHMP) concluded that the risks, particularly the risk of potentially fatal overdose, are greater than the benefits. The Committee therefore recommended that the marketing authorizations for these medicines be withdrawn across the European Union. The withdrawal will be gradual to allow time for the safe transfer of patients to appropriate alternative therapies, in line with national recommendations.

Dextropropoxyphene is a painkiller used to treat acute and chronic pain. It has been available as a prescription-only medicine for about 40 years, either on its own or in combination primarily with paracetamol, as tablets, capsules, suppositories and solutions for injection.

The Agency's recommendation has been forwarded to the European Commission for the adoption of a legally binding decision.

Reference: *Press Release*, Doc. Ref. EMEA/401062/2009. 25 June 2009 at http://www.emea.europa.eu/pdfs/human/opinion

Besifloxacin: approved for bacterial conjunctivitis

United States of America — The Food and Drug Administration (FDA) has approved besifloxacin ophthalmic suspension 0.6 percent (Besivance®) for the treatment of bacterial conjunctivitis (non-viral).

Bacterial forms of conjunctivitis are common in childhood but can occur in people of any age. Symptoms of bacterial conjunctivitis include red eyes, swelling, eyelids sticking together, itching, watering and a white or yellow sticky discharge from the eyes. Bacterial conjunctivitis is generally a condition that runs its course in 7–14 days.

Patients using the drug in clinical trials had a faster rate of resolution of infection than those treated with a solution containing only a preservative. The drug was shown to be effective in treating patients age one year and older.

Adverse events were reported in less than three percent of patients in clinical trials. Adverse reactions included redness of the eyes, blurred vision, eye pain, irritation and itching, and headache.

Reference: *FDA News Release*, 6 July 2009 at http://www.fda.gov

Prasugrel: approved for angioplasty patients

United States of America — The Food and Drug Administration (FDA) has approved the blood-thinning drug prasugrel (Effient® tablets) to reduce risk of blood clots forming in patients who undergo angioplasty.

During an angioplasty, a balloon is used to open the artery that has been narrowed by atherosclerotic plaque.Often, a stent is inserted into the blood vessel to help keep the artery open after the procedure. Platelets in the blood can clump around the procedure site, causing clots that may lead to heart attack, stroke, and death.

The fraction of patients who had subsequent non-fatal heart attacks was reduced from 9.1% in patients who received Plavix® to 7.0% in patients who received Effient®. While the numbers of deaths and strokes were similar with both drugs, patients with a history of stroke were more likely to have another stroke while taking Effient®. In addition, there was a greater risk of significant, sometimes fatal bleeding seen in patients who took Effient®.

The drug's labeling will include a boxed warning alerting physicians that the drug can cause significant, sometimes fatal, bleeding.

Reference: *FDA News Release*, 10 July 2009 at http://www.fda.gov

Pemetrexed: approved for advanced lung cancer

United States of America — The Food and Drug Administration (FDA) has approved pemetrexed (Alimta®), the first drug available for maintenance therapy of advanced or metastatic lung cancer.

Pemetrexed disrupts metabolic processes that are dependent on the B-vitamin folate, a necessary ingredient for cell replication. Non-small cell lung cancer has several subtypes, including squamous cell, large cell, adenocarcinoma and mixed histology cancers. In a 600-patient clinical trial, people with predominantly squamous cell cancer did not benefit from Alimta® but those with other subtypes of non-small lung cancer survived an average 15.5 months following treatment compared with 10.3 months for patients who received an inactive substance (placebo). All patients in the study received standard medical care.

Reported adverse events included damage to blood cells, fatigue, nausea, loss of appetite, tingling or numbness in the hands and feet, and skin rash.

Alimta® was initially approved in 2004 for the treatment of patients with mesothelioma, a cancer frequently related to asbestos exposure. The drug was later approved for the treatment of patients with non-small cell lung cancer whose disease worsened on prior chemotherapy drugs and also as an initial therapy for advanced non-small cell lung cancer.

Reference: *FDA News Release*, 2 July 2009 at http://www.fda.gov

Dronedarone: approved for heart rhythm disorder

United States of America — The Food and Drug Administration (FDA) has approved dronedarone (Multaq®) to help maintain normal heart rhythm in patients with a history of atrial fibrillation or atrial flutter. The drug is approved for use in patients whose hearts have returned to normal rhythm or will undergo drug or electric-shock treatment to restore a normal heart beat.

Multaq® may cause critical adverse reactions, including death, in patients with recent severe heart failure. The drug's label will contain a boxed warning cautioning that the drug should not be used in severe heart failure patients.

In a multinational clinical trial with more than 4600 patients, Multaq® reduced cardiovascular hospitalization or death from any cause by 24%, when compared with placebo. Most of that effect represents reduced hospitalizations, especially those related to atrial fibrillation.

The most common adverse reactions reported by patients in clinical trials were diarrhoea, nausea, vomiting, fatigue and weakness.

Reference: *FDA News Release*, 2 July 2009 at http://www.fda.gov

First advanced therapy medicinal product approved

European Union — The European Medicines Agency (EMEA) has recommended the first marketing authorization for an advanced therapy medicinal product following a positive opinion from the Agency's Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP). The CAT, is a multidisciplinary committee that brings together experts in gene therapy, somatic cell therapy and tissue engineering.

ChondroCelect® is a cell-based medicine that is used to repair defects in the cartilage of the femoral condyle (the end of the thighbone) in the knee. It consists of chondrocytes (cartilage-forming cells) that are taken from a healthy region of the patient's cartilage, grown outside the body, and then re-implanted during surgery.

This is the first product to benefit from the new legal and regulatory framework for advanced therapy medicinal products (Regulation (EC) No. 1394/2007). This framework is designed to ensure the free movement of advanced medicines within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field while guaranteeing the highest level of health protection for patients.

Reference: *Press Release*, Doc. Ref. EMEA/CHMP/394741/2009. 26 June 2009 at http://www.emea.europa.eu/pdfs/human/opinion

Gemifloxacin: withdrawal of marketing authorization application

European Union — The European Medicines Agency (EMEA) has been formally notified of the decision to withdraw an application for a centralized marketing authorization for the medicine Factive® (gemifloxacin), 320 mg film-coated tablets. Factive® was expected to be used for the treatment of bacterial infections causing mild to moderate community-acquired pneumonia and acute exacerbation of chronic bronchitis.

At the time of the withdrawal, it was under review by the Agency's Committee for Medicinal Products for Human Use (CHMP). In its official letter, the company stated that the withdrawal of the application was based on the CHMP's view that the data provided did not allow the Committee to conclude on a positive benefit-risk balance.

Reference: *Press Release*, Doc. Ref. EMEA/382408/2009. 23 June 2009 at http://www.emea.europa.eu/

Saxagliptin approved for diabetes

United States of America — The Food and Drug Administration (FDA) has approved saxagliptin (Onglyza®), a once-daily tablet to treat Type 2 diabetes in adults. The medication is intended to be used with diet and exercise to control high blood sugar levels. Saxagliptin is in a class of drugs known as dipeptidyl peptidase-4 (DPP-4) inhibitors which stimulate the pancreas to make more insulin after eating a meal.

The most common side effects observed with saxagliptin are upper respiratory tract infection, urinary tract infection, and headache. Other side effects include allergic-like reactions such as rash and hives.

Approval of Onglyza® was primarily based on the results of eight clinical trials. The application seeking FDA approval was submitted before December 2008 when the agency recommended that manufacturers of new diabetes drugs

carefully design and evaluate their clinical trials for cardiovascular safety. Although saxagliptin was not associated with an increased risk for cardiovascular events in patients who were mainly at low risk for these events, the FDA is requiring a postmarket study that will specifically evaluate cardiovascular safety in a higher risk population.

Reference: *FDA News Release*, 31 July 2009 at http://fda.hhs.gov

Contusugene ladenovec: withdrawal of application for marketing

European Union — The European Medicines Agency (EMEA) has been formally notified by the manufacturer of the decision to withdraw its application for a centralized marketing authorization for the medicine contusugene ladenovec (Contususgene ladenovec Gendux®) suspension for injection expected to be used for the treatment of squamous cell carcinoma in head and neck cancer.

In its official letter, the company stated that the withdrawal of the application was based on the difficult financial situation of its parent company which prohibits them to fund further activities related to this application.

***Reference**: Press Release*, Doc. Ref. EMEA/412751/2009. 23 July 2009 at http://www.emea.europa.eu

Rotigotine transdermal patch: restrictions lifted

European Union — The European Medicines Agency has recommended that the supply and treatment restrictions for rotigotine transdermal patch (Neupro®), be lifted. Once this recommendation is endorsed by the European Commission, the ban on prescribing Neupro® to patients not yet taking the medicine will be reversed. Doctors in the European Union will then be able to prescribe Neupro® to all patients in accordance with the approved product information. Prescriptions will no longer be limited to one month.

Rotigotine transdermal patch is currently indicated for the treatment of Parkinson disease and restless legs syndrome. It is applied as transdermal patches that deliver the active substance, rotigotine, across the skin.

At its May 2008 meeting, the Agency's Committee for Medicinal Products for Human Use (CHMP) recommended immediate changes to the storage conditions for Neupro following reports of crystallisation of the active substance in some patches. The recommendations included the requirement that the medicine be stored in a refrigerator at a temperature of between 2 and 8 °C.

Following assessment of the cold-chain system that has been put in place by the company, the CHMP is now re-assured that no significant crystallisation should occur under these storage conditions and that Neupro® supplied to patients now meets the required quality standards.

Reference: *Press Release*, Doc. Ref. EMEA/CHMP/322964/2009. 29 May 2009

Impact of European Clinical Trials Directive

The Impact on Clinical Research of European Legislation Project (ICREL) was a one-year project financed by the European 7th Framework Programme and coordinated by the European Forum for Good Clinical Practice (EFGCP). The European Clinical research Infrastructures Network (ECRIN), the European Organization for research and Treatment of Cancer (EORTC), as well as the Hospital Clínic of Barcelona and the Ethics Committee of the Medical University of Vienna collaborated in this project.

Its aim was to measure and analyse the direct and indirect impact of the Clinical Trials Directive 2001/20/EC and related legislations in the EU on all categories of clinical research and on the different stakeholders: commercial and non-commercial sponsors, ethics committees and competent authorities. This initiative responds to the need to adapt the current legislation and will help determine the most relevant pathways for improvement.

Directive 2001/20/EC was adopted with the objective of harmonizing the EU regulatory environment for clinical research, improving the protection of participants, optimizing the use of safety information, and ensuring the credibility of data through strengthened responsibility of the sponsors and harmonized trial authorization procedures for Member States.

However, this legislation only protects participants in clinical trials on medicinal products. It requires almost similar procedures for all types of clinical trials with medicinal products from registration studies on innovative treatments to studies comparing treatment strategies using marketed drugs or applying minimally invasive procedures. Academic institutions and industry, including SMEs, face major difficulties in fulfilling sponsor responsibilities.

The Clinical Trials Directive objectives were transposed into divergent national legislations, partly missing the harmonization goal and making multinational trials, in particular, difficult to perform. This could raise doubts about the competitiveness and attractiveness of the EU for clinical research. The ICREL project was designed to measure the impact of the current EU legislation, analysing its direct and indirect consequences.

In order to reach a maximum of information, a survey was conducted. The first results of this survey were presented and discussed during a conference in Brussels in December 2008. Conclusions of the meeting are presented in a final report which has been published by the European Commission.

Reference: European Forum for Good Clinical Practice (EFGCP) at http://www.efgcp.be/ICREL/

WHO list of recently prequalified medicinal products

The following products have recently been added to the list of prequalified products by the WHO Prequalification of Medicines Programme. (http://www.who.int/prequal). This additional list covers the period 1 January 2009 to 2 July 2009.

Product	Presentation	Manufacturer
Abacavir(as sulfate) +Lamivudine+Zidovudine	Tablets 60mg +30mg+60mg	Matrix Laboratories Sinnar, Maharashtra,India
Ciprofloxacin	Infusion 2mg/ml	Claris Life Sciences Ahmedabad, Gujarat, India
Efavirenz	Tablets 200mg	Strides Arcolab, Bangalore, India
Efavirenz	Tablets 600mg	Strides Arcolab, Bangalore, India
Efavirenz	Tablets 600mg	Hetero Drugs, Hyderabad, India

Continued ...

WHO list of recently prequalified medicinal products *(Continued)*

Product	Presentation	Manufacturer
Lamivudine +Nevirapine+Zidovudine	Film-coated tablets 150mg+200mg+300mg	Cipla Goa, India
Lamivudine +Nevirapine+Zidovudine	Tablets 150mg +200mg+300mg	Matrix Laboratories Sinnar, Maharashtra, India
Lamivudine +Stavudine	Tablets 150mg+30mg	Aurobindo Pharma Hyderabad, India
Lamivudine +Stavudine	Tablets 150mg+40mg	Aurobindo Pharma Hyderabad, India
Lopinavir +Ritonavir	Tablets 200mg+50mg	Matrix Laboratories Sinnar, Maharashtra, India
Lopinavir +Ritonavir	Tablets 100mg+25mg	Matrix Laboratories Sinnar, Maharashtra, India
Lamivudine +Zidovudine	Tablets 30mg+60mg	Matrix Laboratories Andhra Pradesh, India
Nevirapine	Oral susp. 50mg/5ml	Cipla, Unit-1, Goa India
Tenofovir disoproxil fumarate	Tablets 300mg	Cipla, Goa, India
Oseltamivir (as phosphate)	Capsules 75mg	Cipla, Goa, India
Artemether +Lumefantrine	Tablets 20mg+120mg	Cipla, Patalganga, India
Artemether +Lumefantrine	Dispersible Tablets 20mg+120mg	Novartis Pharma Suffern, USA
Ethinylestradiol +Levonorgestrel	Tablets 30µg+150µg	Bayer Schering Pharma Weimar, Germany
Levonorgestrel	Tablets 30µg	Bayer Schering, Weimar, Germany
Cycloserine	Capsules 250mg	Aspen Pharmacare Port Elizabeth, South Africa
Isoniazid +Pyrazinamide+Rifampicin	Tablets 30mg+150mg+60mg	Macleods Pharmaceuticals Kachigam, Daman, India
Rifampicin +Isoniazid	Tablets 60mg+30mg	Macleods Pharmaceuticals Kachigam, Daman, India
Pyrazinamide	Tablets 400mg	Micro Labs, Hosur, Tamilnadu, India
Pyrazinamide	Tablets 500mg	Micro Labs, Hosur, Tamilnadu, India

Current Topics

Forum on international pharmaceutical crime

The Permanent Forum on International Pharmaceutical Crime (PFIPC) comprises members from 15 countries throughout the world: Australia, Belgium, Canada, Germany, Ireland, Israel, Italy, Netherlands, New Zealand, Singapore, South Africa, Spain, Switzerland, United Kingdom and United States of America. Members come from both pharmaceutical regulatory and law enforcement components of member countries with the objective of combating worldwide pharmaceutical crime.

International Conference on Pharmaceutical Crime
The Swiss Agency for Therapeutic Products, Swissmedic, as a member of PFIPC and the International Laboratory Forum on Counterfeit Medicines (ILFCM) has organized the annual conference for these two organizations in Bern from 8–12 June 2009.

A total of 33 delegates from 18 countries attended the conference. Participants included enforcement experts and representatives from international organizations that work to fight against pharmaceutical crime. The conference enabled delegates to exchange experience and information about trends and activities and develop joint projects to improve international collaboration. Particular emphasis was placed on preparing coordinated action against illegal Internet trade in therapeutic products.

The PFIPC also supports the work of the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), an initiative of the World Health Organization (www.who.int/impact/en/). IMPACT is aimed at combating counterfeit medicines in countries with a high proportion of counterfeit products but with insufficient enforcement facilities of their own. Many experts from the PFIPC work in international organizations and promote global collaboration.

Experts from ILFCM international control laboratories in 10 countries met in parallel to this conference to exchange experiences. The meeting featured presentations on new technological developments in the analysis of counterfeit pharmaceuticals and focused on tracking new illegal products. These medicines, which are mainly sold over the Internet without any correct indication of ingredients often contain new active substances of largely unknown effect and which may be hazardous when ingested by humans.

Discussions in both conferences showed once again that repeated published warnings about purchasing pharmaceuticals from illegal sources, especially over the Internet, are justified. International pharmaceutical crime is on the increase and illegally sold medicines are a major risk to the health of the general public.

Reference: http://www.swissmedic.ch/aktuell/

Illegal online medicine suppliers targeted

The first international Internet day of action co-coordinated by the Permanent Forum on International Pharmaceutical Crime (PFIPC), INTERPOL and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT), has targeted illegal online sale of medicines to

the public. This action has resulted in a series of arrests and the seizure of potentially harmful medicines in operations carried out around the world. Codenamed Pangea, the operation focused on those individuals behind Internet sites which illegally sell and supply unlicensed or prescription-only medicines claiming to treat a range of ailments.

While many countries have previously carried out individual law enforcement activities targeting 'Internet pharmacies', Operation Pangea was the first time that action was taken on an international scale, with participating countries. (Australia, Canada, Germany, Ireland, Israel, New Zealand, Singapore, Switzerland, United Kingdom and United States of America.)

Locations in each country were identified, with investigators visiting residential and commercial addresses relating to Internet sites believed to be selling unlicensed or prescription-only medicines claiming to treat many conditions such as diabetes, obesity or hair loss.

Investigations in a number of countries are still ongoing, with the final results from Operation Pangea to be released upon their conclusion. For more information on individual activities and operations, please contact the national enforcement agencies in the countries concerned.

Reference: Illegal online medicine suppliers targeted in first international Internet day of action. *Interpol media release.* http://www.interpol.int

Elimination of river blindness in Mali and Senegal

The first evidence that onchocerciasis elimination is feasible with ivermectin treatment has been published in the open-access journal *PLoS Neglected Tropical Diseases*. Onchocerciasis often blinds people, as well as causing debilitating skin disease. Over 37 million people are infected, often living in poor, rural African communities. The multi-country study showed that treatment with ivermectin stopped further infections and transmission in three specific endemic areas in Africa.

Ivermectin kills the larvae but not the adult worms of *Onchocerca volvulus*, the parasite that causes the disease, so annual or biannual treatments are required to prevent resurgence. Donations of the drug by the manufacturer to countries where onchocerciasis is endemic have resulted in annual treatments to all eligible community members — over 60 million people in 26 African countries in 2008.

This new study in three areas in Mali and Senegal where onchocerciasis was endemic has provided the first evidence of the feasibility of onchocerciasis elimination with ivermectin in endemic areas in Africa. The studies showed that after 15 to 17 years of six-monthly or annual treatments, only a few infections remained in the human population and transmission levels were below predicted thresholds for elimination.

References:

1. News on UNICEF/UNDP/WorldBank/WHO-TDR http://www.who.int/tdr/svc/news-events

2. Full article available at http://www.plosntds.org/article/info%3Adoi%2F10.1371%2Fjournal.pntd.0000 497

3. TDR press release, 21 July 2009 http://www.who.int/tdr/svc/news-events/news/onchocerciasis-elimination

Moxidectin for river blindness in phase III clinical trials

A clinical trial is being launched in three African countries of a medicine that could

speed up elimination of onchocerciasis, one of the leading infectious causes of blindness across Africa. The medicine, moxidectin, is being investigated for its potential to kill or sterilize the adult worms of *Onchocer-ca volvulus* which cause onchocerciasis.

Onchocerciasis, also called river blindness, is transmitted by the blackfly which breeds in fast flowing rivers. Blindness is the most incapacitating symptom of the disease which also causes debilitating skin disease.

The development of moxidectin for onchocerciasis is being conducted through a collaboration of the Special Programme for Research and Training in Tropical Diseases, which is executed by the World Health Organization (WHO/TDR), and Wyeth Pharmaceuticals. The work ranges from the development of a formulation for human use and initial studies in healthy volunteers, to clinical studies and community studies in Africa.

WHO/TDR, working in partnership with African investigators and institutions, is building capacity and managing the conduct of clinical trials conducted in Africa. If the development is successful and results in a positive scientific opinion from the European Medicines Evaluation Agency (EMEA), the manufacturer will request approval by national regulatory authorities in the countries where onchocerciasis is endemic.

In conducting this trial, TDR will be working with African investigators and institutions. Fifteen hundred people at four sites in Ghana, Liberia and the Democratic Republic of Congo will be enrolled in the study. Preparation has been ongoing since 2007 and included building a clinical research centre in Lofa County, Liberia, and in Nord-Kivu in the Democratic Republic of Congo (DRC). Buildings not used since the war in Ituri, DRC, have been renovated. All centres have been provided with necessary equipment and the research teams trained on how to conduct the trial according to international standards.

The trial will take place over the next two and a half years. Currently, the disease is controlled by ivermectin which has been donated for more than twenty years by the pharmaceutical company Merck & Co. Inc. for use in onchocerciasis endemic countries. Treatment with ivermectin has enabled significant progress in the control of onchocerciasis, and currently reaches more than 60 million people in Africa annually. However, ivermectin kills the *O. volvulus* larvae but not the adult worms, so annual treatments for an extended period of time (at least 11–14 years) are required to ensure disease control.

If moxidectin kills not only the larvae but also sterilizes or kills the adult worms, it has the potential to interrupt the disease transmission cycle within around six annual rounds of treatment. The medicine could be distributed through community-directed mechanisms set up in collaboration among APOC, African control programmes, and NGOs for the distribution of ivermectin.

Reference: World Health Organization. Moxidectin could dramatically speed up elimination of disease across Africa. *Press release*, 1 July 2009 at http://apps.who.int/tdr/svc/news-events/news/phase3-trial-moxidectin

Malaria: evaluation of rapid diagnostic tests

The largest-ever independent, laboratory-based evaluation of rapid diagnostic tests (RDTs) for malaria has shown that some tests on the market perform exceptionally well in tropical temperatures and can detect even low parasite densities in blood samples, while other tests were only able to detect the parasite at high parasite densities.

The evaluation was co-sponsored by the WHO Regional Office for the Western Pacific (WPRO), WHO-based Special Programme for Research and Training in Tropical Diseases (TDR) and the Foundation for Innovative New Diagnostics (FIND). Testing was performed at the US Centers for Disease Control and Prevention (CDC). Forty-one commercially available RDTs went through a blinded laboratory evaluation.

The findings will serve as a tool for countries to make informed choices from among the dozens of tests commercially available and on the purchase and use of rapid diagnostics that are best suited to local conditions. This performance evaluation will also inform procurement and prioritization for diagnostic test entry into the WHO Prequalification Diagnostics Programme and WHO Procurement Schemes. Donor agencies also regularly refer to WHO recommendations on diagnostics when making their own purchases.

In addition to product testing FIND , TDR and WHO have also collaborated to establish procedures and quality assured facilities for routine lot testing of rapid diagnostics in Asia and Africa. Evaluation of malaria diagnostic tests by WHO and partners has found variation in test performance.

During the evaluation, samples of blood from patients infected with *P. falciparum* and *P. vivax* in diverse geographic locations were diluted to achieve both a low parasite density and high parasite densities . At low parasite density, samples were tested against two rapid tests per lot (2 lots) and at high parasite density samples were tested against one rapid test per lot (2 lots).

Conclusions from the findings:

- Several RDTs demonstrated consistent detection of malaria at low parasite densities, have low false-positive rates, are stable at tropical temperatures, are relatively easy to use, and can detect P*. falciparum, P. vivax* infections, or both.
- Performance between products varied widely at low parasite density (200 parasites/microlitre); however, most products showed a high level of detection at 2000 to 5000 parasites/microlitre.
- *P. falciparum* tests targeting the histidine rich protein 2 (HRP2) antigen demonstrated the highest detection rates, but some tests targeting Plasmodium lactate dehydrogenase (pLDH) also exhibited high detection rates.
- Test performance varied between lots, and widely between similar products, confirming the advisability of lot testing post-purchase and prior to use in the field.
- The results highlight the need for manufacturers to have adequate reference materials for product development and lot-release. The WHO-FIND Malaria RDT Evaluation Programme, in collaboration with the CDC, will soon offer quality standard panels to manufacturers to assist in this process.

A second round of performance evaluations for 29 products is currently being carried out by TDR, FIND and CDC, with results due to be published in 2010. An executive summary of findings along with the detailed evaluation of test performance results are provided in the report available online at http://www.who.int/tdr.

References

1. Special Programme for Research & Training in Tropical Diseases (TDR). *News Release,* 24 April 2009 at http://www.who.int/tdr

2. Foundation for Innovative New Diagnostics (FIND) at http://www.finddiagnostics.org

ATC/DDD Classification

ATC/DDD Classification (Temporary)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology, 24 March 2009. Comments or objections to the decisions from the meeting should be forwarded to the WHO Collaborating Centre for Drug Statistics Methodology at whocc@fhi.no. If no objections are received, the new ATC codes and DDDs will be considered final and included in the January 2010 issue of the ATC index.The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy.

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Agents for atopic dermatitis, excluding corticosteroids		D11AH
Angiotensin II antagonists, other combinations		C09DX
Other blood products		B05AX
Other throat preparations		R02AX
New ATC 5th level codes:		
	alfuzosin and finasteride	G04CA51
	alogliptin	A10BH04
	bendamustine	L01AA09
	biapenem	J01DH05
	bisoprolol, combinations	C07AB57
	blood plasma	B05AX03
	canakinumab	L04AC08
	carisbamate	N03AX19
	cefozopran	J01DE03
	cholic acid	A05AA03
	dapoxetine	G04BX14
	denosumab	M05BX04
	erythrocytes	B05AX01
	fluoromethylcholine (^{18}F)	V09IX07
	flurbiprofen	R02AX01
	indacaterol	R03AC18
	iodine (^{124}I) 2beta-carbomethoxy-3beta-(4iodophenyl)-tropane	V09AX02
	maribavir	J05AX10
	nomegestrol and estrogen	G03AA14
	ofatumumab	L01XC10

ATC level	INN/Common name	ATC code
	ofloxacin	S02AA16
	pioglitazone and alogliptin	A10BD09
	prasugrel	B01AC22
	pravastatin and fenofibrate	C10BA03
	sodium iodide (^{124}I)	V09FX04
	stem cells from umbilical cord blood	B05AX04
	tapentadol	N02AX06
	telmisartan and amlodipine	C09DB04
	thrombocytes	B05AX02
	valsartan, amlodipine and hydrochlorothiazide	C09DX01
	valsartan and aliskiren	C09DX02

INN/Common name	Previous ATC code	New ATC code
ATC code changes:		
cromoglicic acid	D11AX17	D11AH03
pimecrolimus	D11AX15	D11AH02
tacrolimus	D11AX14	D11AH01

Previous name	New name	New ATC code
ATC name changes:		
hydroxybutyric acid	sodium oxybate	N01AX11
hydroxybutyric acid	sodium oxybate	N07XX04

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
alitretinoin	20	mg	O	D11AX19
biapenem	1.2	g	P	J01DH05
cefozopran	4	g	P	J01DE03
dapoxetine	30	mg	O	G04BX14
degarelix	2.7	mg	P	L02BX02
etravirine	0.4	g	O	J05AG04
flurbiprofen	44	mg	O	R02AX01
lacosamide	0.3	g	O,P	N03AX18
prasugrel	10	mg	O	B01AC22
rivaroxaban	10	mg	O	B01AX06
ustekinumab	0.54	mg	P	L04AC05

ATC/DDD Classification

ATC/DDD Classification (Final)

The following anatomical therapeutic chemical (ATC) classifications and defined daily doses (DDDs) were agreed by the WHO International Working Group for Drug Statistics Methodology in October 2008. They will be included in the January 2010 issue of the ATC index. The inclusion of a substance in the lists does not imply any recommendation of use in medicine or pharmacy. The WHO Collaborating Centre for Drug Statistics Methodology can be contacted at whocc@fhi.no

ATC level	INN/Common name	ATC code
New ATC level codes (other than 5th level):		
Peripheral opioid receptor antagonists		A06AH
New ATC 5th level codes:		
	aciclovir, combinations	D06BB53
	alvimopan	A06AH02
	asenapine	N05AH05
	bacitracin	J01XX10
	bazedoxifene	G03XC02
	becaplermin	A01AD08
	benzethonium chloride	D08AJ08
	bromfenac	S01BC11
	casopitant	A04AD13
	cefcapene	J01DD17
	cevimeline	N07AX03
	cilostazol	C04AX33
	corifollitropin alfa	G03GA09
	dalbavancin	J01XA04
	dapsone	D10AX05
	dexmethylphenidate	N06BA11
	doxercalciferol	H05BX03
	eltrombopag	B02BX05
	eperisone	M03BX09
	everolimus	L01XE10
	fluocinolone acetonide	S02BA08
	golimumab	L04AB06
	iclaprim	J01EA03
	lansoprazole, amoxicillin and clarithromycin	A02BD0
	lisinopril and amlodipine	C09BB03

ATC level	INN/Common name	ATC code
	meningococcus, tetravalent purified polysaccharide antigen conjugated	J07AH08
	meptazinol	N02AX05
	methylnaltrexone bromide	A06AH01
	mitiglinide	A10BX08
	nabiximols	N02BG10
	nalfurafine	V03AX01
	oritavancin	J01XA05
	pazopanib	L01XE11
	pegloticase	M04AX02
	phenazone	S02DA03
	potassium acetate	B05XA17
	pralatrexate	L01BA05
	regadenoson	C01EB21
	saxagliptin	A10BH03
	silodosin	G04CA04
	sodium fluoride (^{18}F)	V09IX06
	sodium levofolinate	V03AF10
	stavudine, lamivudine and nevirapine	J05AR07
	tamsulosin and dutasteride	G04CA52
	vinflunine	L01CA05

INN/Common name	Previous ATC code	New ATC code
ATC code changes:		
clotiapine	N05AX09	N05AH06
paricalcitol	A11CC07	H05BX02

** Please note that the changes will not be implemented before January 2010*

Previous name	New name	New ATC code
ATC name changes:		
Diazepines, oxazepines and thiazepines	Diazepines, oxazepines, thiazepines and oxepines	N05AH

New DDDs:

INN/common name	DDD	Unit	Adm.R	ATC code
cefcapene	0.45	g	O	J01DD17
cefotiam	1.2	g	O	J01DC07
cevimeline	90	mg	O	N07AX03
cilostazol	0.2	g	O	C04AX33
dabigatran etexilate	0.22	g	O	B01AE07
doripenem	1.5	g	P	J01DH04
eperisone	0.15	g	O	M03BX09
febuxostat	80	mg	O	M04AA03
icatibant	30	mg	P	C01EB19
meptazinol	1.2	g	O,P	N02AX05
methylnaltrexone bromide	6	mg	P	A06AH01
micafungin	0.1	g	P	J02AX05
mitiglinide	30	mg	O	A10BX08
polymyxin B	3	MU	O	A07AA05
rilonacept	23	mg	P	L04AC04
romiplostim	30	mcg	P	B02BX04
sodium levofolinate	30	mg[1)]	P	V03AF10
tafluprost	0.3	ml[2)]		S01EE05

(1) Expressed as levofolinic acid
(2) Single dose package

Change of DDDs

INN/common name	Previous DDD	New temporary DDD	ATC Code
Risperidone*	1.8 mg P depot	2.7 mg P depot	N05AX08

** Please note that the changes will not be implemented before January 2010*

Recent Publications, Information and Events

Good clinical laboratory practices

In 2006, WHO/TDR convened a meeting of organizations engaged in clinical trials in disease endemic countries to discuss the applicability of Good clinical laboratory practices (GCLP) guidelines to their work. It was agreed that GCLP would be a valuable tool for improving quality laboratory practice. In line with that agreement, WHO/TDR recently acquired copyright to GCLP guidelines that were originally published in 2003 by a working party of the Clinical Committee of the British Association of Research Quality Assurance (BARQA), with the aim of disseminating them widely in developing countries and developing related training materials. Compliance with GCLP guidelines will allow clinical laboratories to ensure that safety and efficacy data is repeatable, reliable, auditable and easily reconstructed in a research setting. Additionally, GCLP guidelines set a standard for compliance by laboratories involved in the analysis of samples from TDR-supported clinical trials.

Reference: Special Programme for Research & Training in Tropical Diseases (TDR). Good Clinical Laboratory Practice (GCLP). DOI: 10.2471/TDR.09.978-924-1597852. 13 March 2009 at http://www.who.int/tdr

Laboratory diagnostic tools for tuberculosis control

There is currently a lack of information available to national tuberculosis programmes and funding and technical agencies on new TB diagnostic tools under development and in implementation. With this in mind, *New laboratory diagnostic tools for tuberculosis control* describes 19 new or improved diagnostic tools from many initiatives under way worldwide. Three of the tools described in this document have already been endorsed by WHO and are being implemented by countries, while others are still under development or in the pilot phase and expected to be ready for use in the coming years.

The brochure stands in as an interim document until a more complete blueprint of current R&D efforts can be developed. The purpose is not to recommend specific tools, but rather to provide summary information about tools being developed and becoming available so that all who play a part in TB control, especially in national TB programmes, can make well-informed decisions when retooling.

Reference: Stop TB Partnership: Retooling Task Force and New Diagnostic Working Group at http://apps.who.int/tdr/svc/publications/non-tdr-publications/diagnostic-tool-tb

WorldPharma2010: clinical pharmacology

The 16th World Congress on Basic and Clinical Pharmacology will be held from 17–23 July 2010 in Copenhagen, Denmark

The WorldPharma2010 event will include a two-day focused conference on Clinical pharmacology in emerging countries. Other sessions will include:

- Addiction and doping: neurobiological and clinical basis of emerging treatments.

- Developments in treatment of sexual dysfunction and diseases of the lower urinary tract.
- Drugs for half the world: paediatric clinical pharmacology.
- Endothelium in health and disease.
- G protein-coupled 7TM receptors: from molecular to physiological function.
- Inflammation and immunopharmacology: new tools for old diseases.
- Ion channelopathies: new windows on complex disease and therapy.
- Ion channels in analgesia and anaesthesia.
- Maximizing benefits and minimizing harm from drugs.
- Natural products: past and future?
- New approaches and targets in psychiatry.
- Nuclear receptor targets for treatment of diseases.
- Pharmacoepidemiology, current controversies and opportunities.
- Simulation and data modelling in drug development. Better drugs faster?
- The heart gone wrong; stabilization of cardiac function.
- Translational science in the metabolic syndrome.
- Transmembrane transport: perspectives for disease and drug discovery.

Reference: http://www.WorldPharma2010.org

Ethical guidelines for epidemiology

The newly published and revised CIOMS *International Ethical Guidelines for Epidemiological Studies* are intended to draw the attention of investigators, sponsors and ethical review committees to the need to consider carefully the ethical implications of research protocols and the manner in which research is conducted in order to attain high scientific and ethical standards in epidemiological studies and research.

Reference: Council for International organizations of Medical Sciences (CIOMS) at http://www.cioms.ch

Dengue: evaluation of immunoglobulin M tests

Dengue infection can produce a broad spectrum of symptoms and range from mild febrile illness to severe disease. Clinical features are often nonspecific and therefore require laboratory confirmation. Accurate but sophisticated methods, including virus isolation or polymerase chain reaction (PCR), require advanced equipment and infrastructure.

Serological assays that can detect specific immunoglobulin M (IgM) or immunoglobulin G (IgG) antibodies to dengue virus are widely available. These assays can provide an alternative to virus isolation or PCR to support the diagnosis of dengue fever. First-time (primary) dengue virus infections typically have a stronger and more specific IgM response and subsequent (secondary) infections show a weaker IgM response but a strong IgG response. These differing IgM response patterns to infection underscore the need to evaluate the sensitivity and specificity of commercially available tests, especially for diagnosis of secondary dengue virus infections.

WHO/TDR and the Paediatric Dengue Vaccine Initiative have collaborated to evaluate commercially available anti-dengue virus IgM diagnostic tests. A network of seven laboratories in Asia and Latin America has been established to carry out the work. *Evaluation of commercially available anti-dengue virus immunoglobulin M tests* describes the results of an evaluation of nine commercially available anti-dengue virus IgM tests, using a panel of well-characterized, archived serum specimens from patients with confirmed dengue virus infections and from patients with other potentially confounding infections and conditions.

Reference: World Health Organization Special Programme for Research & Training in Tropical Diseases (TDR). Evaluation of commercially available anti-dengue virus immunoglobulin M tests. *Diagnostics Evaluation Series No. 3.* at http://www.who.int/tdr

WHO/HAI student manual on pharmaceutical promotion

Medicines are a vital part of improving and maintaining health. Healthcare professionals, such as doctors and pharmacists, play a key role in ensuring that medicines are prescribed and used rationally.

However, numerous concerns have been raised about the relationship between healthcare professionals and the pharmaceutical industry — particularly the industry's influence on prescribing and dispensing decisions. This influence can lead to less than optimal treatment choices and can even be detrimental to patient health.

Research shows that while in training, many healthcare professionals receive little or no instruction on how to assess pharmaceutical promotion and how to understand its often subtle influence on their behaviour. In response, WHO and Health Action International (HAI) have developed a new publication: *Understanding and Responding to Pharmaceutical Promotion – A Practical Guide*. This draft manual can assist educators and healthcare professionals in teaching medical and pharmacy students about pharmaceutical promotion.

Reference: World Health Organization at http://www.who.int/medicines and Health Action International at http://www.haiweb.org

WHO/ PHARM S/NOM 1570
Distr.: GENERAL
ENGLISH ONLY

GUIDELINES ON THE USE OF INTERNATIONAL NONPROPRIETARY NAMES (INNs) FOR PHARMACEUTICAL SUBSTANCES

Programme on International Nonproprietary Names (INN)
Division of Drug Management & Policies
World Health Organization
Geneva

GUIDELINES ON THE USE OF INTERNATIONAL NONPROPRIETARY NAMES (INNs) for Pharmaceutical Substances

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List of Annexes

Information on the INN Programme and the INN request form
are available on INTERNET:
http://www.who.ch/programmes/dmp/innmain.htm

1. General introduction

The present guidelines on the use of INNs are intended as a general explanation of the INN selection process. They have been developed for drug regulatory authorities for use in the marketing authorization/ registration of products, drug manufacturers who are requesting new INNs and those using INNs, patent authorities/offices, trade-mark attorneys and trade-mark specialists, scientists, teachers, health professionals, as well as any person interested in nomenclature.

1.1 General information on the INN system

An International Nonproprietary Name (INN) identifies a pharmaceutical substance or active pharmaceutical ingredient by a unique name that is globally recognized and is public property. A nonproprietary name is also known as a generic name.

The INN system as it exists today was initiated in 1950 by a World Health Assembly resolution WHA3.11 and began operating in 1953, when the first list of International Nonproprietary Names for pharmaceutical substances was published. The cumulative list of INNs now stands at some 7000 names designated since that time, and this number is growing every year by some 120 - 150 new INNs.

Since its inception, the aim of the INN system has been to provide health professionals with a unique and universally available designated name to identify each pharmaceutical substance. The existence of an international nomenclature for pharmaceutical substances, in the form of INNs, is important for the clear identification, safe prescription and dispensing of medicines to patients, and for communication and exchange of information among health professionals and scientists worldwide.

As unique names, INNs have to be distinctive in sound and spelling, and should not be liable to confusion with other names in common use. To make INNs universally available they are formally placed by WHO in the public domain, hence their designation as "nonproprietary". They can be used without any restriction whatsoever to identify pharmaceutical substances.

Another important feature of the INN system is that the names of pharmacologically-related substances demonstrate their relationship by using a common "stem". By the use of common stems the medical practitioner, the pharmacist, or anyone dealing with pharmaceutical products can recognize that the substance belongs to a group of substances having similar pharmacological activity. For example all iodine-containing contrast media are given the prefix *io-*, while all ß-adrenoreceptor antagonists the suffix *-olol*. The use of stems is described later in more detail.

The extent of INN utilization is expanding with the increase in the number of names. Its wide application and global recognition are also due to close collaboration in the process of INN selection with numerous national drug nomenclature bodies. The increasing coverage of the drug-name area by INNs has led to the situation whereby the majority of pharmaceutical substances used today in medical practice are designated by an INN. The use of INNs is already common in research and clinical documentation, while

the importance of the programme is growing further due to expanding use of generic names for pharmaceutical products.

The names which are given the status of an INN are selected by the World Health Organization on the advice of experts from the WHO Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations. The process of INN selection follows three main steps:

- a request/application is made by the manufacturer or inventor,
- after a review of the request a proposed INN (prop. INN) is selected and published for comments,
- after a time-period for objections has lapsed, the name will obtain the status of a recommended INN (rec. INN) and is published as such.

The procedures relating to each of these steps are described in the present document in full detail.

INNs are selected in principle only for single, well-defined substances that can be unequivocally characterized by a chemical name (or formula). It is the policy of the INN programme not to select names for mixtures of substances, while substances that are not fully characterized are included in the INN system in exceptional cases only. INNs are not selected for herbal substances (vegetable drugs) or for homoeopathic products. It is also the policy of the INN programme not to select names for those substances that have a long history of use for medical purposes under well-established names such as those of alkaloids (e.g. morphine, codeine), or trivial chemical names (e.g. acetic acid).

The INN is usually designated for the active part of the molecule only, to avoid the multiplication of entries in cases where several salts, esters, etc. are actually used. In such cases, the user of the INN has to create a modified INN (INNM) himself ; *mepyramine maleate* (a salt of *mepyramine* with *maleic acid*) is an example of an INNM. When the creation of an INNM would require the use of a long or inconvenient name for the radical part of the INNM, the INN programme will select a short name for such a radical (for example, *mesilate* for *methanesulfonate*).

Names of pharmaceutical preparations, such as used in pharmacopoieal monograph titles, usually consist of two elements, the first designating the active substance (an INN is used here), and the other designating the dosage form of the product. Rules for creating such names fall outside the INN programme and are not discussed here.

In the process of INN selection, the rights of existing trade-mark owners are fully protected. If in the period of four months following the publication of a proposed INN, a formal objection is filed by an interested person who considers that the proposed INN is in conflict with an existing trade-mark, WHO will actively pursue an arrangement to obtain a withdrawal of such an objection or will reconsider the proposed name. As long as the objection exists, WHO will not published it as a recommended INN.

With the growing number of INNs and trade-marks, the possibility of conflicts between the two has gradually increased, even with full protection of the rights of existing trade-marks. The main source of conflict is usually an attempt by a manufacturer to propose a new trade-mark containing stems established in the INN programme. If protection is granted to such a name, this may diminish the freedom of the INN programme in selecting further INNs in the same series of substances. To prevent such occurrences, the matter was taken up in a resolution of the World Health Assembly *WHA46.19*. This issue is discussed in more detail in section 4.

Further background information on the INN programme may be found in Annex 1.

1.2 Use of INNs

Nonproprietary names are intended for use in pharmacopoeias, labelling, product infromation, advertising and other promotional material, drug regulation and scientific literature, and as a basis for product names, e.g. for generics. Their use is normally required by national or, as in the case of the European Community, by international legislation. As a restult of ongoing collaboration, national names such as British Approved Names (BAN), Dénominations Communes Françaises (DCF), Japanese Adopted Names (JAN) and United States Accepted Names (USAN) are nowadays, with rare exceptions, identical to the INNs.

Some countries have defined the minimum size of characters in which the generic nonproprietary name must be printed under the trade-mark labelling and advertising. In several countries the generic name must appear prominently in type at least half the size of that used for the proprietary or brand-name. In some countries it has to appear larger than the trade-mark name. Certain countries have even gone so far as to abolish trade-marks within the public sector.

To avoid confusion, which could jeopardize the safety of patients, trade-marks cannot be derived from INNs and, in particular, must include their common stems. As already menitoned the selection of further names within a series will be seriously hindered by the use of a common stem in a brand-name.

2. Elements in the INN system

2.1 Proposed INNs

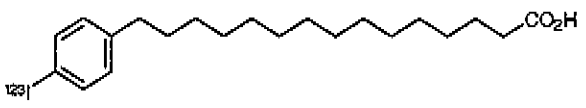
The selection of a new INN relies on a a strict procedure. Upon receipt of an INN request form, the WHO Secretariat examines the suggested names for conformity with the general rules, for similarities with published INNs and potential conflicts with existing names, including published INNs and trademarks. A note summarizing the result of these checks is added and the request is subsequently forwarded to the INN experts for comments. Once all experts agree upon one name, the applicant is informed of the selected name.

Newly selected, proposed INNs are then published in *WHO Drug Information*, which indicates a deadline for a 4-month objection period. This period is allowed for comments and/or objections to the published names to be raised. The reasons for any objection must be stated clearly and these will be evaluated by the experts for further action. Users are invited to refrain from using the proposed name until it becomes a recommended INN, in order to avoid confusion should the name be modified.
Two lists of proposed INNs are published yearly. An example is set out below.

acidum iocanlidicum (^{123}I)

iocanlidic (^{123}I) acid	15-(*p*-[^{123}I]iodophenyl)pentadecanoic acid *radiodiagnostic agent*
acide iocanlidique (^{123}I)	acide 15-(4-[^{123}I]iodophényl)pentadécanoïque *produit à usage radiodiagnostique*
ácido iocanlídico (^{123}I)	ácido 15-(*p*-[^{123}I]iodofenil)pentadecanoico *agente de radiodiagnóstico*

$C_{21}H_{33}{}^{123}IO_2$ 74855-17-7



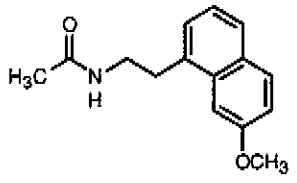
2.2 Recommended INNs

The final stage of the selection process is the recommended INN. Once a name has been published as a recommended INN it will not normally be modified further and is ready for use in labelling, publications, on drug information. It will serve to identify the active pharmaceutical substance during its life-time worldwide. Since the name is available in the public domain it may be used freely. However, it should not be registered as a trademark since this would prevent its use by other parties (see also chapter 4.).

Recommended INNs are published in the *WHO Drug Information* as a consequence of the objection procedure applied to proposed INNs (see 2.1 above). As from 1997, two lists of proposed INNs are published yearly and as from list 37 of recommended INNs, graphic formulae are also included for better identification of the substances.

An example of an entry in the list may be found below:

agomelatinum	
agomelatine	*N*-[2-(7-methoxy-1-naphthyl)ethyl]acetamide
agomélatine	*N*-[2-(7-méthoxynaphtalén-1-yl)éthyl]acétamide
agomelatina	*N*-[2-(7-metoxi-1-naftil)etil]acetamida
	$C_{15}H_{17}NO_2$



2.3 Names for radicals and groups

During the 1975 meeting on Nonproprietary Names for Pharmaceutical Substances the experts discussed the issue of INNs for salts and esters and noted that requests had frequently been received for INNs for salts, esters, or combination products of substances for which INNs already existed. At that time, the experts decided that INNs for the simple salt and esters should be devised from the INN in conformity with normal chemical practice.

Some of the radicals and groups involved are, however, of such complex composition that it makes it inconvenient to use the chemical nomenclature. It was thus decided that in such cases, shorter nonproprietary names are selected for these inactive moieties and published in proposed lists under the title "Names for Radicals and Groups". Separate names for salts and esters derived from this procedure are not published. If a "radical and group name" is used in conjunction with an INN, they are referred to as International Nonproprietary Name (Modified) or INNM.

A comprehensive list of radicals and groups may be obtained from the Distribution and Sales unit or the INN Secretariat (*INNs: Names for radicals and groups, combined summary list, WHO/PHARM S/NOM 1506, updated regularly*).

2.4 Modified INNs (INNMs)

In principle, INNs are selected only for the active part of the molecule which is usually the base, acid or alcohol. In some cases, however, the active molecules need to be expanded for various reasons, such as formulation purposes, bioavailability or absorption rate. In 1975 the experts designated for the selection of INN decided to adopt a new policy for naming such molecules. In future, names for different salts or esters of the same active substance should differ only with regard to the inactive moiety of the molecule. For example, *oxacillin* and *ibufenac* are INNs and their salts are named *oxacillin sodium* and *ibufenac sodium*. The latter are called modified INNs (INNMs).

Before the existence of this rule, some INNs were published for salts. In such cases, the term "modified INN" may also be used for a base or acid. For example, *levothyroxine sodium* was published as an INN and *levothyroxine* may thus be referred to as an INNM.

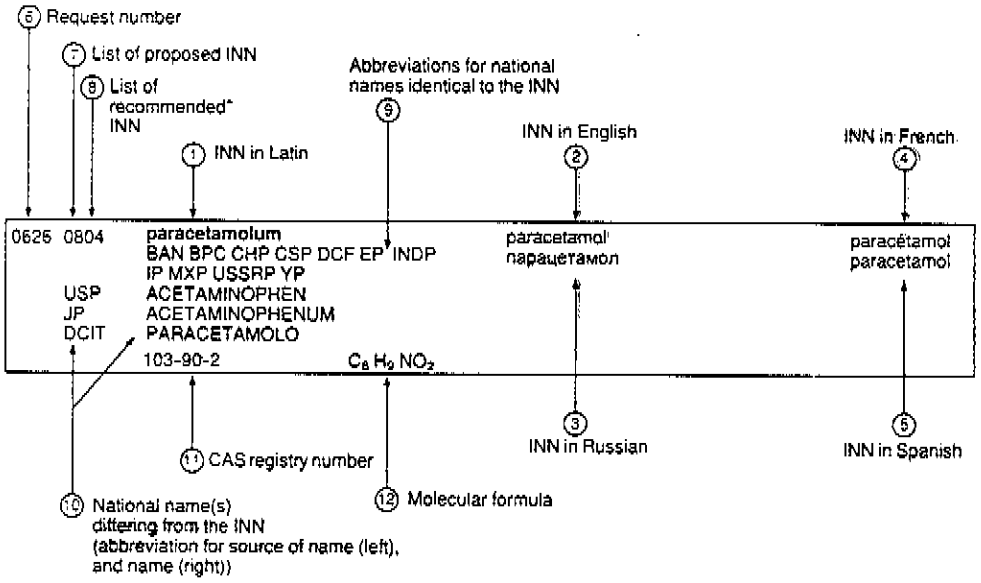
Please see also chapter 2.4 for radicals and groups (see also 2.4) which are used in conjunction with INNs and which are also referred to as INNM.

2.5 Cumulative list

All names selected as proposed and recommended INNs are published in a *Cumulative list*, which is updated periodically. The generic names are presented in alphabetical order by Latin name. Each entry includes:

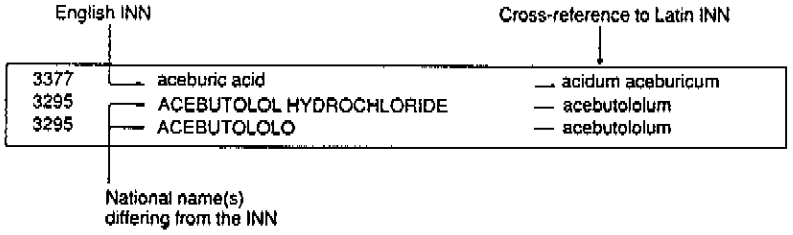
- equivalent nonproprietary names: in Latin, English, French, Russian and Spanish;
- a reference to the INN list in which the name was originally proposed or recommended, or last amended;
- reference to names of substances that have been abandoned or never been marketed;
- reference to national nonproprietary names;
- reference to pharmacopoeial monographs or similar official references;
- reference to names issued by the International Organization for Standardization (ISO);
- reference to the Convention of Psychotropic Substances, if applicable;
- reference to the List of Narcotic Drugs under International Control, if applicable;
- the molecular formula;
- its Chemical Abstracts Service (CAS) number.

The layout for information contained in the *Cumulative list* of INNs is as follows:



* An asterisk in place of a recommended list number signifies that an objection has been raised to the proposed name.

Note: Cross-references are provided for entries corresponding to (a) English, French and Spanish INN that appear in different alphabetical positions from the Latin INN and (b) national names that differ from the INN. Entries for (a) are printed in lower-case letters (as in the example of aceburic acid, below) while entries for (b) are printed in capitals (as in the examples of ACEBUTOLOL HYDROCHLORIDE and ACEBUTOLOLO).



3. Principles for selection of INNs

3.1 General rules

General rules were established at the beginning of the INN programme in order to guide the members of the INN committee and to allow health professionals to understand the rationale for a number of new names. At first, some countries used shortened chemical names as generic names, but this system was found to be very limited, since many molecules contain similar elements and groups, such as phenol, chlor, methyl or benzene-rings, in their chemical structures. In addition, a name that indicates relationship to a group of pharmacological similarly-acting substances is more meaningful to users.

In its Twentieth Report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds over the years. The current version of the *General principles for guidance in devising international nonproprietary names for pharmaceutical substances* is reproduced in Annex 2.

3.2 Use of stems

Usually, an INN consists of a random, fantasy prefix and a common stem; substances belonging to a group of pharmacologically related substances show their relationship by the use of a common stem. Sometimes sub-stems are established to differentiate between different related groups of substances, e.g. *-olol* for b-adrenoreceptor antagonists and antihypertensives, *-teplase* for tissue-type-plasminogen activators and *-uplase* for urokinase-type-plasminogen activators.

A list of common stems used in the selection of INNs may be found in Annex 3.

3.3 Stereoisomers

An INN for a new chemical entity does not routinely specify the stereoisomeric state of the molecule in the nonproprietary name. If the stereochemistry has been determined, then this information is presented in the chemical name(s) to identify the substance. An INN can, therefore, identify the racemic mixture (e.g. ibuprofen, tetramisole), the *levo-* isomer (e.g. amifostine, lofentanil, prenalterol, remoxipride, quadazocine), or the *dextro* form (e.g. butopamine). Subsequently if an INN is needed for a different enantiomer or for the racemic form, the following prefixes should be added to the existing INN:

(a) For the *levo* form, the *lev-/levo-* prefix is used, e.g. levocarnitine, levamisole.
(b) For the *dextro* form, the *dex-* prefix is used, e.g. dexamisole, dexibuprofen.
(c) For the *racemic* form, the *rac-/race-* prefix is used, e.g. racepinefrine.

3.4 Radioactive compounds

A name for a drug substance containing a radioactive atom should list, in the following order:

(1) the name of the substance containing the radioactive atom,
(2) the isotope number,
(3) the element symbol, and
(4) the name of the carrier agent, if any,

e.g. cyanocobalamin (^{60}Co), technetium (^{99m}Tc) bicisate, technetium (^{99m}Tc) sestamibi.

3.5 Specific groups of biological compounds

Because of the complexity of certain new types of pharmaceutical products, such as compounds produced by biotechnology, general rules are not always easily formulated. Some of these substances may already have descriptive names assigned by other institutions such as the *International Union of Biochemistry (IUB), International Union of Pure and Applied Chemistry* (IUPAC), *Joint Commission on Biochemical Nomenclature* (JCBN). These names may not be suitable as INNs.

Annex 4 summarizes nomenclature schemes for groups of biological compounds
(for details and examples please also see document WHO/PHARM S/NOM 15: *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances,* updated regularly).

4. Protection of INNs

Lists of both proposed and recommended INNs are sent together with a *note verbale* by the Director-General to WHO Member States (at present 191), to national pharmacopoeia commissions and to other bodies designated by Member States. In his *note verbale,* the Director-General of the World Health Organization requests that Member States should take such steps as are necessary to prevent the acquisition of proprietary rights on the name, including prohibiting registration of the name as a tradename.

Over the years, the need to maintain the integrity of the INN system has become urgent. This is reflected in the following extract from the Fifth Report of the WHO Expert Committee on the Use of Essential Drugs which met in November 1991[1]:

> **"The procedure for selecting INNs allows manufacturers to contest names that are either identical or similar to their licensed trade marks. In contrast, trade mark applications are disallowed, in accordance with the present procedure, only when they are identical to an INN.A case for increased protection of INNs is now apparent as a result of competitive promotion of products no longer protected by patents. Rather than marketing these products under generic name, many companies apply for a trade mark derived from an INN and, in particular, including the INN common stem. This practice endangers the principle that INNs are public property; it can frustrate the rational selection of further INNs for related substances, and it will ultimately compromise the safety of patients by promoting confusion in drug nomenclature."**

These concerns were debated during the sixth International Conference of Drug Regulatory Authorities (ICDRA), in Ottawa, in October 1991.

Based on recommendations made by the WHO Expert Committee on the use of Essential Drugs the resolution WHA46.19 on *Nonproprietary Names for pharmaceutical substances* was adopted in May, 1993 during the Forty-sixth World Health Assembly requesting Member States to:

> ■ ***"enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic nam used in the labelling and advertising of pharmaceutical products are always displayed prominently;***
> ■ ***to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trade-marks, to promote and market multisource products introduced after patent expiration;***
> ■ ***to develop policy guidelines on the use and protection of international nonproprietary names,and to discourage the use of names derived from INNs, and particularly names including established INN stems as trade-marks."***

In the Director General's *note verbale* attention is drawn to this resolution concerning the use and protection of International Nonproprietary Names (INNs).
The full text of the resolution is reproduced in Annex 5.

As a matter of principle, it may thus be recommended that trade marks should not be derived from INNs. In particular, the intentional incorporation of meaningful INN stems in trade marks should be avoided.

Similarly, inclusion of elements from biochemical nomenclature (like *-feron* from interferon, or *-leukin* from interleukin) in trade marks in anticipation is discouraged since these elements are likely to be utilized as stems within the INN nomenclature. Their inclusion in trade marks could pre-empt the logical development of the INN nomenclature.

[1] WHO Technical Report Series, No. 825, 1992.

In accordance with resolution WHA46.19, registration of an INN together with a firm's name is perfectly acceptable, as long as it does not prevent another manufacturer from using the same approach.

5. How to apply for an INN

5.1 Procedure for selection of INNs

The selection of INNs is based on the *Procedure for selection of international nonproprietary names for pharmaceutical substances.* The text adopted is set out in World Health Assembly resolution WHA3.11 [Text adopted by the Executive Board of WHO in resolution EB15.R7 (*Off. Rec. Wld Health Org.*, 1955, **60**, 3) and amended by the Board in resolution EB43.R9 (*Off. Rec. Wld Hlth Org.*, 1969, **173**, 10).]. The application/request form for INN is attached as Annex 6 in its updated version.

In countries with national nomenclature commissions, applications for international nonproprietary names should be made through the national authorities (addresses - see Annex 7). In countries without a national nomenclature commission, requests for INNs may be forwarded directly to WHO. Applications for INNs should be addressed to:

Secretary of the INN Programme
Quality Assurance - INNs
Drug Management and Policies
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
***Internet:* koppkubels@who.ch**
***Fax* : +41 22 791 07 46**
***Tel.* : +41 22 791 36 36/36 60**

5.2 INN request form

Before a suggested name can be evaluated by the INN Secretariat, complete information must be provided on a request form to facilitate uniform handling of the data and to assure that pertinent items have not been omitted. It is important that the information is as comprehensive as possible. If parts of this information are missing or explanations are unclear or incomplete, the INN Secretariat will request the applicant to furnish the missing data. This can result in delay because selection of an INN requires the availability of all relevant information to the INN experts.

The following explanations will help applicants to complete the INN form. If additional information is needed, an applicant may contact the INN Secretariat at the World Health Organization, DMP/QAS, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland. (Telephone: +41/22/791 36.36/36.60. Facsimile: +41/22/ 791.07.46. Internet: *koppkubels@who.ch*).

Suggested names in order of preference

An applicant may make 3 suggestions for an INN relating to the acid, base or alcohol of a specific chemical entity under investigation. The suggested name should be a single word and not inconveniently long.

Nonproprietary names are developed by a system that relates compounds with chemical, pharmacological or therapeutic similarity. Therefore, whenever justified, the suggested name must incorporate the established common stem. A list of stems may be found in the document entitled *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances (WHO/PHARM S/NOM 15)* which is updated regularly.

Occasionally stems require modification. For example, some drugs inhibit a-adreno-receptors as well as ß-adrenoreceptors and exhibit a specific structural variation from the "*-olol*" prototype. Accordingly, for this type of drug, the stem was modified by one letter to "*-alol*". This change introduces a nuance in the

naming of related groups of drugs that may not be apparent to every observer but would be understood by someone familiar with the naming conventions of the ß-adrenoreceptor antagonists and related compounds. The important point is that similar compounds have a common element in the name that imparts useful information.

It is imperative that the newly suggested name does not conflict with existing chemical names, other nonproprietary names or trade-marks. Therefore, the INN Secretariat requests the applicant to verify the absence of conflicts with existing chemical names, common names for insecticides, other nonproprietary names, and trade-marks. Some firms routinely perform exhaustive searches for possible conflicts with a suggested INN and for pharmacologically and chemically related compounds with already assigned INNs; the INN Secretariat would appreciate receiving this information to avoid search duplication.

Chemical name and description

Chemical information should be as complete and as current as possible. Information on stereochemistry should be included if known. The chemical names will be in accordance with the nomenclature rules of the International Union of Pure and Applied Chemistry (**IUPAC**) as interpreted by the Chemical Abstracts Service (8th collective period); the Chemical Abstracts Index names in their current style may also be included as additional information. The chemical name provided by the manufacturer is reviewed for accuracy and to confirm that its construction follows accepted chemical nomenclature rules.

A description is used to identify a substance that is insufficiently defined to be assigned an IUPAC and CAS chemical name. This description will be superseded by the chemical name when the drug substance is fully characterized.

Precautions are taken to ensure confidentiality of the material submitted to WHO, but an applicant should not attempt to obtain an INN before all patent procedures are completed and until full chemical information can be made available to WHO.

Graphic formula

Without a graphic formula, it may be difficult to determine if an INN already exists. In addition, the graphic formula is necessary to relate the new drug to existing compounds in the same chemical family. Guidelines for drawing structures may be found in the document entitled *Graphic representation of chemical formulae in the publications of International Nonproprietary Names for pharmaceutical substances (WHO/PHARM/95.579)*, available from the INN Secretariat upon request.

Molecular formula

A one-line molecular formula constructed in accordance with accepted chemical practices should be supplied. The molecular formulas should be given in the following manner, e.g. $C_{21}H_{28}N_2$.

Chemical Abstracts Service (CAS) registry number

If a CAS registry number has been assigned to a new compound before it is submitted to the INN Secretariat, the number should be included on the form. If no number has yet been assigned, the manufacturer should obtain the CAS registry number from Chemical Abstracts Services for publication in the INN lists. Proof of the entry will be required.

Tradenames (known or contemplated)

If a trade-mark has been issued for the drug, it should be entered on the form. List any national or international trade-marks (and manufacturers) and the name of the country where the trade-mark is registered.

Any other name or code

Sometimes, long before a nonproprietary name or a trade-mark has been selected for a new compound, it may acquire a trivial name that has been used in the laboratory and scientific literature. The INN Secretariat would like to be made aware of such names but requests manufacturers not to create, use, or in any way encourage the creation of trivial names for new drugs. The fact that a trivial name has become accepted in the literature will not ensure its adoption as a nonproprietary name and may only cause confusion when an official nonproprietary name is selected. It is therefore recommended to use codes before the publication of a recommended nonproprietary name and indicate these on the request form to the INN Secretariat as an additional reference.

Principal therapeutic use(s) and posology

It is important to know the therapeutic category for the new compound as such information may determine the stem selected for the nonproprietary name. Pertinent reprints presenting evidence of the claimed therapeutic use should be included with the application (for terminology, please see *Pharmacological Action and Therapeutic Use of Drugs, a list of terms*, English/French/Spanish, 1996 (*PHARM/96.320*).

Pharmacological action

The pharmacological action should be explained in as much detail as possible, since it may also influence the stem selected for the compound. Again, pertinent reprints must be included to support the claimed action (for terminology, please see above).

Verso side of request form

Date of clinical trial

As a general guide, the development of a drug should progress up to the point of clinical trials (phase II) before an application is submitted to the INN Secretariat for name selection. An approximate date when clinical trials began is requested. The intent of this request is to assure that clinical trials are under way. It is the belief that if a drug has entered clinical trials, there is a reasonable expectation that it will be marketed and thus the name selected will have been developed for that need and purpose.

In case the development is stopped, the manufacturer should inform the INN Secretariat as soon as possible, in order to halt the selection process.

Availability of suggested names

The originator of the INN request confirms with his signature that the suggestion is made on the understanding that, insofar as is known, none of the suggested names are either registered or pending registration.

Permission to publish the CAS registry number

The applicant herewith confirms that the CAS registry number sent to the INN Secretariat is correct and may be used in the INN lists.

Additional comments

This section allows the applicant to give additional comments and/or information.

6. References for supporting material

Documents:

- *The use of common stems in the selection of international nonproprietary names (INN) for pharmaceutical substances* (WHO/PHARM S/NOM 15) INN Programme, WHO, Geneva - *updated regularly*
- *Graphic representation of chemical formulae in the publications of international nonproprietary names (INN) for pharmaceutical substances* (WHO/PHARM/95.579), INN Programme, WHO, Geneva
- *Pharmacological Action and Therapeutic Use of Drugs, list of terms*, English/French Spanish, 1996, (*PHARM/96.320*), WHO, Geneva
- *INNs: Names for radicals and groups, combined summary list*, WHO/PHARM S/NOM1506, INN Programme, WHO, Geneva - *updated regularly*
- *Definition of INNs for Substances Prepared by Biotechnology*, PHARM S/NOM 1348,INN Programme, WHO, Geneva

Publications:

- *Cumulative List of INNs, No. 9*, 1996, WHO, Geneva
- *WHO Drug Information* (quarterly journal published by the World Health Organization)

ANNEX 1

Background information on the INN Programme

The activities of national nomenclature commissions are coordinated in order to achieve international standardization in nomenclature under the auspices of WHO according to *article 2a* and *2u* of its constitution (adopted in 1946 in New York):

"In order to achieve its objective, the functions of the World Health Organization shall be:

(a) to act as the directing and coordinating authority on international health work; ...
(u) to develop, establish and promote international standards with respect to food, biological, pharmaceutical and similar products; ..."

The WHO programme on the selection of international nonproprietary names (INN) emerged really as an extension of the WHO programme on the unification of pharmacopoeias and the preparation of the International Pharmacopoeia requested by the very first World Health Assembly in July 1948 in resolution *WHA1.27*. The meeting of an Expert Committee on Unification of Pharmacopoeias in 1949 studied the preparation of general rules for nomenclature, and drew up a plan that was adopted in 1950 by a resolution of the World Health Assembly (*WHA3.11*).

The World Health Organization's (WHO) international nomenclature programme was thus established in 1953 when Member countries adopted a resolution at the World Health Assembly officially initiating the programme on International Nonproprietary Names (**INN**) for pharmaceutical substances [French : **D**énominations **C**ommunes **I**nternationales]; [Spanish : **D**enominaciones **C**omunes **I**nternacionales - **DCI**].

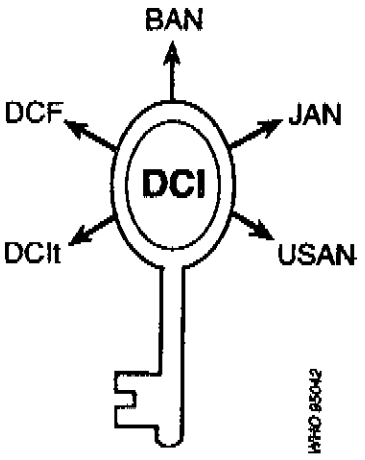
The official "Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances" and the "General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances" on which the whole programme is based were adopted by the Executive Board in 1955 in resolution *EB15.R7*. The Procedure has remained unchanged -- except for the replacement of the words "INNs for Pharmaceutical Preparations" by "*INNs for Pharmaceutical Substances*" (res. *EB43.R9*). However, the General Principles have evolved and revisions were regularly approved in the reports of the Sub-Committee meetings submitted to the Executive Board. Since 1969 the Director-General is authorized by the Executive Board to make such revisions of the General Principles as may seem desirable in the light of advances in science and of experience as may be suggested by the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated to deal with the selection of nonproprietary names (INN experts) in accordance with the above-mentioned Procedure (res. *EB37.R9*).

From 1950 onwards the programme was dealt with by the Sub-Committee of the Expert Committee on the Unification of Pharmacopoeias. The first task of the Sub-Committee was to establish contacts with national pharmacopoeia commissions that had already established programmes on the unification of drug nomenclature as those carried out under the *Comité de Nomenclature* of the *Commission permanente de la Pharmacopée Française*, the Nomenclature Committee of the British Pharmacopoeia Commission, the Council of Drugs of the American Medical Association in the USA and the Nomenclature Committee of the Nordic Pharmacopoeia Council in the Scandinavian countries. The purpose of these contacts was to coordinate the activities of such existing national nomenclature programmes.

Between 1950 and 1966 the Sub-Committee met 16 times. The earlier meetings were concerned with developing the Procedure and the General Principles and the first list of proposed INNs was only published in 1953. In 1967 the Sub-Committee became the Expert Committee on Nonproprietary Names for Pharmaceutical Preparations and later the Expert Committee on Nonproprietary Names for Pharmaceutical Substances. This Expert Committee only met in 1967, 1968, 1970 and 1975. In the other years, and since 1976, the meetings were held in a less formal way and

referred to as Consultations on the Selection of INNs. The justification for this less formal approach is that the main report of the Committee consists of the officially published INNs selected during its meetings.

The composition of the INN meetings over almost 40 years has been characterized by a great stability. The average number of participants is 6-8 experts, mostly people with responsible positions in - or secretaries of - national nomenclature commissions, and only some 30 people have been involved over the years. At present the Expert group is composed of experts from France, Indonesia, Japan, Nigeria, Poland, Spain, the United Kingdom and USA.



BAN: British Approved Name
DCF: Dénomination Commune Française
DCIt: Denominazione Comune Italiana
JAN: Japanese Accepted Name
USAN: United States Approved Name

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ANNEX 2

General principles for guidance in devising International nonproprietary names for pharmaceutical substances

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, "f" should be used instead of "ph", "t" instead of "th", "e" instead of "ae" or "oe", and "i" instead of "y"; the use of the letters "h" and "k" should be avoided."

When devising an INN it is important to be aware of possible language problems . Since the name is used worldwide, not only should certain letters be avoided, but experts need to be aware of unsuitable connotations in the major languages spoken in the world.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use. [1]Where a stem is shown without any hyphens it may be used anywhere in the name.

Latin	***English***	
-acum	-ac	anti-inflammatory agents of the ibufenac group
-actidum	-actide	synthetic polypeptides with a corticotropin-like action
-adolum	-adol }	analgesics
-adol-	-adol-}	analgesics
-astum	-ast	antiasthmatic, antiallergic substances not acting primarily as antihistaminics
-astinum	-astine	antihistaminics
-azepamum	-azepam	diazepam derivatives
-bactamum	-bactam	b-lactamase inhibitors

[1] An extensive listing of stems is contained in the working document WHO/PHARM S/NOM15 which is regularly updated and can be requested from the INN Secretariat, WHO, Geneva.

Latin	*English*	
bol	bol	steroids, anabolic
-buzonum	-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	-cain-	antifibrillant substances with local anaesthetic activity
-cainum	-caine	local anaesthetics
cef-	cef-	antibiotics, cefalosporanic acid derivatives
-cillinum	-cillin	antibiotics, derivatives of 6-amino- penicillanic acid
-conazolum	-conazole	systemic antifungal agents, miconazole derivatives
cort	cort	corticosteroids, except prednisolone derivatives
-dipinum	-dipine	calcium channel blockers, nifedipine derivatives
fibratum	-fibrate	clofibrate derivatives
gest	gest	steroids, progestogens
gli-	gli-	sulfonamide hypoglycaemics
io-	io-	iodine-containing contrast media
-ium	-ium	quaternary ammonium compounds
-metacinum	-metacin	anti-inflammatory substances, indometacin derivatives
-mycinum	-mycin	antibiotics, produced by *Streptomyces strains*
-nidazolum	-nidazole	antiprotozoal substances, metronidazole derivatives
-ololum	-olol	b-adrenoreceptor antagonists
-oxacinum	-oxacin	antibacterial agents, nalidixic acid derivatives
-pridum	-pride	sulpiride derivatives
-pril(at)um	-pril(at)	angiotensin-converting enzyme inhibitors
-profenum	-profen	anti-inflammatory substances, ibuprofen derivatives
prost	prost	prostaglandins
-relinum	-relin	hypophyseal hormone release-stimulating peptides
-terolum	-terol	bronchodilators, phenethylamine derivatives
-tidinum	-tidine	histamine H_2-receptor antagonists
-trexatum	-trexate	folic acid antagonists
-verinum	-verine	spasmolytics with a papaverine-like action
vin-	vin-)	vinca alkaloids
-vin-	-vin-)	vinca alkaloids

ANNEX 3

LIST OF COMMON STEMS USED IN THE SELECTION OF INNs

STEM	*DEFINITION* ***substem, if available***
-ac	anti-inflammatory agents, ibufenac derivatives
-actide	synthetic polypeptides with a corticotropin-like action
-adol or -adol-	analgesics
-adom	analgesics, tifluadom derivatives
-afenone	antiarrhythmics, propafenone derivatives
-aj-	antiarrhythmics, ajmaline derivatives
-aldrate	antacids, aluminium salts
-alox	antacids, aluminium derivatives
-amivir see *vir*	
andr or -stan- or -ster-	steroids, androgens
-anserin	serotonin receptor antagonists (mostly 5-HT_2)
-antel	anthelminthics (undefined group)
-apine	see *-pine*
-arabine	arabinofuranosyl derivatives
-arit	antiarthritic substances, acting like clobuzarit and lobenzarit (mechanism different from anti-inflammatory type substances, e.g. *-fenamates* or *-profens*)
-arol	anticoagulants, dicoumarol derivatives
arte-	antimalarial agents, artemisinin related compounds
-ase	enzymes; *-dismase* (superoxide dismutase activity), *-pase* (lipase) *-teplase* (tissue plasminogen activators), *-uplase* (urokinase-type-plasminogen activators)
-ast	antiasthmatic, antiallergics, not acting primarily as antihistaminics; *-lukast (* leukotriene receptor antagonist); *-trodast* (thromboxane A_2 receptor antagonists, antiasthmatics)
-astine	antihistaminics
-azenil	benzodiazepine receptor antagonists/agonists (benzodiazepine derivatives)
-azepam	diazepam derivatives
-azepide	cholecystokinin receptor antagonist
-azocine	narcotic antagonists/agonsists related to 6,7-benzomorphan
-azoline	antihistaminics or local vasoconstrictors, antazoline derivatives
-azosin	antihypertensive substances, prazosin derivatives
-bactam	b-lactamase inhibitors
-bamate	tranquillizers, propanediol and pentanediol derivatives
barb	hypnotics, barbituric acid derivatives
-bendazole	anthelminthics, tiabendazole derivatives
bol	anabolic steroids
-bradine	bradycardic agents

STEM	***DEFINITION*** ***substem, if available***
-buzone	anti-inflammatory analgesics, phenylbutazone derivatives
-cain-	Class I antiarrhythmics, procainamide and lidocaine derivatives (antifibrillants with local anaesthetic activity)
-caine	local anaesthetics
calci	Vitamin D analogues/derivatives
-carbef	antibiotics, carbacepham derivatives
-carnil	benzodiazepine receptor antagonists/agonists (carboline derivatives)
-cavir	see *vir*
cef-	antibiotics, cefalosporanic acid derivatives
cell- or cel- or -cell-	cellulose derivatives *cell-ate* (cellulose ester derivatives); *-cellose* (cellulose ether derivatives)
-cic	hepatoprotective substances with a carboxylic acid group
-cidin	naturally occurring antibiotics (undefined group)
-cillin	antibiotics, 6-aminopenicillanic acid derivatives
-citabine	nucleoside antiviral or antineoplastic agents, cytarabine or azarabine derivatives
-clone	hypnotic tranquillizers
-cog	blood coagulation factors; *(-)eptacog* (blood coagulation VII); *(-)octocog* (blood coagulation factor VIII); *(-)nonacog* (blood coagulation factor IX)
-conazole	systemic antifungal agents, miconazole derivatives
cort	corticosteroids, except prednisolone derivatives
-crinat	diuretics, etacrynic acid derivatives
-crine	acetylcholinesterase inhibitors, tacrine derivatives
-cromil	antiallergics, cromoglicic acid derivatives
-curium	see *-ium*
-cycline	antibiotics, tetracycline derivatives
-dan	cardiac stimulants, pimobendan derivatives
-dapsone	antimycobacterials, diaminodiphenylsulfone derivatives
-dermin	see *-ermin*
-dil	vasodilators
-dipine	calcium channel blockers, nifedipine derivatives
-dismase	see *-ase*
-dopa	dopamine receptor agonists, dopamine derivatives, used as antiparkinsonism/prolactin inhibitors;
-dox	antibacterials, quinoline dioxide derivatives
-dralazine	antihypertensives, hydrazinephthalazine derivatives
-drine	sympathomimetics; *-frine*: sympathomimetic, phenethyl derivatives
-dronic acid	calcium metabolism regulator, pharmaceutical aid
-ectin	antiparasitics, ivermectin derivatives
-entan	endothelin receptor antagonists
-eptacog	see *-cog*

STEM	***DEFINITION*** ***substem, if available***
erg	ergot alkaloid derivatives
-eridine	analgesics, pethidine derivatives
-ermin	growth factors; *-dermin* (epidermal growth factors); *-fermin* (fibrinoblast growth factors); *-nermin* (tumour necrosis factor); *-sermin* (insulin-like growth factors)
estr	estrogens
-etanide	diuretics, piretanide derivatives
-exakin	see *-kin*
-exine	mucolytic, bromhexine derivatives
-fenamic acid	anti-inflammatory, anthranilic acid derivatives *-fenamate* ("*-fenamic acid*" derivatives)
-fenin	diagnostic aids; (phenylcarbamoyl)methyl iminodiacetic acid derivatives
-fenine	analgesics, glafenine derivatives - (subgroup of fenamic acid group)
-fentanil	narcotic analgesics, fentanil derivatives
-fermin	see *-ermin*
-fiban	fibrinogen receptor antagonists (glycoprotein IIb/IIIa receptor antagonists)
-fibrate	clofibrate derivatives
-flapon	5-lipoxygenase-activating protein (FLAP) inhibitor
-flurane	general inhalation anaesthetics, halogenated alkane derivatives
-formin	antihyperglycaemics, phenformin derivatives
-fos (-vos)	insecticides, anthelmintics, pesticides etc., phosphorous derivatives
-fos- or fos-	various pharmacological categories belonging to -fos (other than above)
-fradil	calcium channel blockers acting as vasodilators
-frine	see *-drine*
-fungin a	ntifungal antibiotics
-fylline	*N*-methylated xanthine derivatives
gab	gabamimetic agents
gado-	diagnostic agents, gadolinium derivatives
-gatran	thrombin inhibitor, antithrombotic agents
gest	steroids, progestogens
-giline	MAO-inhibitors type B
-gillin	antibiotics produced by *Aspergillus* strains
gli	antihyperglycaemics, sulfonamide derivatives
-golide	dopamine receptor agonists, ergoline derivatives
-gramostim	see *-stim*
-grastim	see *-stim*
-grel- or -grel	platelet aggregation inhibitors
guan-	antihypertensives, guanidine derivatives
-icam	anti-inflammatory, isoxicam derivatives
-ifene	antiestrogens, *clomifene* and *tamoxifen* derivatives
-ilide	Class III antiarrhythmics, sematilide derivatives
imex	immunostimulants

STEM	***DEFINITION*** ***substem, if available***
-imod	immunomodulators, both stimulant/suppressive and stimulant
-imus	immunosuppressants (other than antineoplastics)
io-	iodine-containing contrast media
-io- or iod-	iodine containing compounds other than contrast media
-iptan	serotonin ($5HT_1$) receptor agonists, sumatriptan derivatives
-irudin	hirudin derivatives
-isomide	antiarrhythmics, disopyramide derivatives
-ium	quarternary ammonium compounds; *-curium* (curare-like substances)
-izine	diphenylmethyl piperazine derivatives; *-rizine* (antihistaminics/cerebral (or peripheral) vasodilators)
-kacin	antibiotics, kanamycin and bekanamycin derivatives (obtained from *Streptomyces kanamyceticus*);
-kalant	potassium channel blockers
-kalim	potassium channel activators, antihypertensive
-kef-	enkephalin agonists
-kin	interleukin type substances; *-nakin* (Il-1 derivatives) *-leukin* (Il-2 derivatives) *-plestim* (Il-3 derivatives) *-exakin* (Il-6 derivatives)
-kinra	interleukin receptor antagonists; *-nakinra* (Il-1 receptor antagonists)
-kiren	renin inhibitors
-leukin	see *-kin*
-lipastat	see *-stat*
-lukast	see *-ast*
-mab	monoclonal antibodies (for details please see page .....)
-mantadine	adamantane derivatives; *-mantine, -mantone*
-meline	cholinergic agents, arecoline derivatives
-mer	polymers
-mesine	sigma receptor ligands
-mestane	aromatase inhibitors
-metacin	anti-inflammatory, indometacin derivatives
-micin	antibiotics obtained from various *Micromonospora*
-monam	monobactam antibiotics
-morelin	see *-relin*
-mostim	see *-stim*
-motine	antivirals, quinoline derivatives
-moxin	monoamine oxidase inhibitors, hydrazine derivatives**not part of definition
-mustine	antineoplastic, alkylating agents, (b-chloroethyl)amine derivatives
-mycin	antibiotics, produced by *Streptomyces strains*
nab	cannabinol derivatives
-nakin	see *-kin*

STEM	*DEFINITION* ***substem, if available***
-nakinra	see *-kinra*
nal-	narcotic antagonists/agonists related to normorphine
-nercept	tumor necrosis factor antagonist
-nermin	see *-ermin*
nic	nicotinic acid or nicotinoyl alcohol derivatives
-nicate	antihypercholesterolaemic and/or vasodilating nicotinic acid esters
-nidazole	antiprotozoals, metronidazole derivatives
nifur-	5-nitrofuran derivatives
-nixin	anti-inflammatory, anilinonicotinic acid derivatives
-nonacog	see *-cog*
-octocog	see *-cog*
-olol	b-adrenoreceptor antagonists; *-alol*: aromatic ring -CH-CH2-NH-R related to -olols
-olone	steroids other than prednisolone derivatives
-opamine	dopaminergic agents dopamine derivatives used as cardiac stimulant/antihypertensives/diuretics
-onide	steroids for topical use, acetal derivatives
-(o)nidine	antihypertensives, clonidine derivatives
-orex	anoretics
orphan	narcotic antagonists/agonists, morphinan derivates; *-orphine, -orphinol, orphone*
-oxacin	antibacterials, nalidixic acid derivatives
-oxan(e)	benzodioxane derivatives
-oxanide	antiparasitics, salicylanides and analogues
-oxef	antibiotics, oxacefalosporanic acid derivatives
-oxetine	antidepressants, fluoxetine derivatives
-pafant	platelet-activating factor antagonists
-pamide	diuretics, sulfamoylbenzoic acid derivatives
-pamil	coronary vasodilators, verapamil derivatives
-parcin	glycopeptide antibiotics
-parin	heparin derivatives including low molecular mass heparins
-penem	analogues of penicillanic acid antibiotics modified in the five-membered ring
-peridol	see *-perone*
-peridone	see *-perone*
-perone	tranquillizers, neuroleptics, 4'-fluoro-4-piperidinobutyrophenone derivatives; *-peridol* (antipsychotics, haloperidol derivatives); *-peridone* (antipsychotics, risperidone derivatives)
-pidem	hypnotics/sedatives, zolpidem derivatives
-pin(e)	tricyclic compounds; *-apine* (psychoactive); *-cilpine* (antiepileptic); *-dipine (see -dipine)* *-zepine* (antidepressant/neuroleptic); *-oxepin, -oxopine, -sopine, -tepines*
-piprazole	psychotropics, phenylpiperazine derivatives
-pirox	antimycotic pyridone derivatives
-planin	antibacterials (*Actinoplanes* strains)

STEM	*DEFINITION* ***substem, if available***
-platin	antineoplastic agents, platinum derivatives
-plestim	see *-stim*
-plon	pyrazolo[.]pyrimidine derivatives, used as anxiolytics, sedatives, hypnotics
	-poetin erythropoietin type blood factors
	-porfin benzoporphyrin derivatives
-pramine	substances of the imipramine group
-prazole	antiulcer, benzimidazole derivatives
pred	prednisone and prednisolone derivatives; *-methasone* or *-metasone, -betasol*
-pressin	vasoconstrictors, vasopressin derivatives
-pride	sulpiride derivatives
-pril(at)	angiotensin-converting enzyme inhibitors
-prim	antibacterials, trimethoprim derivatives
-profen	anti-inflammatory agents, ibuprofen derivatives
prost	prostaglandins; *-prostil* (prostaglandins, anti-ulcer)
-prostil	see *-prost*
-quinil	benzodiazepine receptor partial agonists (quinoline derivatives)
-racetam	amide type nootrope agents, piracetam derivatives
-relin	prehormones or hormone-release stimulating peptides: *-morelin* (growth hormone release-stimulating peptides); *-tirelin* (thyrotropin releasing hormone analogues)
-relix	hormone-release inhibiting peptides
-renone	aldosterone antagonists, spironolactone derivates
-restat (or -restat-)	see *-stat*
retin	retinol derivatives
-ribine	ribofuranil-derivatives of the *pyrazofurin* type
rifa-	antibiotics, rifamycin derivatives
-rinone	cardiac stimulants, amrinone derivatives
-rizine	see *-izine*
-rozole	aromatase inhibitors, imidazole-triazole derivatives
-rubicin	antineoplastic antibiotics, daunorubicin derivatives
sal	salicylic acid derivatives: *-sal-, salazo-, -salazine/-salazide, -salan*
-sartan	angiotensin II receptor antagonists, antihypertensive (non-peptidic)
-semide	diuretics, furosemide derivatives
-sermin	see *-ermin*
-serpine	derivatives of *Rauwolfia* alkaloids
-setron	serotonin receptor antagonists (5-HT_3) not fitting into other established groups of serotonin receptor antagonists
som-	growth hormone derivatives
-spirone	anxiolytics, buspirone derivatives
-stat (or -stat-)	enzyme inhibitors: *-lipastat* (pancreatic lipase inhibitors); *-restat* or *-restat-* (aldose-reducing inhibitors);

STEM	*DEFINITION* ***substem, if available***
	-vastatin (antilipidemic substances, HMG CoA reductase inhibitors)
-steine	mucolytics, other than bromhexine derivatives
-ster-	androgens/anabolic steroids: *-testosterone, -sterone, -ster-, -gesterone, -sterone, sterol, ster,* *-(a)steride* (antineoplastics)
-stim	colony stimulating factors: *-grastim* (granulocyte colony stimulatory factor (G-CSF) type substances; *-gramostim* (granulocyte macrophage colony stimulating factor (GM-CSF) type substances); *-mostim* (macrophage stimulating factors (M-CSF) type substances); *-plestim* (interleukin-3 analogues and derivatives)
sulfa-	anti-infectives, sulfonamides
-sulfan	antineoplastic, alkylating agents, methanesulfonates
-tecan	antineoplastics, topoisomerase I inhibitors
-tepa	antineoplastics, thiotepa derivatives
-teplase	see *-ase*
-terol	bronchodilators, phenethylamine derivatives [previously *-prenaline* or *-terenol*]
-terone	antiandrogens
-tiazem	calcium channel blockers, diltiazem derivatives
-tide	peptides and glycopeptides (for special groups of peptides see *-actide, -pressin, -relin, -tocin)*
-tidine	histamine H_2-receptor antagonists, cimetidine derivatives
-tirelin	see *-relin*
-tizide	diuretics, chlorothiazide derivatives
-tocin	oxytocin derivatives
-toin	antiepileptics, hydantoin derivatives
-trexate	folic acid analogues
-tricin	antibiotics, polyene derivatives
-triptyline	antidepressants, dibenzo[*a,d*]cycloheptane or cyclopheptene derivatives
-troban	thromboxane A_2-receptor antagonists; antithrombotic agents
-trodast	see *-ast*
trop	atropine derivatives
-uplase	see *-ase*
-uracil	uracil derivatives used as thyroid antagonists and as antineoplastics
-uridine	uridine derivatives used as antiviral agents and as antineoplastics; also *-udine*
-vastatin	see *-stat*
-verine	spasmolytics with a papaverine-like action
vin- or -vin-	vinca alkaloids
vir	antivirals (undefined group): *-amivir* (neuraminidase inhibitors); *-cavir* (carbocyclic nucleosides); *-virsen* (antisense oligonucleotides)
-virsen	see *vir*

STEM	*DEFINITION* ***substem, if available***
-vudine	antiviral; antineoplastics, zidovudine derivatives
-xanox	antiallergic respiratory tract drugs, xanoxic acid derivatives
-zafone	alozafone derivatives
-zepine	see *-pine*

Explanatory note:
The hyphens indicate the position of the stem, prefix, infix or suffix, within the INN. In the event that the hyphen is absent, the stem may be used in any position within the name.

The following common stems have been discontinued:

STEM	*DEFINITION*
mer- or -mer-	mercury-containing drugs, antimicrobial or diuretic (deleted from General Principles in List 28 prop. INN)
mito-	antineoplastics, nucleotoxic agents (deleted from General Principles in List 24 prop. INN)
-ol	alcohols and phenols (deleted from Generla Principles in 14th report)
-quine, quin	quinoline derivatives (deleted from General Principles in List 28 prop. INN)
-stigmine	anticholinesterases (deleted from General Principles in List 24 prop. INN)

ANNEX 4

Specific groups of biological compounds

Peptides, glycopeptides, proteins and glycoproteins (general approach)

The INN experts have adopted the following general scheme for the naming of peptides/proteins:

1. selection of a *stem* for the main compound, e.g. *-poetin* (for erythropoietin derivatives), *-irudin* (for hirudin derivatives), *-cog* (for blood coagulation factors);
2. designation of *subgroups* by expanding the stem, e.g. *-eptacog, -octacog;*
3. selection of a *random prefix* for compounds with differences in aminoacid sequence;

In addition for *glycosylated compounds:*

4. selection of a Greek letter spelt out as a second part of a two-word name for glycosylated compounds with identical amino acid sequence and different glycosylation pattern.

Blood coagulation factors

The following stems, infixes and suffixes, have been selected up to date for recombinant blood coagulation factors:

blood coagulation factors:	*-cog*
factor VII :	*(-)eptacog*
factor VIII :	*(-)octocog*
factor IX :	*(-)nonacog*

A prefix will be necessary if the amino acid sequence does not match that of the naturally occurring material. In accordance with the general policy, *alfa, beta,* etc., will be added for the glycoproteins. When the additional statement "activated" is needed, i.e. for the blood coagulation factor VIIa, it should be spelt out in full and added in parenthesis after the name.

Colony stimulating factors

A general stem for all colony stimulating factors was selected and substems for the various categories were designated:

colony stimulating factors : *-stim*

combination of two different types of colony stimulating factors:	*-distim*
granulocyte colony stimulating factor (G-CSF) type substances :	*-grastim*
granulocyte macrophage colony stimulating factor (GM-CSF) type substances :	*-gramostim*
macrophage stimulating factor (M-CSF) type substances :	*-mostim*
interleukin-3 analogues and derivatives:	*-plestim*

Enzymes

The common stems for enzymes, in general, is *-ase.* Substems are referring to the origin of the substances, e.g. tissue plasminogen activator and urokinase-type plasminogen activators.

enzymes : *-ase*

enzyme with superoxide dismutase activity :	*-dismase*
tissue-type plasminogen activators :	*-teplase*
urokinase-type plasminogen activators :	*-uplase*

Further examples of enzymes may be found in *WHO/PHARM S/NOM 15*

Erythropoietins

In the case of erythropoietins it was decided to select *epoetin* together with a Greek letter to differentiate between compounds of the same amino acid sequence as human erythropoietin which vary in the glycosylation pattern. INNs with different amino acid sequence will be named using the *-poetin* stem and a random prefix.

erythropoietin type blood factors : *-poetin*

Growth factors

The general stem assigned for growth factors is *-ermin*. Substems allow distinction between the various types of growth factors, for example epidermal growth factors, fibrinoblast growth factors and insulin-like growth factors.

When selecting a name for tumor necrosis factors (TNF) these were also classified as growth factors.

growth factors : *-ermin*

epidermal growth factors :	*-dermin*
fibrinoblast growth factors :	*-fermin*
tumor necrosis factors (TNF):	*-nermin*
platelet-derived growth factor:	*-plermin*
insulin-like growth factors :	*-sermin*
transforming growth factor:	*-termin*

Growth hormones

The characteristic stem for this group of compounds is the prefix *som-*. For substances other than human, suffixes are added to indicate the species specificity of the structure are as follows:

growth hormones: *som-*

bovine-type substances :	*-bove*
porcine-type substances:	*-por*
salmon-type substances :	*-salm*

Hirudin analogues

Hirudin is a well-established name for an anticoagulant isolated from medicinal leeches. Hirudin analogues are non-glycosylated polypeptides produced by recombinant biotechnology. The stem *-irudin* will be used for hirudin compounds, a random prefix will allow to differentiate for different amino acid sequences.

hirudin analogues : *-irudin*

Hormone release stimulating peptides

The common stem selected for hormone release stimulating peptides is *-relin*. INNs for hormone-release inhibiting peptides should include the stem *-relix*.

hormone-release stimulating peptides : *-relin*

growth hormone release stimulating peptides :	*-morelin*
thyrotropin releasing hormone analogues:	*-tirelin*

hormone-release inhibiting peptides : *-relix*

Interleukins

The first general stem selected for interleukins was *-leukin*, which was derived from the name *interleukin* assigned by the *International Union of Biochemistry* (IUB) - *International Union of Pure and Applied Chemistry* (IUPAC) - *Joint Commission on Biochemical Nomenclature* (JCBN). Randomly assigned prefixes should distinguish between the different compounds.

Based on the needs for naming further interleukins, the following stem system was accepted for recombinant interleukins :

interleukin	*INN stem*
Il-1	*-nakin*
Il-2	*-leukin*
Il-3	*-plestim*
Il-6	*-exakin*
IL-8	*-octakin*
IL-11	*-elvekin*
receptor antagonist:	*-kinra*
Il-1	*-nakinra*

It was agreed to publish the INNs for glycosylated interleukins with *alfa, beta*, etc, in accordance with the general policy for naming glycosylated proteins.

Pituitary hormones

The name selected by the IUPAC-IUB have, to date, been chosen for compounds with identical amino acid sequence as the naturally occurring human hormone. Addition of a Greek letter as second name will allow to differentiate for different glycosylation pattern for compounds produced by biotechnology.

The following scheme is at present in use :

pituitary hormones : *-tropin*
follicle stimulating hormones : *(-)follitropin*
luteinizing hormones : *(-)lutropin*

Monoclonal antibodies

The following scheme for common stems has been developed for naming monoclonal antibodies:

I.	*General stem:*		*-mab*
II.	*Sub-stems for source of product:*		
		human	*-u-*
		rat	*-a-*
		hamster	*-e-*
		primate	*-i-*
		mouse	*-o-*
		chimeras	*-xi-*
		humanized	*-zu-*

The distinction between chimeric and humanized antibodies is as follows:

A chimeric antibody is one that contains contiguous foreign-derived amino acids comprising the entire variable region of both heavy and light chains linked to heavy and light constant regions of human origin.

A humanized antibody has heavy (H) and light (L) chain variable (V) regions, consisting of the amino acids comprising the complementarity-determining region (CDR) segments (and possibly frameword residues)

from foreign antibodies inserted appropriately among variable regions framework segments of human-derived amino acid residues, linked to H and L constant regions of human origin.

III. *Sub-stems for disease or target group:*

bacterial	*-ba(c)-*
cardiovascular	*-ci(r)-*
immunomodulator	*-li(m)-*
infectious lesions	*-le(s)-*
viral	*-vi(r)-*
tumors:	
colon	*-co(l)-*
testis	*-go(t)-*
ovary	*-go(v)-*
mammary	*-ma(r)-*
melanoma	*-me(l)-*
prostate	*-pr(o)-*
miscellaneous	*-tu(m)-*

Whenever there is a problem in pronunciation, the final letter of the sub-stems for diseases or targets may be deleted, e.g. *-co(l)-, vi(r), li(m),* etc.

IV. *Prefix:*

The prefix should be random, e.g. the only requirement is to contribute to a euphonious and distinctive name.

IV. *Second word:*

If the product is radiolabelled or conjugated to another chemical, such as a toxin, dentification of this conjugate is accomplished by use of a separate, second word or acceptable chemical designation. For monoclonals conjugated to a toxin, the *tox-* stem must be included as part of the name selected for the toxin.

If the monoclonal antibody is used as a carrier for a radioisotope, the latter will be listed first in the INN, e.g. technetium (^{99m}Tc) pintumomab.

ANNEX 5

WHA46.19 Nonproprietary names for pharmaceutical substances

The Forty-sixth World Health Assembly,

Recalling resolution WHA31.32 on the importance of using nonproprietary names in establishing national drug formularies;

Noting the fundamental contribution of the WHO programme on international nonproprietary names (INN) to effective communication in medicine, and the challenge inherent in maintaining the nomenclature as new substances are introduced into clinical use;

Acknowledging with satisfaction the increasing contribution of generic products to national drug markets in both developed and developing countries;

Noting the current trend to market products with the same active ingredient as, and intended to be clinically interchangeable with, a product currently on the market (multisource products) under trade-marks or brandnames derived from stems or other descriptors for international nonproprietary names nomenclature;

Recognizing that such use, particularly in respect of single-ingredient prescription drugs, may compromise the safety of patients by creating confusion in prescribing and dispensing medicines and by interfering with the orderly development of the nomenclature for international nonproprietary names;

Aware of the concern expressed by the International Conference of Drug Regulatory Authorities at its last meeting about the increasing use of pharmaceutical brandnames that are very similar to or derived from international nonproprietary names;

Noting the recommendation made by the WHO Expert Committee on the Use of Essential Drugs, in its fifth report,[1] on the need to discourage, as a matter of urgency, the use of trade-marks that are derived from international nonproprietary names,

1. REQUESTS Member States:

(1) to enact rules or regulations, as necessary, to ensure that international nonproprietary names (or the equivalent nationally approved generic names) used in the labelling and advertising of pharmaceutical products are always displayed prominently;
(2) to encourage manufacturers to rely on their corporate name and the international nonproprietary names, rather than on trade-marks, to promote and market multisource products introduced after patent expiration;

(3) to develop policy guidelines on the use and protection of international nonproprietary names, and to discourage the use of names derived from INNs, and particularly names including established INN stems as trade-marks;

2. CALLS ON the Director-General to intensify his consultations with governments and representatives of the pharmaceutical industry on ways of reducing to a minimum the problems arising from drug nomenclatures that may create confusion and jeopardize the safety of patients.

Twelfth plenary meeting, 12 May 1993
A46/VR/12

[1] *WHO Technical Report Series*, No. 825, 1992.

ANNEX 6

Procedure for the selection of international nonproprietary names for pharmaceutical substances

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefore.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the "*General principles for guidance in devising International Nonproprietary Names*". The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*[1] and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

(i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

B. Such notice shall:

(i) set forth the name under consideration;
(ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;
(iii) identify the substance for which a name is being considered;
(iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;
(v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent theacquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization.*[1]

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization.*[2]

A. Such objection shall:

(i) identify the person objecting;
(ii) state his interest in the name;
(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

[1] The title of this publication was changed to *WHO Chronicle* in January 1959. From 1987 onwards lists of INNs are published in *WHO Drug Information*.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or tra de-name.

ANNEX 7

Applications for INNs through national authorities (addresses)

a) National Nomenclature Commissions:

France: **DCF** - Dénominations Communes Françaises

Agence du Médicament
Direction des Laboratoires et des Contrôles
Unité Pharmacopée
145-147 boulevard Anatole France
F-93285 Saint-Denis Cedex
France

Italy: **DCIt** Commission - Denominazione Communi Italiane

Director-General
Pharmaceutical Division
Ministero della Sanità
Viale della Civiltà Romana 7
I-00144 Roma
Italy

Japan: **JAN** - Japanese Accepted Names

Japanese Ministry of Health and Welfare
New Drugs Division
Pharmaceuticals Affairs Bureau
1-2-2, Kasumigaseki, Chiyoda-ku
Tokyo 100
Japan

United Kingdom: **BAN** - British Approved Names

The Secretary
British Pharmacopoeia Commission
Market Towers
1 Nine Elms Lane
London SW8 5NQ
United Kingdom

USA: **USAN** - United States Adopted Names

The Secretary
United States Adopted Names Council
American Medical Association
515 North State Street
Chicago, Illinois 60610
USA

b) Other national nomenclature authorities:

Belgium:

L'Inspecteur en chef-Directeur
Ministère de la Santé Publique et de l'Environnement
Inspection générale de la Pharmacie
Cité administrative de l'Etat
Quartier Vésale 333
B-1010 Bruxelles
Belgium

China:

The Deputy Chief
Drug Standard Division II
The Chinese Pharmacopoeia Commission
Ministry of Health
Temple of Heaven
Beijing 100050
People's Republic of China

Hungary:

Director-General
National Institute of Pharmacy
P.O. Box 450
1372 Budapest 5
Hungary

ANNEX 8

WORLD HEALTH ORGANIZATION **ORGANISATION MONDIALE DE LA SANTE**	**Request for an international nonproprietary name (INN)** **Demande de dénomination commune internationale (DCI)**

Authority or manufacturer:
Autorité ou fabricant:

Name of applicant / *nom du demandeur:*
Name of responsible officer / *nom du responsable:*
Address / *adresse:*

Telephone No/*No. de téléphone:* Fax No./*No. de fax*

We hereby request the World Health Organization to establish a free and unrestricted INN for the pharmaceutical substance described below.
L'OMS est priée de bien vouloir établir une DCI à usage libre pour la substance pharmaceutique en question.

For completion by WHO/
A remplir par l'OMS

No:
Date:
Copies forwarded:

Date:

Acknowledged:

SUGGESTED NAMES (in order of preference): 1.....
DENOMINATIONS PROPOSÉES
(par ordre de préférence) 2.....

3.....

CHEMICAL NAME OR DESCRIPTION (INCLUDING STEREOCHEMICAL INFORMATION):
NOM OU DESCRIPTION CHIMIQUE (Y COMPRIS DE L'INFORMATION SUR LA STÉRÉOCHIMIE)

GRAPHIC FORMULA:
FORMULE GRAPHIQUE

MOLECULAR FORMULA:
FORMULE BRUTE

CHEMICAL ABSTRACTS SERVICE (CAS) REGISTRY NUMBER:
NUMÉRO DU REGISTRE CAS

TRADE NAME (known or contemplated):
NOM COMMERCIAL (connu ou envisagé)

ANY OTHER NAME OR CODE:
AUTRE NOM OU CODE

PRINCIPAL THERAPEUTIC USES AND POSOLOGY; PHARMACOLOGICAL ACTION:
UTILITÉ THÉRAPEUTIQUE ET POSOLOGIE; ACTION PHARMACOLOGIQUE

For completion by WHO/
A remplir par l'OMS

WHO 5233* PHA (9/97) - 1000

PTO/TSVP

1. The process of selecting an INN should be initiated during that period of investigation when the compound is undergoing clinical study in human subjects. Please indicate the date when clinical trials began:
La procédure de sélection d'une DCI débute pendant la période d'investigation au cours de laquelle la substance fait l'objet d'études cliniques sur des sujets humains. Veuillez indiquer à quelle date ont débuté les essais cliniques:

2. This proposal is made on the understanding that insofar as is known, none of the suggested names is either registered or pending registration.
En présentant cette proposition, le signataire déclare qu'à sa connaissance aucune des dénominations suggérées n'a été déposée ou n'est sur le point de l'être.

3. The Undersigned confirms that the Chemical Abstracts Service (CAS) number is correct and permission is granted to WHO to publish it in the INN publications.
Le soussigné confirme que le numéro dans le registre du CAS est correcte et que l'OMS est autorisée à le publier dans les publications relatives aux DCIs.

ADDITIONAL COMMENTS:
REMARQUES

Date ..... *Signature* .....

Naming Biologics

The USAN Council is involved in coining names for various biological products: insulins, interferons, interleukins, growth hormones, colony-stimulating factors, cytokines, monoclonal antibodies and coagulation factors. With increasing development of highly purified biological extracts and recombinant materials, the council has had a greater role in assigning names and developing nomenclature rules for these agents.

Please use the following MS Word document sequence templates to submit in a table format:

- Sequence template (DOC) required when submitting all proteins and peptides
- Sequence template (DOC) required when submitting monoclonal antibodies

USAN and INN requirements for biological substances include the following:

All Proteins and Peptides

- Complete mature amino acid sequence (DOC) in a MS Word document
- Single-letter codes for each amino acid, displayed in groups of 10 characters with 5 groups per line and a number indicating the position of the last amino acid at the end of each line
- Positions of all disulfide bridges and post-translational modifications should be listed after the sequence
- Glycosylation patterns (including site, type of sugar, etc.)
- For recombinant proteins: Expression system and comparison with native sequence

Monoclonal Antibodies

- **Complete mature amino acid sequence (DOC)** in a MS Word document
- Single-letter codes for each amino acid, displayed in groups of 10 characters with 5 groups per line and a number indicating the position of the last amino acid at the end of each line
- Glycosylation patterns (including site, type of sugar, etc.)
- Precursor nucleotide sequence with spaces between codons and translation, with numbered lines
- **CDR-IMGT (DOC)**
- IG class and subclass, IG format
- Species or taxonomy related structure (chimeric, humanized, etc.)
- Name and/or structure of targeted antigen
- List of all disulfide bridges and their locations
- Expression system
- Clone name(s) and laboratory code name(s)

Cell Therapies

- Name/code designation
- Characterization/description
- Cell source
- List and description of manipulation (culture conditions included)
- If genetic manipulation: the detailed description of the vector and insert should be provided

Nucleic Acids

Nucleic acids include DNA vaccines, oligonucleotides and gene therapy products.

- Full nucleotide sequence with pertinent regions (e.g., coding regions, control regions) delineated
- For gene therapies, schematic map of the product and an annotated sequence that delineates relevant sections

All Pegylated Substances

- Details of pegylation: end group, polymer chain (with average number of repeat units to two significant figures), details of the linker, point of attachment of the linker to the active moiety

When naming Monoclonal Antibodies the following items are <u>required</u> to be submitted with your application materials:

USAN Requirements for Monoclonal Antibodies

- ✓ Complete mature amino acid sequence in a Microsoft Word document
- ✓ Single-letter codes for each amino acid, displayed in groups of 10 characters with 5 groups per line and a number indicating the position of the last amino acid at the end of each line
- ✓ Glycosylation patterns, including site and type of sugar, etc.
- ✓ Precursor nucleotide sequence with spaces between codons and translation, with numbered lines
- ✓ CDR-IMGT and sequence analysis of the variable regions showing percentage of human content (if –ximab, -zumab, or -umab is requested; 85%+ -zumab or -umab, <85% -ximab)
- ✓ IG class and subclass, IG format
- ✓ Species or taxonomy related structure (chimeric, humanized, etc.)
- ✓ Name and/or structure of targeted antigen
- ✓ List of all disulfide bridges and their locations
- ✓ Expression system
- ✓ Clone name(s) and laboratory code name(s)
- ✓ If appropriate, the closest human V, J, and C genes and alleles (results obtained with IMGT/DomainGapAlign tool)

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to IMGT/mAb-DB

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IMMUNOGENETICS
INFORMATION SYSTEM®

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IMGT/mAb-DB query page

Version: 1.5.5 (2017-03-09)

Citing IMGT/mAb-DB:
Poiron, C. et al., JOBIM 2010, Paper 13 (2010). Abstract PDF

mAb-DB
Today is Friday, Jul 14 2017
Database contains 747 entries
642 -IG
24 -FPIA
38 -CPCA
39 -RPI

If the display of drop-down list is not optimal with Internet Explorer, use Firefox, Opera or Chrome.
Please enable Javascript, as it is required by this query interface to work properly.

Search by:

IMGT/mAb-DB ID -

General Query

Search Clear

INN -

INN number -

Common name -

INN proposed list - and before and after

INN recommended list - and before and after

Proprietary name -

Search Clear

Species -

IMGT receptor type all any IG FPIA CPCA RPI none

IG class and subclass (for complete IG)

-
any
none
IgA - nd
IgE - nd

IG format (for IG fragments or constructs)

-
any
none
(scFv - heavy - kappa) - (scFv - heavy - lambda)
(scFv - kappa - heavy) - (scFv - heavy - kappa)

FPIA receptor identification

-
any
none
[CD4 (p55, T cell surface antigen T4/Leu-3) - IGHG2_Fusion - CD4 (p55, T cell surface antigen T4/Leu-3) - IGKC] - dimer
[CTLA4 (cytotoxic T-lymphocyte-associated protein 4, CD152)]2 - IGHG1 Fc

CPCA receptor identification

-
any
none
CR1 (complement receptor type 1, C3b/C4b receptor, C3BR, Knops blood group, KN, CD35) 41-238_peptidyl-myristoylated
CD4 (p55, T cell surface antigen T4/Leu-3) - Pseudomonas aeruginosa exotoxin A

RPI receptor identification

-
any
none
TNFRSF1A (tumor necrosis factor receptor (TNFR) superfamilly member 1A, TNFAR, TNF-RI, TNF-R-I, p55, CD120a) soluble form (TNF
IFNAR2 (interferon alpha/beta receptor 2, IFNABR)

Origin clone species -

Origin clone name -

Fused with -

Radiolabelled with -

Conjugated with -

ADC linker -

ADC INN radical -

Entries in IMGT/2Dstructure-DB -

Entries in IMGT/3Dstructure-DB -

Search Clear

Show targets used in ☐ bispecific

Specificity target kinds -

Specificity target name

any
Bacteria -- Bacillus anthracis -- anthrax protective antigen (PA)
Bacteria -- Bordetella pertussis -- toxin
Bacteria -- Clostridium difficile -- toxin A
Bacteria -- Clostridium difficile -- toxin B
Bacteria -- Clostridium perfringens -- toxin
Bacteria -- Escherichia coli -- shiga toxin type 1 (shiga toxin-producing Escherichia coli (STEC), stx1, Stx1, Stx-1, Shiga-like toxin 1, SLT-
Bacteria -- Escherichia coli -- shiga toxin type 2 (shiga toxin-producing Escherichia coli (STEC), stx2, Stx2, Stx-2, Shiga-like toxin 2, SLT-
Bacteria -- Pseudomonas aeruginosa -- PcrV
Bacteria -- Pseudomonas aeruginosa -- serotype IATS O11

OR type a specificity

Search Clear

Clinical indication -

Clinical domain -

Application -

Expression system -

Development technology -

Company -

Development status -

External references -

Regulatory decision year -

Search Clear

Author -

Article Name -

Journal Name -

PMID -

Find entries with biosimilars ☐

Biosimilar general Query

Biosimilar Company -

Biosimilar Trademark -

Search Clear

Displayed fields:

Check all | None

IMGT/mAb-DB ☑	INN ☑	INN number ☑	INN Prop. list ☑
INN Rec. list ☑	Common name ☑	Proprietary name ☑	
IMGT receptor type ☑	Species ☑	Radiolabelled/ Conjugated/ Fused ☑	Format ☑
Receptor identification ☑	IMGT/2Dstructure-DB ☑	IMGT/3Dstructure-DB ☑	
Origin clone species ☑	Origin clone name ☑	Specificity target name and species ☑	
Clinical indication ☑	Development status ☑	Regulatory / external references ☑	Company ☑
Expression system ☑	Development technology ☑	FDA / EMEA / NCI number or ATC code ☑	References ☑
Application ☑	Clinical domain ☑	Clinical Studies ☑	Biosimilars ☑
Development Technology ☑	Beta info ☐		

IMGT/mAb-DB documentation | IMGT/mAb-DB query page

Created: 03/04/2009
Database development: Yan Wu, Claire Poiron, Denis Moreno, Souphatta Sasorith, Mélissa Cambon and Patrice Duroux
Database scientific officer: Marie-Paule Lefranc

IMGT Home page | IMGT Repertoire (IG and TR) | IMGT Repertoire (MHC) | IMGT Repertoire (RPI) | IMGT Index | IMGT Scientific chart | IMGT Education

IMGT® Founder and Executive Director Emeritus: Marie-Paule Lefranc Marie-Paule.Lefranc@igh.cnrs.fr
IMGT® Director: Sofia Kossida Sofia.Kossida@igh.cnrs.fr
Bioinformatics manager: Véronique Giudicelli Veronique.Giudicelli@igh.cnrs.fr
Computer manager: Patrice Duroux Patrice.Duroux@igh.cnrs.fr
Webmaster: Amélie Houles

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IMGT/mAb-DB: the IMGT® database for therapeutic monoclonal antibodies

C. Poiron, Y. Wu, C. Ginestoux, F. Ehrenmann, P. Duroux and M-P Lefranc
IMGT®, the international ImMunoGeneTics information system®, Laboratoire d'ImmunoGénétique Moléculaire LIGM, Université Montpellier 2, Institut de Génétique Humaine IGH, CNRS UPR 1142, 141 rue de la Cardonille, F-34396 Montpellier cedex 05, France
Marie-Paule.Lefranc@igh.cnrs.fr

Im Muno Gene Tics Information system®
http://www.imgt.org

IMGT/mAb-DB is the monoclonal antibodies database of IMGT®, the international ImMunoGeneTics information system® (http://www.imgt.org) that is the global reference in immunogenetics and immunoinformatics.
IMGT/mAb-DB provides a unique expertised resource on immunoglobulins (IG) or monoclonal antibodies (mAb) with clinical indications, and on fusion proteins for immune applications (FPIA). IMGT/mAb-DB is a relational database using the open source MySQL (http://www.mysql.com) management system database.
Since 2008, amino acid sequences of mAb (suffix -mab) and of FPIA (suffix -cept) from the World Health Organization(WHO)/International Nonproprietary Name (INN) Programme have been entered in IMGT®.
Lefranc, M.-P. mAbs, 3:1-2 (2011)

IMGT/mAb-DB Query page

The IMGT/mAb-DB Query page allows requests on several fields.
These are organized in 5 sections:

1. IMGT/mAb DB ID
2. INN and other names
3. characteristics and structure
4. specificity (target name and target species)
5. clinical indication, development status and clinical domain.

Your query: IMGT/mAb-DB INN = alemtuzumab

IMGT/mAb-DB ID	INN (International Nonproprietary Name)	INN Num.	INN Prop. list	INN Rec. list	Common name	Proprietary name
11	alemtuzumab	8005	83 (2000)	45 (2001)	Campath-1H, LDP-03	CAMPATH® (US) MABCAMPATH® (EU)

IMGT/mAb-DB species	Isotype and format	IMGT/2Dstructure-DB	IMGT/3Dstructure-DB	Specificity (target) [origin]	Origin clone species	Origin clone name
Humanized	IgG1κ	8005	1bey 1ce1	CD52 [*Homo sapiens*]	*Rattus norvegicus*	YTH34.5HL

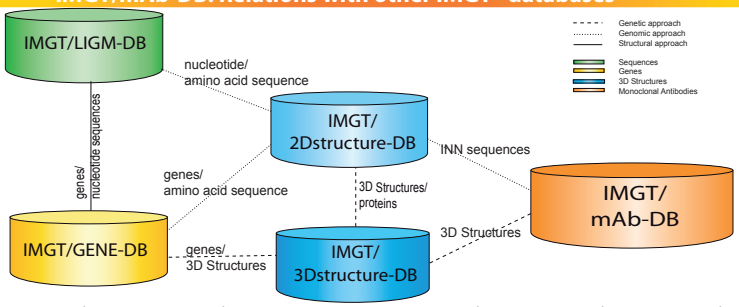
Company	Clinical indication	Development status	Regulatory agency status and year	Application	Clinical domain	FDA / EMA / NCI number or ATC code
Berlex Inc. (Wayne NJ USA) (US) / Genzyme Corp. (Cambridge MA USA) (EU) / Millennium Pharmaceuticals Inc. (Cambridge MA USA) (EU/US)	Chronic lymphocytic leukemia (CLL)	Phase M	FDA approval May 2001	Therapeutic	Hematology, Oncology	FDA: (BLA) 103948
	Kidney transplant rejection	Phase I/II		Diagnostic	Immunology	NCI: C1681
	Multiple sclerosis (MS)	Phase I/II		Therapeutic	Immunology	Drugnum: 702

A query on a name allows to retrieve the International Nonproprietary Name (INN) and INN lists numbers as provided by the World Health Organization (WHO)/INN Programme, the Common name from literature, the Proprietary name if the antibody or fusion protein for immune application (FPIA) is a registered trademark (symbol ®).

For each entry, IMGT/mAb-DB provides the origin species (human, rat, murine, humanized or chimeric), the isotype and format, links to IMGT/2Dstructure-DB (amino acid sequences and IMGT Colliers de Perles), links to IMGT/3Dstructure-DB (3D structures), specificity (target), origin clone species and origin clone name.

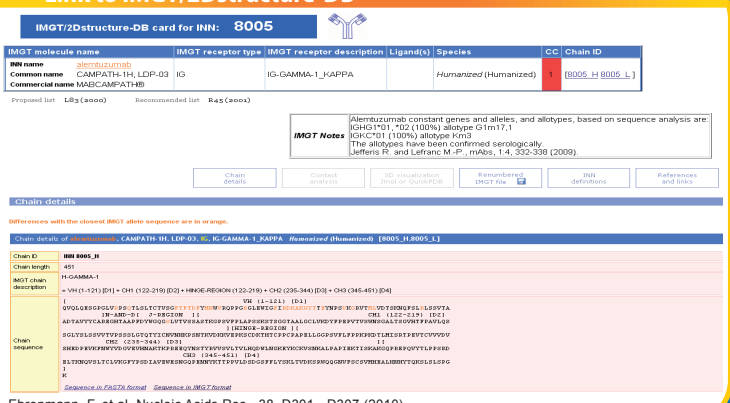
IMGT/mAb-DB also provides information on company, clinical indication (more than 200 in the database), developement status, organization that approved the drug such as Food and Drugs Administration (FDA) or European Medicines Agency (EMA), application (diagnostic or therapeutic) and clinical domain.

IMGT/mAb-DB: Relations with other IMGT® databases



In November 2010, IMGT/mAb-DB contains 343 entries (175 -mab, 15 -cept), 213 have an INN and, among them, 81 have sequences in IMGT/2Dstructure-DB and 14 have 3D structures in IMGT/3Dstructure-DB. By providing links to IMGT/2Dstructure-DB and IMGT/3Dstructure-DB for entries available in these databases, IMGT/mAb-DB facilitates comparative studies of antibodies and FPIA, and of their constitutive chains, even if 3D structures are not yet available.

Link to IMGT/2Dstructure-DB



Ehrenmann, F. et al. Nucleic Acids Res., 38, D301 - D307 (2010)

mAbs and FPIA approved for therapeutic and diagnostic use (in 2010)

5 Human mAbs	adalimumab (2002) HUMIRA® / TRUDEXA®	panitumumab (2006) VECTIBIX™	golimumab (2009) SIMPONI™	canakinumab (2009) ILARIS®	ustekinumab (2009) STELARA™		
5 Murine mAbs	muromonab-CD3 (1992) ORTHOCLONE OKT3®	edrecolomab (1995) PANOREX®	ibritumomab tiuxetan (2002) ZEVALIN®	tositumomab (2003) BEXXAR®	capromab * (1996) PROSTASCINT®		
5 Chimeric mAbs	abciximab (1994) REOPRO®	rituximab (1997) MABTHERA® / RITUXAN®	basiliximab (1998) SIMULECT®	infliximab (1998) REMICADE®	cetuximab (2004) ERBITUX®		
11 Humanized mAbs	daclizumab (1997) ZENAPAX®	palivizumab (1998) SYNAGIS®	trastuzumab (1998) HERCEPTIN®	alemtuzumab (2001) CAMPATH® / MABCAMPATH®	omalizumab (2003) XOLAIR®	ranibizumab (2006) LUCENTIS®	eculizumab (2007) SOLIRIS™
	natalizumab (2008) TYSABRI®	bevacizumab (2008) AVASTIN®	certolizumab pegol (2008) CIMZIA®	nimotuzumab (2008) THERACIM®			
4 FPIA	etanercept (1998) ENBREL®	alefacept (2003) AMEVIVE®	abatacept (2005) ORENCIA®	rilonacept (2008) ARCALYST™			

In September 2010, IMGT/mAb-DB contains 30 monoclonal antibodies and FPIA on the market: 29 of them (25 mAb and 4 FPIA) are for therapeutic use and 1 (shown with *) is for diagnostic use.

Conjugated or radiolabelled mAbs in IMGT/mAb-DB

Monoclonal antibodies can be used:

conjugated with another molecule

→ Calicheamicin, a cytotoxic antitumor antibiotic
Ex: gentuzumab ozogamicin , MYLOTARG®
Scientists believe Alexander the Great was killed by calicheamicin, a dangerous compound produced by a bacteria (*Micromonospora echinospora*) found in water. (Squires N. , Telegraph, 03 August 2010)

→ Exotoxin A from *Pseudomonas Aeruginosa*
Ex: oportuzumab monatox, PROXINIUM™ VICINIUM™

→ Monomethyl auristatin E (MMAE), a synthetic antineoplastic agent
Ex: glembatumumab vedotin

→ Bouganin, from *Bougainvillea spectabilis* Willd toxin
Ex: citatuzumab bogatox

radiolabelled with an isotope

→ Indium-111:
Half-Life 2.80 days, used in nuclear medicine to observe tumors and LCD manufacturing,
Ex: capromab, PROSTASCINT®

→ Iodine-131:
Half-Life 8 days, used in nuclear medicine to observe a thyroid gland and radiotherapy on cancers such as lymphoma,
Ex: tositumomab, BEXXAR®

In November 2010, IMGT/mAb-DB contains: 17 INN **radiolabelled** and 11 INN **conjugated.**

IMGT® founder and director: Marie-Paule Lefranc (Marie-Paule.Lefranc@igh.cnrs.fr)
Bioinformatics manager: Véronique Giudicelli (Veronique.Giudicelli@igh.cnrs.fr)
Computer manager: Patrice Duroux (Patrice.Duroux@igh.cnrs.fr)
Webmaster: Chantal Ginestoux (Chantal.Ginestoux@igh.cnrs.fr)

US 20160376367A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2016/0376367 A1**

Yuan et al. (43) **Pub. Date: Dec. 29, 2016**

(54) **PD-1 ANTIBODY, ANTIGEN-BINDING FRAGMENT THEREOF, AND MEDICAL APPLICATION THEREOF**

(71) Applicants: **SHANGHAI HENGRUI PHARMACEUTICAL CO., LTD.**, Shanghai (CN); **JIANGSU HENGRUI MEDICINE CO., LTD.**, Lianyungang, Jiangsu (CN)

(72) Inventors: **Jijun Yuan**, Shanghai (CN); **Xiangdong Qu**, Shanghai (CN); **Jufang Lin**, Shanghai (CN); **Xin Ye**, Shanghai (CN); **Guoqing Cao**, Lianyungang (CN); **Weikang Tao**, Lianyungang (CN); **Lianshan Zhang**, Lianyungang (CN); **Lei Zhang**, Shanghai (CN); **Li Yang**, Shanghai (CN)

(73) Assignee: **Shanghai Hengrui Pharmaceutical Co., Ltd.**, Shanghai (CN)

(21) Appl. No.: **15/103,758**

(22) PCT Filed: **Nov. 14, 2014**

(86) PCT No.: **PCT/CN14/91090**

§ 371 (c)(1),
(2) Date: **Jun. 10, 2016**

(30) **Foreign Application Priority Data**

Dec. 12, 2013 (CN) 201310681942.6

Publication Classification

(51) **Int. Cl.**
C07K 16/28 (2006.01)

(52) **U.S. Cl.**
CPC ***C07K 16/2818*** (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/20* (2013.01); *C07K 2317/24* (2013.01); *C07K 2317/56* (2013.01); *C07K 2317/567* (2013.01); *C07K 2317/92* (2013.01)

(57) **ABSTRACT**

The present invention provides a human PD-1 antibody, an antigen-binding fragment thereof, and medical use thereof, and further provides a chimeric antibody and humanized antibodies comprising a complementarity-determining region (CDR) of the antibody, a pharmaceutical composition comprising the human PD-1 antibody and the antigen-binding fragment thereof, and use of the antibody in preparing medicines for treating diseases or disorders.

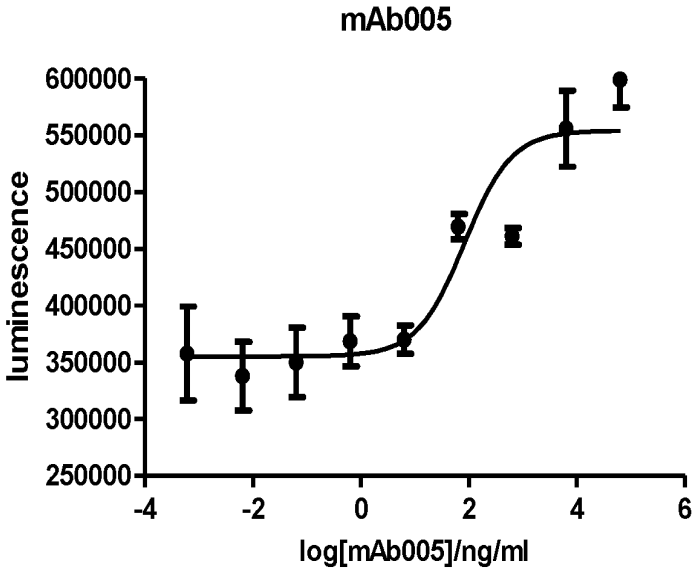


Figure 1

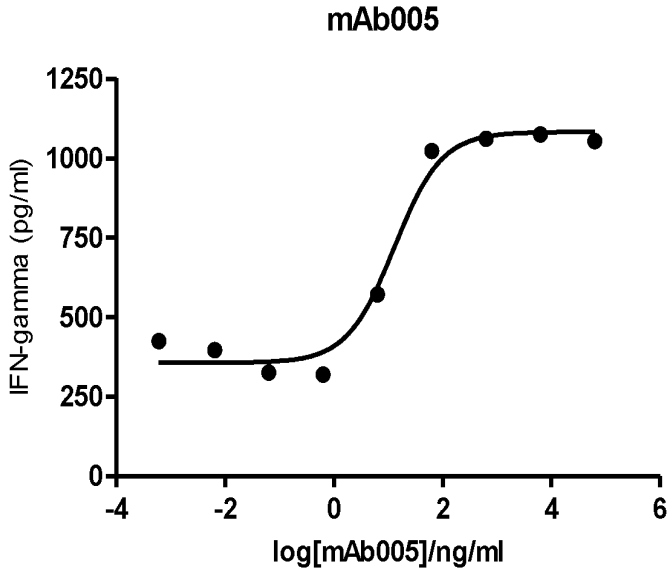


Figure 2

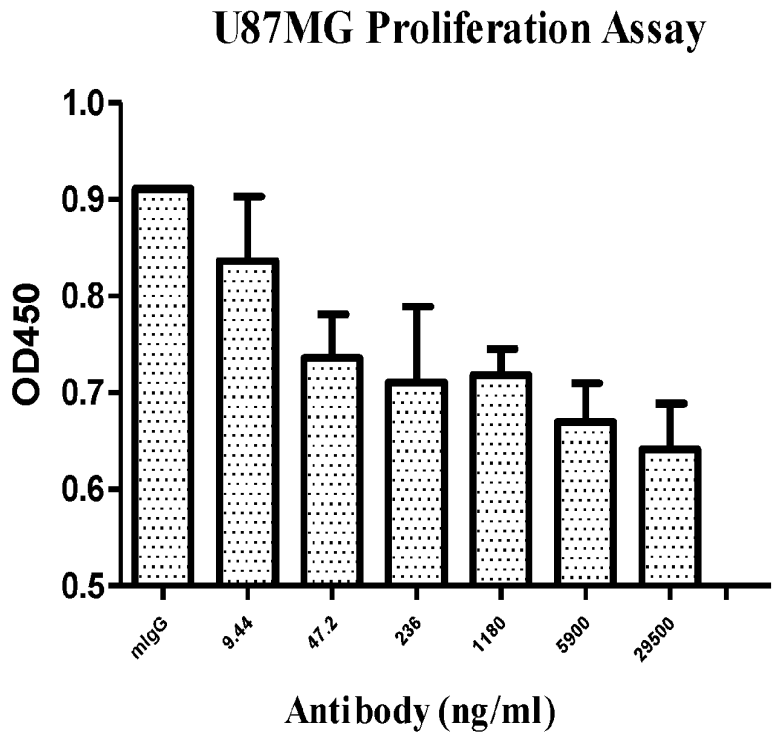


Figure 3

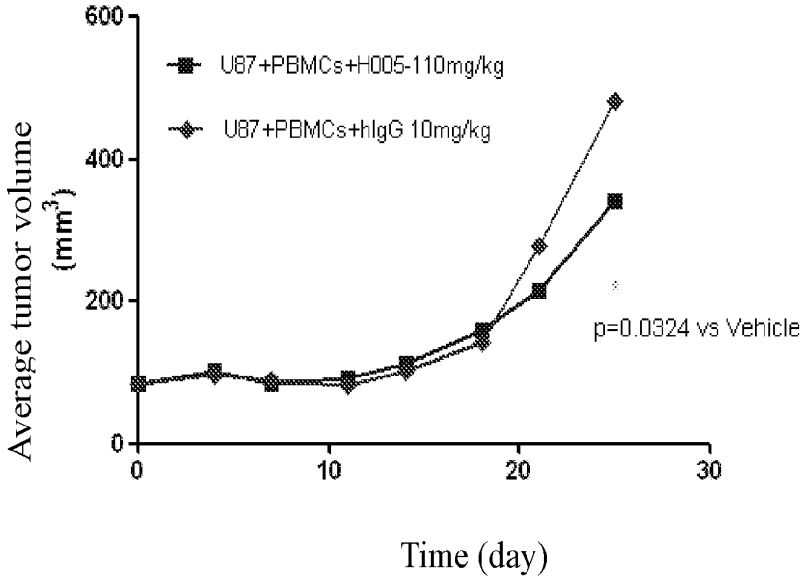


Figure 4

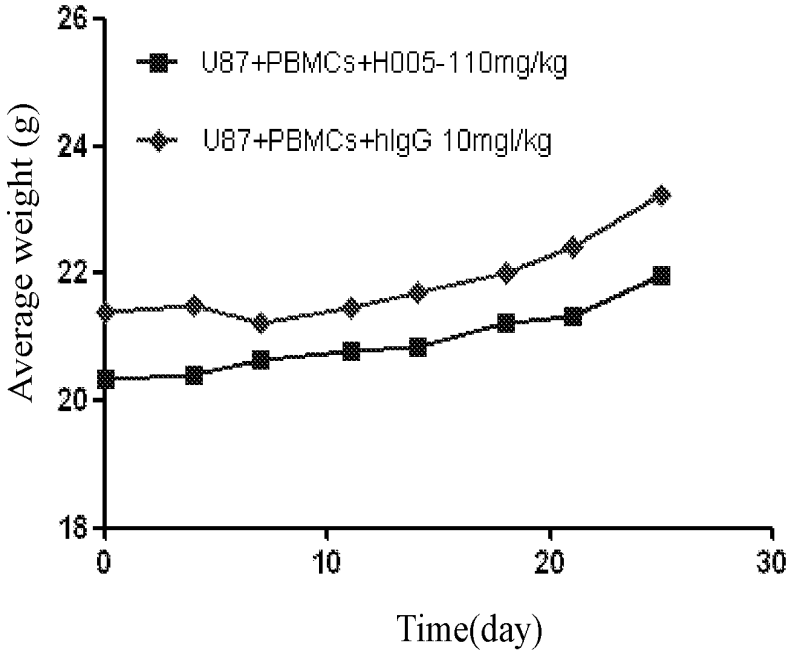

26
24
22
20
18
0
10
20
30
Average weight (g)
Time(day)
U87+PBMCs+H005-110mg/kg
U87+PBMCs+hIgG 10mgl/kg

Figure 5

PD-1 ANTIBODY, ANTIGEN-BINDING FRAGMENT THEREOF, AND MEDICAL APPLICATION THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to a PD-1 antibody, a PD-1 antigen-binding fragment, a chimeric antibody and humanized antibodies comprising the CDR of the PD-1 antibody, as well as a pharmaceutical composition comprising the PD-1 antibody and the antigen-binding fragment thereof, as well as its use as an anti-cancer drug.

BACKGROUND OF THE INVENTION

[0002] Tumor immunotherapy is a hot spot in tumor therapeutic area for a long time, T cell associated cancer immunotherapy is at the core position. Tumor immunotherapy affects tumors by fully utilizing and mobilizing cytotoxic T lymphocytes in patients with tumors; it may be the most effective and safest way for cancer treatment. At the same time, tumor escape is a huge obstacle faced by tumor immunotherapy, in which cancer cells promote rapid growth of the tumor via its inhibitory effect on the immune system.

[0003] There is extremely complex relationship between tumor immune escape mechanism and body's immune response to tumors. In early stage of tumor immunotherapy, tumor-specific killer T cells have biological activity, but lose the killing function in the late stage of tumor growth. So tumor immunotherapy is to utmostly enhance the response of the patient's own immune system to the tumor. The key of tumor immunotherapy is not only to activate the response of the existing immune system, but also to maintain the duration and intensity of the response of the immune system.

[0004] Human T-cell activation in vivo is implemented by a two-signaling-pathway system which not only needs to submit a MHC-antigen peptide via antigen-presenting cells to T cells to provide a first signal, but also requires a series of costimulatory molecules to provide a second signal, and then T cells exhibit normal immune response. This double-signaling system plays a vital role in balance of the immune system, and strictly regulates the different immune responses stimulated by endogenous and exogenous antigens. The absence of a second signal provided by co-stimulatory molecules will result in no response or sustained-specific T cell immune response, consequently leading to tolerance. Therefore, the second signal pathway plays a key regulatory role in the whole process of the immune response.

[0005] Programmed death-1 (PD-1), found in 1992, is a protein receptor expressed in T cell surface, and is involved in cell apoptosis. PD-1 belongs to CD28 family, exhibits 23% homology in amino acid sequence with cytotoxic T lymphocyte antigen 4 (CTLA-4), but is mainly expressed in activated T cells, B cells and myeloid cells, which is different from CTLA. PD-1 has two ligands, PD-L1 and PD-L2 respectively. PD-L1 is mainly expressed in T cells, B cells, macrophages, and dendritic cells (DC), and the expression is upregulated in the activated cells. The expression of PD-L2 is mainly limited to antigen-presenting cells, such as activated macrophages and dendritic cells.

[0006] New studies have detected high expression of PD-L1 protein in human tumor tissues such as breast cancer, lung cancer, stomach cancer, intestinal cancer, renal cancer, melanoma and others, and the expression levels of PD-L1 is closely related to clinical condition and prognosis of patients. For PD-L1 inhibits T cell proliferation through the second signaling pathway, blocking the binding of PD-L1/PD-1 becomes a very promising target in tumor immunotherapy field.

[0007] Currently, there are several multinational pharmaceutical companies engaged in monoclonal antibodies against PD-1, which maximize the self immune response of patients against tumor by blocking the binding of PD-L1/PD-1, and sequentially achieve the killing purpose against tumor cells, such as WO2009114335. In the clinical results of BMS' and Merck's PD-1 monoclonal antibodies, certain response rate have been observed in non-small cell lung cancer, melanoma and renal carcinoma, and the response rate exhibited prominently high relevance with PD-L1 expression in tumors, which suggested that PD-1 antibody exerts a positive effect on tumors.

[0008] The present invention provides a PD-1 antibody with high affinity, high selectivity, and high biological activity.

SUMMARY OF THE INVENTION

[0009] The present invention provides a PD-1 antibody or an antigen-binding fragment thereof, comprising:

[0010] a light chain variable region comprising at least one LCDR selected from those sequences as shown in: SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8; and

[0011] a heavy chain variable region comprising at least one HCDR selected from those sequences as shown in: SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5.

[0012] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the light chain variable region comprises a LCDR1 as shown in SEQ ID NO: 6.

[0013] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the light chain variable region comprises a LCDR2 as shown in SEQ ID NO: 7.

[0014] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the light chain variable region comprises a LCDR3 as shown in SEQ ID NO: 8.

[0015] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the heavy chain variable region comprises a HCDR1 as shown in SEQ ID NO: 3.

[0016] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the heavy chain variable region comprises a HCDR2 as shown in SEQ ID NO: 4.

[0017] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the heavy chain variable region comprises a HCDR3 as shown in SEQ ID NO: 5.

[0018] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the light chain variable region comprises a LCDR1, a LCDR2 and a LCDR3 as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

[0019] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the heavy chain variable region comprises a HCDR1, a HCDR2 and a HCDR3 as shown in SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5, respectively.

[0020] In a preferred embodiment of the present invention, provided is a PD-1 antibody or an antigen-binding fragment thereof, wherein the light chain variable region comprises a LCDR1, a LCDR2 and a LCDR3 as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, respectively; and wherein the heavy chain variable region comprises a HCDR1, a HCDR2 and a HCDR3 as shown in SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5, respectively.

[0021] In a preferred embodiment of the present invention, according to the PD-1 antibody or the antigen-binding fragment thereof provided herein, the antibody is a murine antibody or a fragment thereof.

[0022] In a preferred embodiment of the present invention, according to the murine antibody or the fragment thereof provided herein, the light chain variable region further comprises the light chain FR of murine κ, λ chain or a variant thereof.

[0023] In a preferred embodiment of the present invention, the murine antibody or the fragment thereof provided herein further comprises a light chain constant region of murine κ, λ chain or a variant thereof.

[0024] In a preferred embodiment of the present invention, according to the murine antibody or the fragment thereof provided herein, the heavy chain variable region further comprises the heavy chain FR of murine IgG1, IgG2, IgG3, IgG4 or a variant thereof.

[0025] In a preferred embodiment of the present invention, the murine antibody or the fragment thereof provided herein further comprises a heavy chain constant region of murine IgG1, IgG2, IgG3, IgG4 or a variant thereof.

[0026] In a preferred embodiment of the present invention, according to the PD-1 antibody or antigen-binding fragment provided herein, the antibody is a chimeric antibody or a fragment thereof.

[0027] In a preferred embodiment of the present invention, according to the PD-1 chimeric antibody or the fragment thereof provided herein, the light chain variable region sequence of the chimeric antibody is SEQ ID NO: 10.

[0028] In a preferred embodiment of the present invention, according to the PD-1 chimeric antibody or the fragment thereof provided herein, the heavy chain variable region sequence of chimeric antibody is SEQ ID NO: 9.

[0029] In a preferred embodiment of the present invention, the PD-1 chimeric antibody or the fragment thereof provided herein further comprises a light chain constant region of human κ, λ chain or a variant thereof.

[0030] In a preferred embodiment of the present invention, the PD-1 chimeric antibody or the fragment thereof provided herein further comprises a heavy chain constant region of human IgG1, IgG2, IgG3 or IgG4 or a variant thereof, preferably comprises a heavy chain constant region of human IgG2 or IgG4, or that of IgG1 which has no ADCC (antibody-dependent cell-mediated cytotoxicity) after amino acid mutation.

[0031] In a preferred embodiment of the present invention, according to the PD-1 antibody or the antigen-binding fragment provided herein, the antibody is a humanized antibody or a fragment thereof.

[0032] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the light chain variable region of the humanized antibody further comprises light chain FR of human κ, λ chain or a variant thereof.

[0033] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the light chain FR sequence of the light chain variable region of the humanized antibody is derived from a combination sequence of human germline light chains IGKV1-39 and JK4 as shown in SEQ ID NO: 14, comprising FR1, FR2 and FR3 of IGKV 1-39 and FR4 of JK4.

[0034] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the sequence of the humanized antibody light chain is shown in SEQ ID NO: 12 or a variant thereof.

[0035] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the variant of humanized antibody light chain variable region comprises a 0-10 amino acid mutation in the light chain variable region, preferably A43 S.

[0036] In a preferred embodiment of the present invention, the PD-1 humanized antibody or the fragment thereof provided herein further comprises a light chain constant region of human κ, λ chain or a variant thereof.

[0037] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the heavy chain variable region further comprises a heavy chain FR of human IgG1, IgG2, IgG3, IgG4, or a variant thereof.

[0038] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or fragment thereof provided herein, the heavy chain FR sequence of the heavy chain variable region of the humanized antibody is derived from a combination sequence of human germline heavy chains IgHV3-7 and JH6 as shown in SEQ ID NO: 13, comprising FR1, FR2 and FR3 of IgHV3-7 and FR4 of JH6.

[0039] In a preferred embodiment of the present invention, according to the PD-1 humanized antibody or the fragment thereof provided herein, the sequence of the humanized antibody heavy chain is shown in SEQ ID NO: 11 or a variant thereof; wherein the variant preferably comprises a 0-10 amino acid mutation in the heavy chain variable region, more preferably G44R.

[0040] In a preferred embodiment of the present invention, the PD-1 humanized antibody or the fragment thereof provided herein further comprises a heavy chain constant region of human IgG1, IgG2, IgG3 or IgG4 or a variant thereof, and preferably comprises a heavy chain constant region of human IgG2 or IgG4 which has no ADCC, or that of IgG1 which has no ADCC (antibody-dependent cell-mediated cytotoxicity) after amino acid mutation. The variant is preferably a heavy chain constant region mutation which causes ADCC attenuation or deficiency, and more preferably N297A, L234A, L235A of IgG1, IgG2/4 chimera, and F235E or L234A/E235A of IgG4.

[0041] In a preferred embodiment of the present invention, according to the PD-1 antibody or the antigen-binding fragment provided herein, the antigen-binding fragment is Fab, Fv, sFv or $F(ab')_2$.

[0042] The present invention further provides a DNA molecule encoding the PD-1 antibody or the antigen-binding fragment described above.

[0043] The present invention further provides an expression vector comprising the DNA molecule as described above.

[0044] The present invention further provides a host cell transformed with the expression vector as described above.

[0045] In a preferred embodiment of the present invention, according to the host cell provided herein, the host cell is bacteria, preferably *E. coli.*

[0046] In a preferred embodiment of the present invention, the host cell provided herein is yeast, preferably *Pichia pastoris.*

[0047] The present invention further provides a pharmaceutical composition which comprises the PD-1 antibody or the antigen-binding fragment thereof as described herein and a pharmaceutically acceptable excipient, diluent or carrier.

[0048] The present invention further provides use of the above PD-1 antibody or the antigen-binding fragment, or the pharmaceutical composition containing the same, in the preparation of a medicament for treatment of a PD-1 mediated disease or disorder; wherein the disease is preferably cancer, more preferably PD-L1-expressing cancer; and the cancer is preferably breast cancer, lung cancer, stomach cancer, intestinal cancer, renal cancer, melanoma, and most preferably non-small cell lung cancer, melanoma and renal cancer.

[0049] The present invention further provides a method for treating and preventing the PD-1 mediated disease or disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the PD-1 antibody or the antigen-binding fragment thereof according to the invention, or the pharmaceutical composition comprising the same; wherein the disease is preferably cancer, more preferably PD-L1-expressing cancer; the cancer is preferably breast cancer, lung cancer, stomach cancer, intestinal cancer, renal cancer, melanoma, non-small cell lung cancer, and most preferably non-small cell lung cancer, melanoma and renal cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0050] FIG. **1**: Human peripheral blood mononuclear cell proliferation assay. Result shows that the test PD-1 antibody mAb005 can effectively stimulate the proliferation of human peripheral blood mononuclear cells, with EC50 of 83 ng/ml.

[0051] FIG. **2**: Human peripheral blood mononuclear cell cytokine IFN-γ secretion test. Result shows that the test PD-1 antibody mAb005 can stimulate PBMC proliferation, and effectively stimulate secretion of cytokine IFN-γ at the same time, with EC50 of 13 ng/ml.

[0052] FIG. **3**: inhibitory effect of PD-1 antibody H005-1 on growth of glioma cells.

[0053] FIG. **4**: diagram showing tumor volume change after treatment.

[0054] FIG. **5**: diagram showing weight change of mice after treatment.

DETAILED DESCRIPTION OF THE INVENTION

[0055] 1. Definitions

[0056] In order to more readily understood the invention, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0057] As used herein, the single-letter code and the three-letter code for amino acids are as described in J. biol. chem, 243, (1968) p3558.

[0058] As used herein, "Antibody" refers to immunoglobulin, a four-peptide chain structure connected together by disulfide bonds between two identical heavy chains and two identical light chains. Different immunoglobulin heavy chain constant regions exhibit different amino acid compositions and rank orders, thereby presenting different kinds of antigenicity. Accordingly, immunoglobulins can be divided into five categories, or called immunoglobulin isotypes, namely IgM, IgD, IgG IgA and IgE, their heavy chains are μ chain, δ chain, γ chain, γ chain and ϵ chain, respectively. According to its amino acid composition of hinge region and the number and location of heavy chain disulfide bonds, the same type of Ig can be divided into different sub-categories, for example, IgG can be divided into IgG1, IgG2, IgG3, and IgG4. Light chain can be divided into κ or λ chain considering of different constant regions. Each of the five Igs can have κ or λ chain.

[0059] In the present invention, the antibody light chain variable region mentioned herein further comprises a light chain constant region, which comprises a human or murine κ, λ chain or a variant thereof.

[0060] In the present invention, the antibody heavy chain variable region mentioned herein further comprises a heavy chain constant region, which comprises human or murine IgG1, 2, 3, 4 or a variant thereof.

[0061] Near the N-terminal sequence of the antibody heavy chains and light chains, about 110 amino acid sequence varies largely, known as the variable region (V region); the rest of the amino acid sequence near the C-terminus is relative stable, known as the constant region (C region).Variable region comprises three hypervariable regions (HVR) and four relatively conserved sequence framework region (FR). The three hypervariable regions determine the specificity of the antibody, also known as a complementarity determining region (CDR). Each light chain variable region (LCVR) and each heavy chain variable region (HCVR) is composed of three CDRs and four FRs, with sequentially order from the amino terminal to the carboxyl terminal being: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. Three light chain CDRs refer to LCDR1, LCDR2, and LCDR3; three heavy chain CDRs refer to HCDR1, HCDR2 and HCDR3. The numbers and locations of CDR amino acid residues in LCVR and HCVR of the antibody or the antigen-binding fragment herein correspond with known Kabat numbering criteria (LCDR1-3, HCDE2-3), or correspond with kabat and chothia numbering criteria (HCDR1).

[0062] The term "murine antibody" in the present invention refers to anti-human-PD-1 monoclonal antibody prepared according to the knowledge and skills in the art. During the preparation, a test object was injected with PD-1 antigen, and then hybridoma expressing antibody which possesses desired sequence or functional characteristics was separated. In a preferred embodiment of the present invention, the murine PD-1 antibody or the antigen-binding fragment thereof further comprises a light chain constant region of murine κ, λ chain or a variant thereof, or further comprises a heavy chain constant region of murine IgG1, IgG2, IgG3 or IgG4, or a variant thereof.

[0063] The term "chimeric antibody", is an antibody which is formed by fusing the variable region of a murine

antibody with the constant region of a human antibody, the chimeric antibody can alleviate the murine antibody-induced immune response. To establish a chimeric antibody, hybridoma secreting specific murine monoclonal antibody is firstly established, a variable region gene is cloned from mouse hybridoma cells, then a constant region gene of a human antibody is cloned as desired, the mouse variable region gene is ligated with the human constant region gene to form a chimeric gene which can be inserted into a human vector, and finally the chimeric antibody molecule is expressed in the eukaryotic or prokaryotic industrial system. In a preferred embodiment of the present invention, the light chain variable region of PD-1 chimeric antibody further comprises the light chain FR of murine κ, λ chain or a variant thereof, and the sequence of the light chain variable region is shown in SEQ ID NO: 10. The heavy chain variable region of the PD-1 chimeric antibody further comprises the heave chain FR of murine IgG1, IgG2, IgG3, IgG4 or a variant thereof, and the sequence of the heavy chain variable region is shown in SEQ ID NO: 10. The constant region of a human antibody is selected from the heavy chain constant region of human IgG1, IgG2, IgG3 or IgG4 or a variant thereof, preferably comprises the heavy chain constant region of human IgG2 or IgG4, or that of IgG1 which has no ADCC (antibody-dependent cell-mediated cytotoxicity) after amino acid mutation.

[0064] The term "humanized antibody", also known as CDR-grafted antibody, refers to an antibody generated by grafting murine CDR sequences into a variable region framework of a human antibody, namely, a sequence of human germline antibody framework of different type. Humanized antibody overcomes the disadvantageously strong antibody response induced by the chimeric antibody which carries a large amount of murine protein components. Such framework sequences can be obtained from public DNA database covering germline antibody gene sequences or published references. For example, germline DNA sequences of human heavy and light chain variable region genes can be found in "VBase" human germline sequence database (available on web www.mrccpe.com.ac.uk/vbase), as well as can be found in Kabat, EA, et al, 1991 Sequences of Proteins of Immunological Interest, 5^{th} Ed. In a preferred embodiment of the invention, the murine CDR sequences of PD-1 humanized antibody are selected from SEQ ID NO: 3, 4, 5, 6, 7, 8. Human antibody variable region frameworks were designed and selected such that the light chain FR sequence of the antibody light chain variable region is derived from combination sequence of human germline light chains IGKV1-39 and JK4: SEQ ID NO: 14, comprising FR1, FR2 and FR3 of IGKV 1-39 and FR4 of JK4; the heavy chain FR sequence of the antibody heavy chain variable region is derived from combination sequence of human germline heavy chains IgHV3-7 and JH6: SEQ ID NO: 13, comprising FR1, FR2 and FR3 of IgHV3-7 and FR4 of JH6. To avoid activity decrease during immunogenicity reduction, the variable region of the human antibody is subjected to a minimum back mutation to maintain the activity.

[0065] As used herein, "antigen-binding fragment" refers to a Fab fragment, a Fab' fragment, a F(ab')2 fragment with antigen-binding activity, as well as a Fv fragment sFv fragment binding with human PD-1; comprising one or more CDR regions of antibodies described in the present invention selected from the group consist of SEQ ID NO:3 to SEQ ID NO:8. Fv fragment is a minimum antibody fragment comprising a heavy chain variable region, a light chain variable region, and all antigen-binding sites without a constant region. Generally, Fv antibody further comprises a polypeptide linker between the VH and VL domains, and is capable of forming a structure required for antigen binding. Also, different linkers can be used to connect the variable regions of two antibodies to form a polypeptide, named single chain antibody or single chain Fv (sFv). As used herein, the term "binding with PD-1", means interacting with human PD-1. As used herein, the term "antigenic determinant" of the present invention, refers to discontinuous three-dimensional sites on the antigen, recognized the antibody or the antigen-binding fragment of the present invention.

[0066] As used herein, the term "ADCC", namely antibody-dependent cell-mediated cytotoxicity, refers to cells expressing Fc receptors directly kill target cells coated by an antibody through recognizing the Fc segment of the antibody. ADCC effector function of the antibody can be reduced or eliminated via modification of the Fc segment in IgG The modification refers to mutations of the antibody heavy chain constant region, such as mutations selected from N297A, L234A, L235A in IgG1; IgG2/4 chimera; F235E, or L234A/E235A mutations in IgG4.

[0067] As used herein, fusion protein described in the present invention is a protein product obtained by co-expressing two genes via recombinant DNA technology. Recombinant PD-1 extracellular domain Fc fusion protein obtained by co-expressing a PD-1 extracellular domain and a human antibody Fc fragment via recombinant DNA technology. The PD-1 extracellular domain refers to the moiety of PD-1 outside cytomembrane, the sequence of which is the scribing region of SEQ ID NO: 1 below.

[0068] Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Antibody Experimental Technology Guide of Cold Spring Harbor, Chapter 5-8 and 15. For example, mice can be immunized with human PD-1, or fragments thereof, and the resulting antibodies can then be renatured, purified and sequenced using conventional methods well known in the art. Antigen-binding fragments can also be prepared by conventional methods. The antibody or the antigen-binding fragment of the present invention is genetically engineered to introduce one or more human framework regions (FRs) to a non-human derived CDR. Human FR germline sequences can be obtained from ImMunoGeneTics(IMGT) via their website http://imgt.cines.fr, or from The Immunoglobulin FactsBook, 2001ISBN012441351. Specifically, light chain FR germline for use in the antibody or the antigen-binding fragment of the present invention include A3 and O2. Particular heavy chain FR germline for use in the antibody or the antigen-binding fragment of the present invention include VH3-21 and VH3-23.

[0069] The engineered antibody or antigen-binding fragment of the present invention may be prepared and purified using conventional methods. For example, cDNA sequences encoding a heavy chain (SEQ ID NO: 11) and a light chain (SEQ ID NO: 12) may be cloned and recombined into a GS expression vector. The recombined immunoglobulin expression vector may then stably transfect CHO cells. As a more recommended method well known in the art, mammalian expression of antibodies will result in glycosylation, typically at the highly conserved N-terminal in the FC region.

Stable clones may be obtained through expression of an antibody specifically binding to human PCSK9. Positive clones may be expanded in a serum-free culture medium for antibody production in bioreactors. Culture medium, into which an antibody has been secreted, may be purified by conventional techniques. For example, the medium may be conveniently applied to a Protein A or G Sepharose FF column that has been equilibrated with a compatible buffer. The column is washed to remove nonspecific binding components. The bound antibody is eluted by PH gradient and antibody fragments are detected by SDS-PAGE, and then pooled. The antibody may be filtered and concentrated using common techniques. Soluble aggregate and multimers may be effectively removed by common techniques, including size exclusion or ion exchange. The obtained product may be immediately frozen, for example at −70° C., or may be lyophilized.

[0070] The antibody of the present invention is a monoclonal antibody. Monoclonal antibody or mAb, as used herein, refers to an antibody that is derived from a single clone including but not limited to any eukaryotic, prokaryotic, or phage clone. Monoclonal antibodies and antigen-binding fragments thereof can be recombined, for example, by hybridoma technologies, recombinant technologies, phage display technologies, synthetic technologies (e.g., CDR-grafting), or other technologies known in the art.

[0071] "Administration" and "treatment," as it applies to an animal, human, experimental subject, cell, tissue, organ, or biological fluid, refers to contacting an exogenous pharmaceutical, therapeutic, diagnostic agent, or composition with the animal, human, subject, cell, tissue, organ, or biological fluid. "Administration" and "treatment" can refer, e.g., to therapeutic, pharmacokinetic, diagnostic, research, and experimental methods. Treatment of a cell encompasses contacting a reagent with the cell, as well as contacting a reagent with a fluid, where the fluid is in contact with the cell. "Administration" and "treatment" also means in vitro and ex vivo treatments, e.g., of a cell, by a reagent, diagnostic, binding compound, or by another cell. "Treatment," as it applies to a human, veterinary, or a research subject, refers to therapeutic treatment, prophylactic or preventative measures, to research and diagnostic applications.

[0072] "Treat" means to administer a therapeutic agent, such as a composition comprising any of the binding compounds of the present invention, internally or externally to a patient having one or more disease symptoms for which the agent has known therapeutic activity. Typically, the agent is administered in an amount effective to alleviate one or more disease symptoms in the treated patient or population, whether by inducing the regression of or inhibiting the progression of such symptom(s) to any clinically measurable degree. The amount of a therapeutic agent that is effective to alleviate any particular disease symptom (also referred to "therapeutically effective amount") may vary according to factors such as the disease state, age, and weight of the patient, and the ability of the drug to elicit a desired response in the patient. Whether a disease symptom has been alleviated can be assessed by any clinical measurement typically used by physicians or other skilled healthcare providers to assess the severity or progression status of that symptom. While an embodiment of the present invention (e.g., a treatment method or article of manufacture) may not be effective in alleviating the disease symptom(s) of interest in every patient, it should alleviate the target disease symptom (s) of interest in a statistically significant number of patients as determined by any statistical test known in the art such as the Student's t-test, the chi-square test, the U-test according to Mann and Whitney, the Kruskal-Wallis test (H-test), Jonckheere-Terpstra-test and the Wilcoxon-test.

[0073] "Conservative modifications " or "conservative replacement or substitution" refers to substitutions of amino acids in a protein with other amino acids having similar characteristics (e.g. charge, side-chain size, hydrophobicity/hydrophilicity, backbone conformation and rigidity, etc.), such that the changes can frequently be made without altering the biological activity of the protein. Those of skill in this art recognize that, in general, single amino acid substitutions in non-essential regions of a polypeptide do not substantially alter biological activity (see, e.g., Watson et al. (1987) Molecular Biology of the Gene, The Benjamin/Cummings Pub. Co., p. 224 (4^{th} Ed.)). In addition, substitutions of structurally or functionally similar amino acids are less likely to disrupt biological activity.

[0074] "Consisting essentially of," or its variation as used throughout the specification and claims, indicate the inclusion of any recited elements or group of elements, and the optional inclusion of other elements of similar or different nature than the recited elements, which do not materially change the basic or novel properties of the specified dosage regimen, method, or composition. As a nonlimiting example, a binding compound which consists essentially of a recited amino acid sequence may also include one or more amino acids that do not materially affect the properties of the binding compound.

[0075] "Effective amount" encompasses an amount sufficient to ameliorate or prevent a symptom or sign of a medical condition. Effective amount also means an amount sufficient to allow or facilitate diagnosis. An effective amount for a particular patient or veterinary subject may vary depending on factors such as the condition being treated, the general health of the patient, the route and dose of administration and the severity of side affects. An effective amount can be the maximal dose or dosing protocol that avoids significant side effects or toxic effects.

[0076] "Exogenous" refers to substances that are produced outside an organism, cell, or human body, depending on the context. "Endogenous" refers to substances that are produced within a cell, organism, or human body, depending on the context.

[0077] "Homology" refers to sequence similarity between two polynucleotide sequences or between two polypeptides. When a position in both of the two compared sequences is occupied by the same base or amino acid monomer subunit, e.g., if a position in each of two DNA molecules is occupied by adenine, then the molecules are homologous at that position. The percent of homology between two sequences is a function of the number of matching or homologous positions shared by the two sequences divided by the number of positions compared×100. For example, if 6 of 10 positions in two sequences are matched or homologous when the sequences are optimally aligned, then the two sequences are 60% homologous. Generally, the comparison is made when two sequences are aligned to give maximum percent homology.

[0078] As used herein, the expressions "cell," "cell line," and "cell culture" are used interchangeably and all such designations include progeny. Thus, the words "transformants" and "transformed cells" include the primary subject

cell and cultures derived therefrom without considering the number of transfers. It is also understood that all progeny may not be precisely identical in DNA content, due to deliberate or inadvertent mutations. Mutant progeny that have the same function or biological activity as screened for in the originally transformed cell are included. Where distinct designations are intended, it will be clear from the context.

[0079] As used herein, "polymerase chain reaction" or "PCR" refers to a procedure or technique in which minute amounts of a specific moiety of nucleic acid, RNA and/or DNA, are amplified as described in, e.g., U.S. Pat. No. 4,683,195. Generally, sequence information from the ends of the region of interest or beyond needs to be available, such that oligonucleotide primers can be designed; these primers will be identical or similar in sequence to corresponding strands of the template to be amplified. The 5' terminal nucleotides of the two primers can be identical with the ends of the material to be amplified. PCR can be used to amplify specific RNA sequences, specific DNA sequences from total genomic DNA, and cDNA transcribed from total cellular RNA, bacteriophage or plasmid sequences, etc. See generally Mullis et al. (1987) Cold Spring Harbor Symp. Ouant. Biol. 51:263; Erlich, ed., (1989) PCR TECHNOLOGY (Stockton Press, N.Y.). As used herein, PCR is considered as one, but not the only, example of a nucleic acid polymerase reaction method for amplifying a nucleic acid test sample, comprising the use of a known nucleic acid as a primer and a nucleic acid polymerase to amplify or generate a specific moiety of the nucleic acid.

[0080] "Optional" or "optionally" means that the event or situation that follows may but does not necessarily occur, and the description includes the instances in which the event or circumstance does or does not occur. For example, "optionally comprises 1-3 antibody heavy chain variable regions" means the antibody heavy chain variable region with specific sequence can be, but not necessarily be present.

[0081] "Pharmaceutical composition" refers to one containing a mixture of one or more compounds according to the present invention or a physiologically/pharmaceutically acceptable salt or produg thereof with other chemical components, as well as additional components such as physiologically/pharmaceutically acceptable carriers and excipients. The pharmaceutical composition aims at promoting the administration to an organism, facilitating the absorption of the active ingredient and thereby exerting a biological effect.

DETAILED DESCRIPTION OF THE INVENTION

[0082] Hereinafter, the present invention is further described with reference to examples; however, the scope of the present invention is not limited thereto. In the examples of the present invention, where specific conditions are not described, the experiments are generally conducted under conventional conditions as described in Antibody Tcchnology Laboratory Manual and Mecular Cloning Manual of Cold Spring Harbor, or under conditions proposed by the material or product manufacturers. Where the source of the reagents is not specifically given, the reagents are commercially available conventional reagents.

EXAMPLE 1

Antibody Preparation

[0083] Murine monoclonal antibodies against human PD-1 were generated. Purified recombinant PD-1 extracellular domain Fc fusion protein (PD-1 Fc) (SEQID NO: 1); or CHO cells transfected with PD-1 (SEQ ID NO: 2) was used as an antigen to immunize Balb/C mice and SJL mice. Human PD-1 antigen was purchased from ORIGENE, Cat No. SC117011, NCBI Reference Sequence: NM_005018.1.

PD-1 Fc, recombinant PD-1 extracellular domain Fc fusion protein (SEQ ID NO: 1):
MDMRVPAQLLGLLLLWFPGSRCPGWFPGSRCPGWFLDSPDRPWNPPTFSP

ALLVVTEGNATFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPG

QDCRFBTQLPNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAE

LRVTERRAEVPTAHPSPSPRPAGQFQTLVDKTHTCPPCPAPELLGGPSVF

LFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKP

REEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPEIKTISKAKG

QPREPQVYTLPPSREEMTKNQVSLTCLVKGPYPSDIAVEWESNGQPENNY

KTTPPVLDSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSL

SLSPGK.

PD-1, PD-1 antigen tranfecting cells (SEQ ID NO: 2):
MQIPQAPWPVVWAVLQLGWRPGWFLDSPDRPWNPPTFSPALLVVTEGDNA

TFTCSFSNTSESFVLNWYRMSPSNQTDKLAAFPEDRSQPGQDCRFRVTQL

PNGRDFHMSVVRARRNDSGTYLCGAISLAPKAQIKESLRAELRTERRAEV

PTAHPSPSPRPAGQFQTLVVGVVGGLLGSLVLLVWVLAVICSRAARGTIG

ARRTGQPLKEDPSAVPVFSVDYGELDFQWREKTPEPPVPCVPEQTEYATI

VFPSGMGTSSPARRGSADGPRSAQPLRPEDGHCSWPL.

[0084] Immunization with the PD-1 extracellular domain-Fc fusion protein is devided into high dose (50 μg) and low dose (10 ug) of the purified antigen, immunization with the PD-1 transfected CHO cells uses $0.5-1\times10^7$ cells. Immunization was carried out on day 0, 14, and 35 respectively with Complete Freund's adjuvant; blood was sampled in the retro-orbital site to monitor the immune response. Mice with anti-PD-1 human immunoglobulin titer were obtained by plasma screening ELISA. On day 56, mice with the highest anti-PD-1 human immunoglobulin titer were subjected to boost immunization. 3 days later, mice were sacrificed and the spleen was removed for fusion. Hybridoma fusions were screened and a murine monoclonal antibody mAb005 was obtained. The heavy chain variable region sequence and light chain variable region sequence of the murine monoclonal antibody mAb005 are as follows:

mAb005 HCVR
SEQ ID NO: 9
EVMLVESGGGLVKPGGSLKLSCAASGFTFSSYMMSWVRQTPEKRLEWVAT

ISGGGANTYYPDSVKGRFTISRDNAKNTLYLQMSSLRSEDTALYYCARQL

YYFDYWGQGTTLTVSS

-continued

mAb005 LCVR

SEQ ID NO: 10

DIQMTQSPASQSASLGEGVTITCLASQTIGTWLTWYQQKPGKSPQLLIYT

ATSLADGVPSRFSGSGSGTKFSFKISSLQAEDFVTYYCQQVYSIPWTFGG

GTKLEIK

[0085] CDR sequences are as follows:

Name	Sequence	Numbering
HCDR1	SYMMS	SEQ ID NO: 3
HCDR2	TISGGGANTYYPDSVKG	SEQ ID NO: 4
HCDR3	QLYYFDY	SEQ ID NO: 5
LCDR1	LASQTIGTWLT	SEQ ID NO: 6
LCDR2	TATSLAD	SEQ ID NO: 7
LCDR3	QQVYSIPWT	SEQ ID NO: 8

EXAMPLE 2

Antibody Screening

[0086] In vitro PD-1 antibody ELISA binding assay:

[0087] The PD-1 antibody blocks signaling pathway of PD-1 and its ligand by binding to PD-1 extracellular domain. In vitro ELISA assay is used to detect the binding property of the PD-1 antibody. Biotinylated PD-1 extracellular domain FC fusion protein (PD-1 FC) is coated onto 96-well plates by binding to neutralization avidin. Signal intensity after the addition of the antibody is used to determine the binding property of the antibody and PD-1.

[0088] Neutralization avidin (binding to biotin) was diluted to 1 μl/ml with PBS buffer, pipetted into a 96-well plate with at 100 μl/well and standed for 16h-20h at 4 ° C. The 96-well plate was washed once with PBST (PH7.4 PBS, containing 0.05% tweeen20) after PBS buffer was removed, then the plate was incubated and blocked for 1 h at room temperature with addition of 120 μl/well PBST/1% milk. After removal of the blocking solution, the plate was washed with PBST buffer, followed by addition of 1 μg/ml biotin-labeled PD1-FC which was diluted by PBST/1% milk, and incubated for 1 h at room temperature. After removal of the blocking solution, the plate was washed with PBST buffer for 3 times, followed by addition of the test PD-1 antibody which was diluted to a suitable concentration by PBST/1% milk, and incubated for 1.5 h at room temperature. After removal of reaction system, the plate was washed for 3 times with PBST buffer, followed by addition of 100 μl/well HRP-labeled anti-murine secondary antibody (The Jackson Laboratory) which was diluted by PBST/1% milk, and incubated for 1 h at room temperature. After being washed with PBST for three times, the plate was added with 100 μl/well TMB, and incubated for 5-10 min at room temperature. Then the reaction was terminated with addition of 100 μl/well 1M H_2 SO_4. The absorbance value at 450 nm was read on NOVOStar microplate reader; the ELISA binding EC_{50} value was calculated.

	ELISA, EC50, nM	
Test Antibody	human PD-1	cyno PD-1
mAb005	0.25	0.27

[0089] The results demonstrated that the antibody mAb005 showed excellent binding activity to human PD-1 Fc (human PD-1) and cynomolgus PD-1 Fc (cyno PD-1).

[0090] In vitro blocking assay of binding of PD-1 antibody and PD-1 ligand:

[0091] PD-L1 on the surface of a tumor cell exhibits suppressive effect on the proliferation of T cells by binding to PD-1 on the surface of a T cell. The PD-1 antibody blocks PD-L1/PD-1 signaling pathway by binding to PD-1 so as to stimulate T cell proliferation. PD-1/PD-L1 binding blocking assay is used to detect the blocking activity of PD-1antibody on the signaling pathway.

[0092] In this experiment, a 96-well plate was coated with a PD-1 protein with the extracellular domain fused with FC (PD-1-FC), and incubated with the test PD-1 antibody; later biotin-labeled PD-L1 was added for incubation. After washing the plate, the binding amount of biotin-labeled PD-L1 was detected; the blocking IC_{50} value of PD-1 antibody for ligand PD-L1 binding was calculated.

[0093] PD-1-FC was diluted to 1 μg/ml with PH 9.6 CB buffer (1.59 g Na_2CO_3 and 2.93 g $NaHCO_3$ were dissolved in 1 L of distilled water), pipetted into a 96-well plate at100μl/well and standed for 16 h-20 h at 4° C. The 96-well plate was washed once with PBST (PH7.4 PBS, containing 0.05% tweeen20) after PBS buffer was removed, then the plate was incubated and blocked for 1 h at room temperature with 120 μl/well PBST/1% milk. After removal of the blocking solution, the plate was washed with PBST buffer once, followed by addition of 90 μl of test PD-1 antibody which was diluted to a suitable concentration with sample diluents (PH7.4 PBS containing 5%BSA, 0.05% Tween20), and incubated for 1 h at 4° C. Then 10 X concentrations of biotin-labeled PD-L1 (Beijing Sino Biological Inc.) (10 μg/ml) was added to the plate at 10 μl/well, oscillated and mixed by an oscillator, and incubated at 37° C. for 1 h. After removal of the reaction system, the plate was washed for 6 times with PBST buffer, followed by addition of 100 μl/well Streptavidin—Peroxidase Polymer which was diluted by PBST at a ratio of 1:400, and incubated under oscillation for 50 min at room temperature. After being washed with PBST for 6 times, the plate was added with 100 μl/well TMB, and incubated for 5-10min at room temperature. Then the reaction was terminated with addition of 100 μl/well 1M H_2SO4. The absorbance value at 450 nm was read on the NOVOStar microplate reader; the blocking IC_{50} value of PD-1 for ligand PD-L1 binding was calculated.

Test antibody	LBB assay IC50, nM
mAb005	1.13

[0094] The result showed that the antibody mAb005 was very effective to block the binding of PD-L1 with PD-1.

EXAMPLE 3

Binding Selectivity Assay of PD-1 Antibody in Vitro

[0095] To detect the specific binding activity of PD-1 antibody to other proteins of the PD-1 family, human CTLA4 and human CD28 were used for binding assays. Meanwhile, the PD-1 of mice was also used for binding assays so as to determine the diversity of PD-1 antibody for different species other than human/monkey.

[0096] Selectively binding proteins: human PD-1, human ICOS, human CTLA4, human CD28 and mouse PD-1, (Beijing Sino Biological Inc.), were respectively diluted to 1 μg/ml with PBS buffer, pipetted into a 96-well plate at100μl/well and standed for 16 h-20 h at 4° C. The 96-well plate was washed once with PBST (PH7.4 PBS, containing 0.05% tweeen20) after PBS buffer was removed, then the plate was incubated and blocked for 1 h at room temperature with 120 μl/well PBST/1% milk. After removal of the blocking solution, the plate was washed with PBST buffer for 3 times, followed by addition of the test PD-1 antibody, and incubated for 1.5 h at room temperature. After removal of the reaction system, the plate was washed for 3 times with PBST, followed by addition of 100 μl/well HRP-labeled anti-murine secondary antibody (The Jackson Laboratory) which was diluted by PBST/1% milk, and incubated for 1 h at room temperature. The plate was washed for 3 times with PBST, followed by addition of 100 μl/well TMB, and incubated for 5-10 min at room temperature. Then the reaction was terminated with addition of 100 μl/well 1M H_2SO_4. The absorbance value at 450 nm was read on the NOVOStar microplate reader.

Test Antibody	human PD1-FC	mouse PD1-Fc	human ICOS/Fc	human CTLA4	human CD28
mAb005	2.64	0.07	0.15	0.17	0.12

[0097] The result demonstrated that mAb005 antibody exhibites no specific binding activity to other proteins of the PD-1 family. Meanwhile, mAb has no species cross-reactivity against murine PD-1.

EXAMPLE 4

In Vitro Cell Binding Assay of PD-1 Antibody

[0098] FACS (fluorescence-activated cell sorter) is a test method for detecting interaction of proteins and cells. The test is used for detecting the binding activity of PD-1 antibody to native PD-1 expressed on the cell surface. Cells used in the test are CHO cells highly expressing PD-1 (see Example 1, CHO cells transfected with PD-1 (SEQID NO: 2)).

[0099] The CHO cells highly expressing PD-1 were centrifuged at 1000 rpm for 5 minutes, and the pellet was collected and suspended with 10-15 ml of precooled flow buffer for cell count. Cells were centrifuged at 1000 rpm in 50 ml centrifuge tubes for 5 minutes and collected. After removal of the supernatant, the pellet was resuspended with precooled blocking buffer with density of $0.5\text{-}1.0\times10^7$ cells/ml. After incubation at 4° C. for 30 minutes, re-suspension was pipetted to the 96-well plate at 100 μl/well. The 96-well plate was centrifuged at 1500 rpm for 5 minutes, the supernatant was discarded. 100 μl of primary antibody was added to each well; the cells were resuspended, and incubated in the dark for 60 minutes at 4° C. After centrifugation and discard of the supernatant, 100 μl of FITC-labeled secondary antibody (BD Biosciences) diluted at 1:400 was added. The cells were resuspended and incubated in the dark for 60 minutes at 4° C. Cells were washed twice with flow buffer, resuspended and fixed with 1% paraformaldehyde for flow cytometry assay.

	MFI			
Test Antibody	50 nM	5 nM	0.5 nM	0.05 nM
mAb005	468	319	71.2	14

[0100] The results show that mAb005 antibody can also bind to PD-1 on the cell surface.

EXAMPLE 5

In Vitro Binding Affinity and Kinetic Assay

[0101] Biacore method is a recognized assay which objectively detects the interactional affinity and kinetics of proteins. We analyzed the characterized affinity and binding kinetics of the test PD-1 antibody of the present invention by Biacore (GE).

[0102] According to the instruction of a kit provided by Biacore, the test PD-1 antibody of the present invention was covalently linked to CM5 (GE) chip using a standard amino coupling method. Then a series of gradient concentrations of PD-1 His protein (Beijing Sino Biological Inc.), which were diluted in the same buffer, were loaded into each cycle successively. After that, the samples were regenerated with regenerated reagent in the kit. The antigen-antibody binding kinetics was tracked for 3 minutes and the dissociation kinetics was tracked for 10 minutes. The data obtained was analyzed by GE's BIAevaluation software using 1:1 (Langmuir) binding model. Ka (kon), kd (koff) and KD values determined by the assay were shown in the following table.

Test Antibody	ka (1/Ms)	kd (1/s)	KD (M)
mAb005	1.057E+5	3.769E−4	3.566E−9

[0103] The results showed that the binding Kd value of the antibody mAb005 to PD-1 reached to 3.57 nM.

EXAMPLE 6

In Vitro Cytology Test

[0104] Fresh human peripheral blood mononuclear cells (PBMC) proliferation assay affected by antibody is used to detect the cell activity of the antibody mAb005.

[0105] Fresh human PBMC density was adjusted to 2×10^6/ml, seeded in a 6-well plate at 2 ml/well, and incubated for 6 hours at 37° C., 5%CO_2. After the suspension cells were discarded, each well of adherent cells was mixed with 2 ml of RPMI1640 medium containing 100 ng/ml GM-CSF (granulocyte colony stimulating biological factor) and 100 ng/ml IL-4, and another 1 ml of RPMI1640 medium containing 100 ng/ml GM-CSF and 100 ng/ml IL-4 after

incubation for 2 days, then the cells were continually cultured for 2 days, followed by addition of 100 ng/m1 TNF-α (tumor necrosis factor-α) each well, and cultured for another 2 days to obtain mature dendritic cells. The dendritic cells and allogeneic T cells were respectivelycentrifugated and resuspended at a concentration of 1×10^6/ml and 1×10^5/ml, and pipetted into a 96-well plate at 100 μl/well, followed by addition of 20 μl/well of antibody which was diluted to different concentration gradients with PBS, and the cells were cultured in 37° C., 5% CO_2 incubator for 5 days. Thereafter, 100 μl of cell culture was sampled to detect the cell proliferation with CellTiter-Glo® Luminescent Cell Viability Assay kit. The result was shown in FIG. **1**, indicating that the test PD-1 antibody mAb005 can effectively stimulate the proliferation of human peripheral blood mononuclear cells, with EC50 of 83 ng/ml. The remaining sample was detected for secretion of cytokine IFN-γ. The result was shown in FIG. **2**, demonstrating that the test PD-1 antibody mAb005 could stimulate PBMC proliferation, and effectively stimulate secretion of cytokine IFN-γ at the same time, with EC50 of 13 ng/ml.

EXAMPLE 7

Murine Antibody Humanization

[0106] With reference to the sequences of the light chain variable region (mAb005 LCVR, SEQ ID NO: 10) and the heavy chain variable region (mAb005 HCVR, SEQ ID NO: 9) of the mAb005 antibody, humanized templates best matching with their non-CDR in Germline database were selected. The antibody heavy chain template is IgHV3-7/JH6, selecting for FR1, FR2, FR3 of human germline light chain IGKV1-39 and FR4 of JK4, with sequence of SEQ ID NO: 13; light chain template is IGKV1-39/JK4, selecting for FR1, FR2, FR3 of human germline light chain IGKV1-39, and FR4 of JK4, with sequence of SEQ ID NO: 14.

Human germline heavy chain template
(SEQ ID NO: 13):
EVQLVESGGGLQPGGSLRLSCAASGFTFSSYWMSWVRQAPGKGLEWVANI

KQDGSEKYYVDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARWGQ

GTTVTVSS.

Human germline light chain template
(SEQ ID NO: 14):
DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA

ASSLQSGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCFGGGTKVEIK.

[0107] The CDR of the murine antibody was grafted to the selected humanization template, replacing the CDR of human template, and then recombined with IgG4 constant region to obtain a humanized antibody H005-1. Afterwards, based on three-dimensional structure of the murine antibody, embedded residues, residues directly interacted with the CDR, and residues which significantly influence the conformation of VL and VH were backmutated to obtain humanized antibodies H005-2, H005-3, and H005-4, sequences are as follows.

[0108] Antibody Expression

H005-1 HC
SEQ ID NO: 11
EVQLVESGGGLVQPGGSLRLSCAASGFTFSSYMMSWVRQAPGKGLEWVAT

ISGGGANTYYPDSVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCARQL

YYFDYWGQGTTVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFP

EPVTVSWNSGALTSGVHTPAVLQSSGLYSLSSVVTVPSSSLGTKTYTCNV

DHKPSNTKVDKRVESKYGPPCPPCPAPEAAGGPSVFLFPPKPKDTLMISR

TPEVTCVVVDVSQEDPEVQFNWYVDGVEVHNAKTKPREEQFNSTYRVVSV

LTVLHQDWLNGKEYKCKVSNKGLPSSIEKTISKAKGQPREPQVPPSQEEM

TKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYS

RLTVDKSRWQEGNVFSCSVMHEALHWHYTQKSLSLSLGK

H005-1 LC
SEQ ID NO: 12
DIQMTQSPSSLSASVGDRVTITCLASQTIGTWLTWYQQKPGKAPKLLIYT

ATSLADGVPSRFSGSGSGTDFTLTISSLQPEDFATYYCQQVYSIPWTFGG

GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV

DNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQG

LSSPVTKSFNRGEC

[0109] The HC sequence of the humanized antibody H005-1 with grafted murine CDR is (SEQID NO: 11), the LC sequence of the humanized antibody is (SEQ ID NO: 12). Sites which may affect the antibody activity were subjected to point mutations, the sequences are as follows:

	HC	LC
H005-1	SEQID NO: 11	SEQID NO: 12
H005-2	SEQID NO: 11, G44R	SEQID NO: 12
H005-3	SEQID NO: 11	SEQID NO: 12, A43S
H005-4	SEQID NO: 11, G44R	SEQID NO: 12, A43S

[0110] cDNAs were synthesized according to the amino acid sequences of the light chain and the heavy chain of each humanized antibody (SEQ NO 11, SEQ NO 12 and variants thereof). After the cDNAs were digested with XhoI and BamHI, the obtained cDNA fragments were inserted into pcDNA3.1 expression vectors (Life Technologies Cat. No.V790-20) at BamHI/XhoI restriction sites. The expression vectors and a transfection reagent PEI (Polysciences, Inc. Cat. No.23966) were used to transfect HEK293 cells (Life Technologies Cat. No. 11625019) at 1: 2, and the transfected cells were incubated in a CO_2 incubator for 4-5 days. Expressed antibodies were recovered by centrifugation, and purified according to a conventional method to obtain the humanized antibodies of the present invention.

EXAMPLE 8

Humanized Antibody Activity Data

[0111] Humanized antibodies were subjected to ELISA binding assay (method is the same as that of Example 2), ligand binding blocking assay (method is the same as that of

Example 2), and affinity kinetics experiment (method is the same as that of Example 5) in vitro. The results are shown in the following table:

Test Antibody	ELISA, EC50, nM	LBB assay, IC50, nM	KD(M)
H005-1	0.11	1.27	2.79E−09
H005-2	0.14	1.27	2.98E−09
H005-3	0.15	1.33	2.45E−09
H005-4	0.14	1.36	3.89E−09

[0112] The result showed that humanized antibodies H005-1, H005-2, H005-3 and H005-4 maintained the PD-1 binding activity, with affinity kinetics KD of 2.79, 2.98, 2.45 and 3.89 nM respectively. Simultaneously, all the humanized antibodies effectively exhibited blocking activity against the PD-L1/PD-1 pathway.

EXAMPLE 9

Tumor Cell Growth Inhibition by PD-1 Antibody

[0113] 1. Experimental Materials:

[0114] U87MG cells (glioma cells): purchased from the Chinese Academy of Sciences Cell Bank, Cat. TCHu138;

[0115] PBMCs (peripheral blood mononuclear cells) purchased from the Shanghai Blood Center;

[0116] CD3: purchased from Miltenyi Biotec Cat No. 130-093-387;

[0117] CD28: purchased from Miltenyi Biotec Cat No. 130-093-375;

[0118] Cell Counting Kit-8: available from DOJINDO LABORATORIES, Cat No. CK04;

[0119] mIgG (negative control): purchased from SANTA CRUZ Cat No. sc-2025; using dose of 1660 ng/ml.

[0120] 2. Experimental Methods:

[0121] 1) U87MG cells were cultured in EMEM medium containing 10% FBS and 1% P/S, incubated in a 96-well plate, 1×10^4 cells per well.

[0122] 2) H005-1 antibody was diluted to different concentration gradients (shown in abscissa of FIG. **3**) with PBS, added to the 96-well plate at 10 ul/well, and incubated in 37° C., 5% CO_2 incubator for 4 hours.

[0123] 3) After cell adherence, 80 ul of PBMC cell suspension was added to each well with a cell density of 2×10^4 cells/well, and 10 ul of CD3 antibody and CD28 antibody were added in each well, the the final concentrations of CD3 and CD28 antibodies were both 500 ng/ml.

[0124] 4) After 72 hours of incubation in the 37° C., 5% CO_2 incubator, 10 ul of CCK8 was added to each well for development. 2 hours later, OD450 was determinated.

[0125] 3. Result:

[0126] The result was shown in FIG. **3**, as compared with mIgG (negative control), different concentrations of PD-1 antibody (H005-1) had significant inhibitory effect on U87MG cell growth, and inhibition rate at the highest concentration was about 30%.

EXAMPLE 10

Activity of 11005-1 on Tuberculin-Stimulated PBMC Proliferation

[0127] The activity of the humanized antibody H005-1 on tuberculin-stimulated PBMC proliferation in vitro was detected.

[0128] To 15 ml of fresh PBMCs, about 3×10^7 cells, were added 20 μl tuberculin (Shanghai BiYou Biotechnology, cat#97-8800) and the mixture were incubated for 5 days in the 37° C., 5% CO_2 incubator. On day 6, the cultured cells were centrifugated, and resuspended into fresh medium with a density adjusted to 5×10^5 cells/ml. 190 μl of resuspended cells was planted into each well of a 96-well plate. The humanized antibody H005-1 was added to corresponding wells of the 96-well plate at10 μl/well. The control group and blank group were added with 10 μl of PBS. The Cell culture plate was incubated in the 37° C., 5% CO_2 incubator, and 72 hours later, PBMC Proliferation (Promega, cat #G7571) and IFN-γ secretion (Neo Bioscience, cat #EHC102 g) were determined. The results are as follows:

[0129] Activation Effect of the Test Sample on Tuberculin Stimulated PBMC Proliferation and IFN-γ Secretion

Sample	T cell proliferation EC50(ng/ml)	IFN-λ EC50(ng/ml)
H005-1	15.95 ± 17.15	56.87 ± 48.53

Note:
n = 4

[0130] Experiment results showed that the humanized antibody H005-1 excellently activates exogenous tuberculin stimulated PBMC proliferation and IFN-γ secretion.

EXAMPLE 11

Inhibition of Subcutaneously Inoculated U-87MG Tumor by 11005-1

[0131] 100 ul of U87 cells (5×10^6 cells) was inoculated subcutaneously in right ribs of SCID-Beige mice. When the tumor grew to 80-100 mm^3 after 7 to 10 days, the SCID-Beige mice, getting rid of ones with too large or too small body weight or tumor, were randomly divided into a H005-1 10 mg/kg group and a Human IgG 10 mg/kg group according to the tumor volume, each group of seven mice (DO). Two kinds of PBMCs stimulated by CD3 antibody for 3 days were mixed at a ratio of 1: 1, and injected into the tumor tissues at 5×10^5 cells/60 ul, meanwhile, the test antibody was injected subcutaneously, once per 7 days for total 3 doses. Mice were measured for tumor volume and weighed twice a week. Data was recorded. Tumor volume (V) was calculated as: V=½a×b2, wherein a and b represented length and width, respectively.

[0132] The result was shown in FIG. **4**: tumor volume change after treatment, and FIG. **5**: mice weight change after treatment, indicating that antibody H005-1 excellently inhibited U87MG tumor growth, and had no effect on the body weight of the mice.

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65                  70                  75                  80

Leu Ala Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg
                85                  90                  95

Phe Arg Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val
            100                 105                 110

Val Arg Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile
        115                 120                 125

Ser Leu Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu
    130                 135                 140

Arg Val Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro
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Ser Pro Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Asp Lys Thr His
                165                 170                 175

Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val
            180                 185                 190

Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr
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Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro Glu
    210                 215                 220

Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys
225                 230                 235                 240

Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser
                245                 250                 255

Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys
            260                 265                 270

Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile
        275                 280                 285

Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro
    290                 295                 300

Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu
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            20                  25                  30

Asn Pro Pro Thr Phe Ser Pro Ala Leu Leu Val Val Thr Glu Gly Asp
        35                  40                  45

Asn Ala Thr Phe Thr Cys Ser Phe Ser Asn Thr Ser Glu Ser Phe Val
    50                  55                  60

Leu Asn Trp Tyr Arg Met Ser Pro Ser Asn Gln Thr Asp Lys Leu Ala
65                  70                  75                  80

Ala Phe Pro Glu Asp Arg Ser Gln Pro Gly Gln Asp Cys Arg Phe Arg
                85                  90                  95

Val Thr Gln Leu Pro Asn Gly Arg Asp Phe His Met Ser Val Val Arg
            100                 105                 110

Ala Arg Arg Asn Asp Ser Gly Thr Tyr Leu Cys Gly Ala Ile Ser Leu
        115                 120                 125

Ala Pro Lys Ala Gln Ile Lys Glu Ser Leu Arg Ala Glu Leu Arg Val
    130                 135                 140

Thr Glu Arg Arg Ala Glu Val Pro Thr Ala His Pro Ser Pro Ser Pro
145                 150                 155                 160

Arg Pro Ala Gly Gln Phe Gln Thr Leu Val Val Gly Val Val Gly Gly
                165                 170                 175

Leu Leu Gly Ser Leu Val Leu Leu Val Trp Val Leu Ala Val Ile Cys
            180                 185                 190

Ser Arg Ala Ala Arg Gly Thr Ile Gly Ala Arg Arg Thr Gly Gln Pro
        195                 200                 205

Leu Lys Glu Asp Pro Ser Ala Val Pro Val Phe Ser Val Asp Tyr Gly
    210                 215                 220

Glu Leu Asp Phe Gln Trp Arg Glu Lys Thr Pro Glu Pro Pro Val Pro
225                 230                 235                 240

Cys Val Pro Glu Gln Thr Glu Tyr Ala Thr Ile Val Phe Pro Ser Gly
                245                 250                 255

Met Gly Thr Ser Ser Pro Ala Arg Arg Gly Ser Ala Asp Gly Pro Arg
            260                 265                 270

Ser Ala Gln Pro Leu Arg Pro Glu Asp Gly His Cys Ser Trp Pro Leu
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Gly

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        35                  40                  45

Ala Thr Ile Ser Gly Gly Gly Ala Asn Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Ser Ser Leu Arg Ser Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Ala Arg Gln Leu Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Leu
            100                 105                 110

Thr Val Ser Ser
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            20                  25                  30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ser Pro Gln Leu Leu Ile
        35                  40                  45

Tyr Thr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Lys Phe Ser Phe Lys Ile Ser Ser Leu Gln Ala
65                  70                  75                  80

Glu Asp Phe Val Thr Tyr Tyr Cys Gln Gln Val Tyr Ser Ile Pro Trp
                85                  90                  95

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Met Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ala Thr Ile Ser Gly Gly Gly Ala Asn Thr Tyr Tyr Pro Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
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Ala Arg Gln Leu Tyr Tyr Phe Asp Tyr Trp Gly Gln Gly Thr Thr Val
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Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala
        115                 120                 125

Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu
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        195                 200                 205

Lys Val Asp Lys Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro
    210                 215                 220

Cys Pro Ala Pro Glu Ala Ala Gly Gly Pro Ser Val Phe Leu Phe Pro
225                 230                 235                 240

Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr
                245                 250                 255

Cys Val Val Val Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn
            260                 265                 270

Trp Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg
        275                 280                 285

Glu Glu Gln Phe Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val
    290                 295                 300

Leu His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser
305                 310                 315                 320

Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys
                325                 330                 335

Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu
            340                 345                 350

Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe
        355                 360                 365

Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu
    370                 375                 380

Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe
385                 390                 395                 400

Phe Leu Tyr Ser Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly
                405                 410                 415

Asn Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr
            420                 425                 430

Thr Gln Lys Ser Leu Ser Leu Ser Leu Gly Lys
        435                 440


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<212> TYPE: PRT
<213> ORGANISM: Artificial sequence
<220> FEATURE:
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<223> OTHER INFORMATION: light chain sequence of humanized antibody
H005-1

<400> SEQUENCE: 12

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Leu Ala Ser Gln Thr Ile Gly Thr Trp
20 25 30

Leu Thr Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Thr Ala Thr Ser Leu Ala Asp Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Val Tyr Ser Ile Pro Trp
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 13
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<213> ORGANISM: Artificial sequence
<220> FEATURE:
<223> OTHER INFORMATION: heavy chain framework region sequence of
humanized antibody

<400> SEQUENCE: 13

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1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Glu Lys Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

-continued

```
Ala Arg Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
            100                 105


<210> SEQ ID NO 14
<211> LENGTH: 98
<212> TYPE: PRT
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<223> OTHER INFORMATION: light chain framework region sequence of
      humanized antibody

<400> SEQUENCE: 14

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
            20                  25                  30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Phe Gly Gly Gly Thr Lys Val Glu
                85                  90                  95

Ile Lys
```

1. APD-1 antibody or an antigen-binding fragment thereof, comprising:

a light chain variable region comprising at least one LCDR selected from those sequences as shown in: SEQ ID NO: 6, SEQ ID NO: 7 or SEQ ID NO: 8; and

a heavy chain variable region comprising at least one HCDR region selected from those sequences as shown in: SEQ ID NO: 3, SEQ ID NO: 4 or SEQ ID NO: 5.

2. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the light chain variable region comprises a LCDR1 as shown in SEQ ID NO: 6.

3. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the light chain variable region comprises a LCDR2 as shown in SEQ ID NO: 7.

4. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the light chain variable region comprises a LCDR3 as shown in SEQ ID NO: 8.

5. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the heavy chain variable region comprises a HCDR1 as shown in SEQ ID NO: **3**.

6. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the heavy chain variable region comprises a HCDR2 as shown in SEQ ID NO: **4**.

7. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the heavy chain variable region comprises a HCDR3 as shown in SEQ ID NO: **5**.

8. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the light chain variable region comprises a LCDR1, a LCDR2 and a LCDR3 as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, respectively.

9. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the heavy chain variable region comprises a HCDR1, a HCDR2 and a HCDR3 as shown in SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5, respectively.

10. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the light chain variable region comprises a LCDR1, a LCDR2 and a LCDR3 as shown in SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, respectively; and wherein the heavy chain variable region comprises a HCDR1, a HCDR2 and a HCDR3 as shown in SEQ ID NO: 3, SEQ ID NO: 4 and SEQ ID NO: 5, respectively.

11. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the antibody or the antigen-binding fragment thereof is a murine antibody or a fragment thereof.

12. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the antibody or the antigen-binding fragment thereof is a chimeric antibody or a fragment thereof.

13. The PD-1 antibody or the antigen-binding fragment thereof according to claim **12**, wherein the light chain variable region sequence of the chimeric antibody is: SEQ ID NO: 10.

14. The PD-1 antibody or the antigen-binding fragment thereof according to claim **12**, wherein the heavy chain variable region sequence of the chimeric antibody is: SEQ ID NO: 9

15. The PD-1 antibody or the antigen-binding fragment thereof according to claim **1**, wherein the antibody or the antigen-binding fragment is a humanized antibody or a fragment thereof.

16. The PD-1 antibody or the antigen-binding fragment thereof according to claim **15**, wherein the light chain FR sequence of the light chain variable region of the humanized antibody is derived from a combination sequence of human germline light chains IGKV1-39 and JK4 as shown in SEQ ID NO: 14, comprising FR1, FR2 and FR3 of IGKV 1-39 and FR4 of JK4.

17. The PD-1 antibody or the antigen-binding fragment thereof according to claim **15**, wherein the sequence of the humanized antibody light chain is a sequence as shown in SEQ ID NO: 12 or a variant thereof.

18. The PD-1 antibody or the antigen-binding fragment thereof according to claim **15**, wherein the heavy chain variable region of the humanized antibody further comprises a heavy chain FR of human IgG1, IgG2, IgG3 or IgG4, or a variant thereof.

19. The PD-1 antibody or the antigen-binding fragment thereof according to claim **15**, wherein the heavy chain FR sequence of the heavy chain variable region of the humanized antibody is derived from a combination sequence of human germline heavy chains IgHV3-7 and JH6 as shown in SEQ ID NO:13, comprising FR1, FR2 and FR3 of IgHV3-7 and FR4 of JH6.

20. The PD-1 antibody or the antigen-binding fragment thereof according to claim **15**, wherein the sequence of the humanized antibody heavy chain is a sequence as shown in SEQ ID NO: 11 or a variant thereof.

21. A DNA molecule encoding the antibody or the antigen-binding fragment according to claim **1**.

22. An expression vector comprising the DNA molecule according to claim **21**.

23. A host cell transformed with the expression vector according to claim **22**.

24. The host cell according to claim **23**, wherein the host cell is bacteria.

25. The host cell according to claim **23**, wherein the host cell is yeast.

26. A pharmaceutical composition comprising the PD-1 antibody or the antigen-binding fragment according to claim **1** and a pharmaceutically acceptable excipient, diluent or carrier.

27. A method for treating a PD-1 mediated disease or disorder in a human subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the antibody or the antigen-binding fragment according to claim **1**.

28. The method of claim **27**, wherein the PD-1 mediated disease or disorder is a cancer.

29. The method of claim **28**, wherein the cancer is breast cancer, lung cancer, stomach cancer, intestinal cancer, renal cancer, melanoma or non-small cell lung cancer.

* * * * *

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 June 2012 (28.06.2012)

WIPO | PCT

(10) International Publication Number
WO 2012/088265 A1

(51) International Patent Classification:
A61K 39/00 (2006.01)

(21) International Application Number:
PCT/US2011/066470

(22) International Filing Date:
21 December 2011 (21.12.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
12/974,739 21 December 2010 (21.12.2010) US
61/529,682 31 August 2011 (31.08.2011) US

(71) Applicants *(for all designated States except US)*: **SELEXYS PHARMACEUTICALS CORPORATION**; 840 Research Parkway, Suite 516, Oklahoma City, OK 73104 (US). **OKLAHOMA MEDICAL RESEARCH FOUNDATION**; 825 Ne 13th, Oklahoma City, OK 73104 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **ROLLINS, Scott** [US/US]; 5501 White Fences, Oklahoma City, OK 73131 (US). **ALVAREZ, Richard** [US/US]; 3604 Katherine Court, Edmond, OK 73013 (US). **ROTHER, Russell** [US/US]; 10325 Forest Meadow Drive, Oklahoma City, OK 73151 (US). **KAWAR, Ziad, S.** [US/US]; 333 N W. 5th Street, Apt. #1802, Oklahoma City, OK 73120 (US). **MCEVER, Rodger, P.** [US/US]; 1716 Guilford Lane, Oklahoma City, OK 73120 (US).

(74) Agent: **CORBETT, Christopher, W.**; Dunlap Codding, P.C., P.O. Box 16370, Oklahoma City, OK 73113-2370 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

— *with sequence listing part of description (Rule 5.2(a))*

WO 2012/088265 A1

(54) **Title**: ANTI-P-SELECTIN ANTIBODIES AND METHODS OF THEIR USE AND IDENTIFICATION

(57) **Abstract**: Antibodies are disclosed which bind specifically to P-selectin, block the binding of PSGL-1 to P-selectin, and cause dissociation of preformed P-selectin/PSGL-1 complexes. The disclosure identifies a heretofore unrecognized, near N-terminal, antibody binding domain (a conformational epitope) of P-selectin to which the antibodies (which may be chimeric, human or humanized antibodies for example) bind. Antibodies are disclosed which bind to the conformational epitope of P-selectin and which have a dual function in blocking binding of PSGL-1 to P-selectin, and in causing dissociation of preformed P-selectin/PSGL-1 complexes. Such dual function anti-P-selectin antibodies and binding fragments thereof may be used in the treatment of a variety of acute and chronic inflammatory and thrombotic disorders and conditions. Screening methods for identifying and characterizing such antibodies are also disclosed.

ANTI-P-SELECTIN ANTIBODIES AND METHODS OF THEIR USE AND IDENTIFICATION

[0001] The present invention relates to antibodies and antibody fragments which bind to specific conformational epitopes of P-selectin, and to methods of their use and identification.

[0002] In normal hemostasis and immune surveillance, leukocytes circulate freely in the blood and respond to injury and infection in a sequential process of adhesion signaling mediated by cell adhesion molecules (1-3). In inflammatory and thrombotic disease, this process is dysregulated and can sustain pathology wherein leukocytes attack the body's own tissue and can cause serious and sometimes deadly complications. It is well known that leukocyte adhesion plays a major role in the pathology of many inflammatory and thrombotic disorders such as vasoocclusion in sickle cell disease, reperfusion injury, thrombosis, atherosclerosis, asthma, rheumatoid arthritis, psoriasis and tumor metastasis (4-15) deep venous thrombosis (DVT). P-selectin is also involved in other disease processes, such as tissue and organ damage associated with inflammation, e.g., ischemia-reperfusion injury. P-selectin is thus a target for intervention in human inflammatory and thrombotic diseases.

[0003] Selectins are a family of adhesion proteins which are known to play key roles in the recruitment of leukocytes to activated endothelium and platelets. P-selectin is a member of the selectin family of adhesion glycoproteins which also includes L- and E-selectins (16). The selectins mediate the recruitment, initial tethering and rolling, and adherence of leukocytes to sites of inflammation (1). P-selectin is stored in Weibel-Palade bodies of endothelial cells and alpha-granules of platelets and is rapidly mobilized to the plasma membrane upon stimulation by vasoactive substances such as histamine and thrombin (17).

[0004] Sickle Cell Disease

[0005] Sickle cell disease (SCD) is a rare inherited blood disorder that causes chronic anemia and vasoocclusion, affecting primarily people of African-American heritage in the United States. Sickle cell disease is the most common single gene disorder in African Americans, affecting approximately 1 in 375-600 persons of African ancestry (18, 19). Sickle cell conditions are also common among people of Mediterranean countries, Africa the Caribbean and parts of South and Central America (18, 19).

[0006] SCD is an autosomal recessive disease caused by a single missense

mutation (Val6Ala) in the β-globin gene that renders the mutant hemoglobin less soluble and prone to polymerization upon deoxygenation. The polymerization of hemoglobin causes deformation of the erythrocyte to give the cell a sickled shape (20).

[0007] SCD has three common variants: homozygous sickle cell disease (hemoglobin SS disease), doubly heterozygous sickle hemoglobin C disease (hemoglobin SC disease) and the sickle β-thalassemias. The most common and severe form of the disease occurs in individuals who inherit two copies of the HbS variant (HbSS) and the primary hemoglobin in their red blood cells is sickle hemoglobin. Other individuals can be affected as compound heterozygotes with varying severity of the disease. They have one copy of the HbS variant paired with a copy of another β-globin gene variant. HBSC results in a mild form of the disease. Hb β-thalassemia variants (resulting in the inability to produce the normal βA globin chain (β°) or a reduction in its production (β^{+}) result in a range of clinical severities. HbS β^{0} is a severe form, whereas HbS β^{+} can be moderate or mild based on the contribution of each variant to the total hemoglobin of the patient. Other more rare variants can result if in conjunction with the S gene, another abnormal hemoglobin is inherited from the other parent, such as D, G or O. The predominant form of sickle cell is present in individuals with one copy of HbS and one copy of the normal β-globin gene (HbA). These individuals carry the sickle cell trait (18).

[0008] SCD affects an estimated 50,000-100,000 people in the US (21-24). All individuals that are homozygous or compound heterozygous for HbS show some clinical manifestations of SCD. Symptoms usually appear within the first 6 months of life but there is considerable variability in SCD severity (25). Individuals with HbSS are most severely affected, followed by individuals with HBbS β°-thalassemia (22, 26). In addition to genotype, additional factors affect disease severity such as the levels of fetal hemoglobin and the haplotype of the β-globin cluster, a region that contains 5 genes that code for the β portion of hemoglobin. Despite the capacity to determine genetic risk factors, the ability to predict disease course from birth is limited (27).

[0009] In the USA, sickle cell screening at birth is mandated in all 50 states and the District of Columbia (28) and offers an opportunity for early intervention. Diagnostic testing methodology usually comprises a complete blood count in conjunction with one or more of hemoglobin electrophoresis, isoelectric focusing, high-performance liquid chromatography and DNA testing (22).

[0010] Chronic anemia and hemolysis

[0011] The sickled erythrocyte has a shorter half-life than the normal erythrocyte and results from the instability of HbS and the effects of repeated episodes of hemoglobin polymerization/depolymerization in the circulation. This affects membrane ionic permeability, cellular viscosity and deformability (20) and promotes oxidative membrane damage (29). Sickle cell disease patients are anemic by 2 to 3 months of age and develop symptoms and complications associated with chronic anemia and hemolysis (22, 30) such as renal disease, ophthalmic disorders, leg ulcers, priapism and pulmonary hypertension (26, 31-37). Hemoglobin values for SCD patients range from 6 to 10g/dL and the hemoglobin S molecule has a poor affinity for oxygen. Triggers for transfusion in patients are a hemoglobin value of 5 or less or a precipitous drop in hemoglobin of 2g/dL or more. Transfusions are typically given to restore hemoglobin values to baseline levels established for each patient as excessive hematocrit can precipitate sickling (38). SCD patients are more susceptible to parvovirus B19 infection which can arrest erythropoiesis and lead to aplastic anemia crisis (39).

[0012] Vasoocclusive pain crisis

[0013] Vascular occlusion is central to the clinical course of SCD and likely involves both the micro and macro circulation. Occlusion occurring in the microvasculature can culminate in acute painful episodes or vasoocclusive pain crises. Vasoocclusive pain crisis is the clinical hallmark of microvascular occlusions and accounts for over 90% of hospital admissions of adults SCD patients. It is well known that polymerization of hemoglobin S during deoxygenation and cell sickling leads to blockage of the microvasculature (40). However, it has recently become clear that hemoglobin S polymerization is not solely responsible for vasoocclusion. It has now been demonstrated that such events as sickled red cell lysis, cell membrane damage and oxidative stress, repeated ischemic damage, and microvasculature injury due to the adhesive interactions between sickle red cells and the endothelium that culminate in a proinflammatory environment (41-43). In this environment of chronic vascular inflammation, the adherence of leukocytes, platelets and sickled red cells to activated blood vessel endothelium and to each other is believed to be a primary cause of microvasculature blockage and vasoocclusive pain crisis (43-47). Additional factors such as the rigidity of sickled cells, increased blood viscosity, and local vasoconstriction have also been identified as potentially contributing to the vasoocclusion process.

[0014] Long-term repeated vasoocclusive events and occlusions occurring in the macrovasculature can cause life-threatening complications leading to organ damage and failure, stroke and death (40). There is an approximately 20 to 30 year reduction in life expectancy in sickle cell disease patients (48). Chronic pain in SCD is not just a continuation of the pain of vasoocclusion: it is usually secondary to avascular necrosis of bone at various joints (49). Sickled red cells can become trapped in the spleen causing it to become enlarged and precipitating splenic sequestration crisis causing sudden and severe anemia. Functional asplenia leaves patients susceptible to infection (18). Bone growth retardation, renal (32), ophthalmic (33) and cerebrovascular complications (ranging from clinically evident acute stroke to transient silent ischemic infarct) (50) are seen as major clinical consequences of SCD and vasoocculsive injury (22). Acute chest syndrome is another major complication (51), and is a significant cause of morbidity and mortality (52).

[0015] Pain episodes appear to be triggered by a number of factors including cold, stress and physical exertion (38, 53). The frequency, severity, location and duration of pain crises can vary considerably, even within a specific disease subtype. Patients with homozygous sickle cell and sickle cell β°-thalassemia have a higher frequency of vasoocclusive pain crises than patients with hemoglobin SC and sickle cell- β°-thalassemia genotype (54). Disease severity is thought to depend on a complex interaction of genetic, rheologic and hematologic factors, as well as microvascular and endothelial factors. Crises commonly involve pain in the back, legs, knees, arms, chest and abdomen (53). The frequency of crisis and pain severity varies considerably among patients and in the same patient over time. One study evaluating pain rates in patients ranging from newborns to age 50 years indicated that 5.2 percent of patients with sickle cell disease have three to 10 episodes of severe pain every year (54). In an independent study, over 30% of sickle cell patients in the US (approximately 27,000 patients) have three or more pain crises per year (55). Moreover, a recent study (PiSCES) evaluating health related quality of life issues in SCD patients indicated that pain crisis might be significantly underreported among SCD patients (56).

[0016] Current Therapies For Vascular Occlusion

[0017] Vascular occlusion in SCD patients can manifest in multiple ways including vasoocclusive pain crisis, acute chest syndrome, cerebrovascular events and multiple types of organ failure. Therefore, treatment modalities for vascular occlusion depend on the clinical course and severity of the disease and are generally

symptomatic or palliative in nature. Patient education in the avoidance of initiating factors that precipitate vasoocclusive pain crisis has shown some prophylactic benefit. The two most common symptomatic treatments are blood transfusions and analgesics. Most SCD patients commonly have hemoglobin values between 6 and 10g/dL and hemoglobin values typically drop at least 1 g per dL during a vasoocclusive pain crisis. Severe pain resulting from vasoocclusive crisis can be treated with narcotics but their use is controversial due to concerns of narcotic addiction and tolerance. Other complications with narcotic use are drug-seeking behavior, sedation and respiratory depression. Oxygen management has been utilized to treat vasoocclusive pain crisis despite the lack of strong evidence supporting its effectiveness. Rehydration is also sometime used during vasoocclusive pain crises with some benefit (22, 38).

[0018] Bone marrow transplantation may be considered and can be curative, but its use is restricted to a limited number of patients, and carries a high risk of morbidity and mortality (22).

[0019] Hydroxyurea (Droxia) is the only FDA approved drug for treatment of SCD pain crises. The mechanisms by which it produces its beneficial effects are uncertain but may involve increasing hemoglobin F levels in RBCs thereby decreasing the level of hemoglobin S polymerization. Hydroxyurea is cytotoxic, myelosuppressive and teratogenic (57, 58) which implies a carcinogenic risk to SCD patients. The long-term effects however, on hematologic toxicities, organ damage and carcinogenicity are currently unknown (59, 60).

[0020] In summary, most therapies for vasoocclusive pain crisis in SCD patients provide symptomatic relief and do not address the underlying cause of this debilitating condition. To date only one therapy has been approved by the FDA for the treatment of pain crisis, thus, patients with SCD represent a major unmet medical need in a life-threatening disease with severe morbidities.

[0021] P-selectin as a Therapeutic Target for SCD

[0022] In SCD, as noted above, interactions between sickled red cells, platelets, leukocytes and the microvasculature are P-selectin-dependent processes and result in vasoocclusion and painful crisis. Studies in transgenic mice engineered to express human β hemoglobin S (β^S) have shown that antibody-mediated inhibition of P-selectin function can prevent and/or reduce vasoocclusion, indicating a therapeutic potential for this target. In addition mice expressing the β^S hemoglobin that lack P-selectin (due to gene deletion) do not suffer vasoocclusion, further supporting a key

role for this molecule in this morbidity.

[0023] The hyper-inflammatory state in SCD patients is characterized by activated monocytes and vascular endothelium (61-63). A similar pro-inflammatory phenotype was demonstrated in resting state β^S mice which exhibit elevated levels of peripheral leukocytes and neutrophils, an increased number of rolling and adherent leukocytes, and reduced blood flow volume and red blood cell velocities (64). The β^S mice were hypersensitive to hypoxia/reoxygenation resulting in an inflammatory response represented by a significant increase in the number of adherent and emigrated leukocytes. This inflammatory response was completely blocked by a functionally blocking anti-mouse P-selectin antibody, but not by a functionally blocking anti-mouse E-selectin antibody, demonstrating a critical role for P-selectin in this process.

[0024] P-selectin plays its central role in the recruitment of leukocytes to inflammatory and thrombotic sites by binding to its counter-receptor, P-selectin glycoprotein ligand-1 (PSGL-1) (or a PSGL-1-like receptor on sickled red blood cells), which is a mucin-like glycoprotein constitutively expressed on leukocytes including neutrophils, monocytes, platelets, and on some endothelial cells (68). The ultimate physiologic function of the selectins is to promote extravasation of leukocytes into inflamed or damaged tissues. The initial binding of P-selectin on the endothelium to PSGL-1 on the leukocytes is essential and central to this process. The predominant mechanism for rolling and tethering of leukocytes to activated endothelium and platelets is the binding of leukocyte PSGL-1 to the P-selectin on these cells (68, 69). PSGL-1 binds to P-, L- and E-selectin (70). P-selectin and SGP-3, a glycosulfopeptide modeled from the N-terminus of PSGL-1, have been co-crystallized and the contact residues for lectin-ligand binding have been identified (71).

[0025] The selectins share common structural motifs including a lectin domain (or carbohydrate recognition domain), an epidermal growth factor-like domain (EGF), a varying series of consensus repeats, a transmembrane domain and a cytoplasmic tail (70). As noted, the initial tethering and rolling of leukocytes is mediated by the interaction of P-selectin and PSGL-1. Thus the blocking of P-selectin function by using (1) antibodies to P-selectin, (2) antibodies to PSGL-1, (3) fragments of PSGL-1 or recombinant forms of PSGL-1, (4) small molecules that mimic the binding domain of PSGL-1, and (5) other molecules that disrupt the binding of P-selectin to PSGL-1, can block leukocyte rolling and tethering and thus prevent firm adhesion to endothelial cells or platelets. Mice deficient in P-selectin or PSGL-1 also fail to support leukocyte

tethering and rolling on activated endothelial cells (72, 74). L-selectin plays a dual role in that it is constitutively expressed on circulating leukocytes and can initiate "secondary binding" by interaction with PSGL-1 on other leukocytes (75). This process leads to further recruitment of new leukocytes to the inflamed area. L-selectin binding to PSGL-1 also plays a role in homing of lymphocytes to the high endothelial vasculature (HEV) venules in the secondary lymphatic system (76). E-selectin is transcriptionally regulated and is expressed on activated endothelial cells hours after P-selectin mediated events. E-selectin can bind PSGL-1 with low affinity but can also bind other ligands. Single transgenic knockout mice for each selectin have shown that these molecules possess compensatory selectin mechanisms for leukocyte homing and rolling (77).

[0026] In view of the above, there is a well-established need for new treatments, such as antibodies, that target P-selectin as a means of treating inflammatory and thrombotic diseases by disrupting the binding of P-selectin and PSGL-1. It is therefore a goal of the presently disclosed inventive concepts to block P-selectin binding to PSGL-1 thereby blocking the adherence of blood cells that contribute to vasoocclusion in SCD and other thrombotic disorders as discussed elsewhere herein.

SUMMARY OF THE DISCLOSURE

[0027] The presently disclosed inventive concepts are directed to "dual function" antibodies which bind specifically to P-selectin and which not only block the binding of PSGL-1 to P-selectin, but also dissociate preformed P-selectin/PSGL-1 complexes. The present disclosure describes a heretofore unrecognized antibody binding domain (a conformational epitope) within the lectin domain (e.g., carbohydrate recognition domain, CRD) of P-selectin to which the dual function antibodies (which may be chimeric, human or humanized antibodies or fragments thereof for example) bind. The presently disclosed inventive concepts are therefore directed to anti-P-selectin antibodies or fragments thereof which bind to the conformational epitope described herein and which have a dual function in (1) blocking binding of PSGL-1 to P-selectin, and (2) causing dissociation of preformed P-selectin/PSGL-1 complexes. The presently disclosed inventive concepts in particular are directed to using such dual function anti-P-selectin antibodies or antibody fragments as described herein in treatments for inflammatory, thrombotic or other conditions or disorders in primates (including humans) which involve platelet, sickled red cell, leukocyte, lymphocyte, and/or endothelial cell adhesion, wherein the condition or disorder comprises or is

associated with (but not limited to) at least one of sickle cell vasoocclusive pain crisis, inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis, and enteritis), arthritis (e.g., rheumatoid arthritis, osteoarthritis, and psoriatic arthritis), graft rejection, graft versus host disease, asthma, chronic obstructive pulmonary disease, psoriasis, dermatitis, sepsis, nephritis, lupus erythematosis, scleroderma, rhinitis, anaphylaxis, diabetes, multiple sclerosis, atherosclerosis, thrombosis, tumor metastasis, allergic reactions, thyroiditis, ischemic reperfusion injury (e.g., due to myocardial infarction, stroke, or organ transplantation), and conditions associated with extensive trauma, or chronic inflammation, such as, for example, type IV delayed hypersensitivity, associated for example with infection by Tubercle bacilli, or systematic inflammatory response syndrome, or multiple organ failure. Importantly, the use of such dual function antibodies as described herein in treating these inflammatory diseases allow not only the prevention of inflammation, but also provide a mechanism to treat ongoing inflammatory disease processes in that the antibodies can dissociate preformed P-selectin/PSGL-1. For example, in the case of sickle cell vasoocclusive pain crisis, antibodies having dual function activity not only inhibit or prevent future vasoocclusive events, but also allow the treatment of ongoing vasoocclusion. Other embodiments of the inventive concepts disclosed herein will be apparent in the Detailed Description below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0028] Figure 1 shows a homology comparison at the amino acid level of human and mouse P-selectin indicating the location of lectin, EGF, CR1 and CR2 domains (transition between domains is indicated by arrows ↓). Nonlinear conformational domains A, B, C1, D, E1, C2, E2, C3, and F are indicated by dashed boxes. Amino acid differences are indicated in boldface.

[0029] Figure 2 shows representative two-step BIACORE P-selectin chimera binding data for the anti-P-selectin antibodies G1, G3, G4 and G5 binding to SEQ ID NO:1-4, 7-10, 18 and 19. Note that binding of the G5 antibody in the Biacore two-step binding assay was only performed for SEQ ID NOs: 1, 2, 18 and 19. G4 is a novel anti-P-selectin mouse monoclonal antibody which is produced by hybridoma cells deposited as Patent Deposit Designation PTA-12154 in the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, a recognized public depository.

[0030] Figure 3 shows BIACORE sensograms demonstrating blocking of P-selectin interaction with PSGL-1 using anti-P-selectin antibodies G1, G3, G4 and

hSel001 (hSel001, also known as SelG1, is a humanized form of G1) by the methods described herein. G1, G3, G4 and hSel001 were shown to block interaction of P-selectin to the glycosulfopeptide GSP-6, a PSGL-1 mimetic. G5 binds P-selectin, but did not block. The control is steady state binding of P-selectin to GSP-6.

[0031] Figure 4 shows BIACORE sensograms demonstrating dissociation of the preformed P-selectin/PSGL-1 complex upon exposure to dual function anti-P-selectin antibodies G1, G4 and hSel001. PSGL-1 is represented by GSP-6 peptide, a PSGL-1 mimetic. Initial RU increase shows binding of P-selectin to biotin-GSP-6 coupled to a streptavidin coated BIACORE chip. Once steady state binding of the P-selectin/GSP-6 complex was reached (i.e., after normal dissociation of the complex had reached near-equilibrium), test antibodies were injected and assessed for dissociation properties. G5 bound to the preformed complex, but did not cause its dissociation. G3 did not bind or dissociate the preformed P-selectin/PSGL-1 complex. G1, G4 and hSel001 both bound and caused dissociation of the preformed P-selectin/GSP-6 complex, indicating novel dual function capabilities.

[0032] Figure 5 shows a 3-D representation of a human P-selectin molecule with GSP-6 binding thereto. Lectin and EGF domains are demarcated by a dashed line. Binding region 1 indentifies a Cluster A conformational epitope that is distal to the lectin/ligand binding domain. Test antibody G1 bound to region 1, Cluster A. G4 and hSel001 also bound region 1, Cluster A.

[0033] Figure 6 shows graphs of results of cell-based *in vitro* rolling assays under flow of human neutrophils on low and high density P-selectin. Results demonstrate blocking and/or dissociation of the preformed P-selectin/PSGL-1 complex and subsequent release of neutrophils upon exposure to antibodies G1, G3, G4 and hSel001. Antibodies were introduced at equivalent concentrations of 20μg/ml for the duration of the study. There is a lag time of about 1 minute before the antibody reaches the chamber due to the dead volume of the system. At 1-minute intervals thereafter, cells remaining bound were counted and expressed as % cells bound. Panels (A) and (C) show neutrophils rolling at average velocities of 5μm/s and 6.5μm/s respectively on low density (50 sites /μm^2) membrane P-selectin. Panels (B) and (D) show neutrophils rolling at an average velocity of 1μm/s on high density P-selectin (380 sites/μm^2).

[0034] Figure 7 is a sensogram showing kinetics for G1 and hSel001 binding to P-selectin at a single P-selectin concentration.

DETAILED DESCRIPTION

[0035] Before explaining at least one embodiment of the presently disclosed inventive concepts in detail by way of exemplary drawings, experimentation, results, and laboratory procedures, it is to be understood that the inventive concepts are not limited in their application to the details of construction and the arrangement of the components set forth in the following description or illustrated in the drawings, experimentation and/or results. The inventive concepts are capable of other embodiments or of being practiced or carried out in various ways. As such, the language used herein is intended to be given the broadest possible scope and meaning; and the embodiments are meant to be exemplary - not exhaustive. Also, it is to be understood that the phraseology and terminology employed herein is for the purpose of description and should not be regarded as limiting.

[0036] Unless otherwise defined herein, scientific and technical terms used in connection with the presently disclosed inventive concepts shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g., Sambrook et al. Molecular Cloning: A Laboratory Manual (2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989) and Coligan et al. Current Protocols in Immunology (Current Protocols, Wiley Interscience (1994)), which are incorporated herein by reference. The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0037] All publications and patent applications mentioned in the specification are indicative of the level of skill of those skilled in the art to which the presently disclosed inventive concepts pertain. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

[0038] All of the compositions and/or methods disclosed and claimed herein can be made and executed without undue experimentation in light of the present disclosure. While the compositions and methods of the presently disclosed inventive concepts have been described in terms of preferred embodiments, it will be apparent to those of skill in the art that variations may be applied to the compositions and/or methods and in the steps or in the sequence of steps of the method described herein without departing from the concept, spirit and scope of the inventive concepts. All such similar substitutes and modifications apparent to those skilled in the art are deemed to be within the spirit, scope and concept of the inventive concepts as defined by the appended claims.

[0039] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0040] The use of the word "a" or "an" when used in conjunction with the term "comprising" in the claims and/or the specification may mean "one," but it is also consistent with the meaning of "one or more," "at least one," and "one or more than one." The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or." Throughout this application, the term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value, or the variation that exists among the study subjects. The use of the term "at least one" will be understood to include one as well as any quantity more than one, including but not limited to, 2, 3, 4, 5, 10, 15, 20, 30, 40, 50, 100, etc. The term "at least one" may extend up to 100 or 1000 or more, depending on the term to which it is attached; in addition, the quantities of 100/1000 are not to be considered limiting, as higher limits may also produce satisfactory results.

[0041] The term "about" is used to indicate that a value includes the inherent variation of error for the device, the method being employed to determine the value and/or the variation that exists among study subjects.

[0042] As used in this specification and claims, the words "comprising" (and any form of comprising, such as "comprise" and "comprises"), "having" (and any form of having, such as "have" and "has"), "including" (and any form of including, such as "includes" and "include") or "containing" (and any form of containing, such as "contains" and "contain") are inclusive or open-ended and do not exclude additional, unrecited elements or method steps.

[0043] The term "or combinations thereof" as used herein refers to all permutations and combinations of the listed items preceding the term. For example, "A, B, C, or combinations thereof" is intended to include at least one of: A, B, C, AB, AC, BC, or ABC, and if order is important in a particular context, also BA, CA, CB, CBA, BCA, ACB, BAC, or CAB. Continuing with this example, expressly included are combinations that contain repeats of one or more item or term, such as BB, AAA, MB, BBC, AAABCCCC, CBBAAA, CABABB, and so forth. The skilled artisan will understand that typically there is no limit on the number of items or terms in any combination, unless otherwise apparent from the context.

[0044] The terms "peptide", "polypeptide" and "protein" are used herein to refer to a polymer of amino acid residues. The term "polypeptide" as used herein is a generic term to refer to native protein, protein fragments, or analogs of a polypeptide sequence. Hence, native protein, protein fragments, and analogs are species of the polypeptide genus. The term "isolated peptide/polypeptide/protein" as used herein refers to a peptide/polypeptide/protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated peptide/polypeptide/protein": (1) is not associated with peptides/polypeptides/proteins found in nature, (2) is free of other peptides/polypeptides/proteins from the same source, e.g., free of murine proteins, (3) is expressed by a cell from a different species, and/or (4) does not occur in nature.

[0045] As used herein, the term "amino acid" embraces all molecules, whether natural or synthetic, which include both an amino functionality and an acid functionality and capable of being included in a polymer of naturally-occurring amino acids. Exemplary amino acids include naturally-occurring amino acids; analogs, derivatives and congeners thereof; amino acid analogs having variant side chains;

and all stereoisomers of any of any of the foregoing. Where used herein the term "mouse amino acid" refers to an amino acid residue which is found in mouse P-selectin but is not found in the corresponding position in human P-selectin. Where used herein the term "human amino acid" refers to an amino acid residue which is found in human P-selectin but is not found in the corresponding position in mouse P-selectin.

[0046] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See Immunology--A Synthesis (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland, Mass. (1991)), which is incorporated herein by reference. Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α,α-disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the presently disclosed and claimed inventive concept(s). Examples of unconventional amino acids include: 4-hydroxyproline, α-carboxyglutamate, ε-N,N,N-trimethyllysine, ε-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the lefthand direction is the amino terminal direction and the righthand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0047] The terms "polynucleotide", and "nucleic acid" are used interchangeably. They refer to a polymeric form of nucleotides of any length, either deoxyribonucleotides or ribonucleotides, or analogs thereof. The following are non-limiting examples of polynucleotides: coding or non-coding regions of a gene or gene fragment, loci (locus) defined from linkage analysis, exons, introns, messenger RNA (mRNA), transfer RNA, ribosomal RNA, ribozymes, cDNA, recombinant polynucleotides, branched polynucleotides, plasmids, vectors, isolated DNA of any sequence, isolated RNA of any sequence, nucleic acid probes, and primers. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and nucleotide analogs. If present, modifications to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified, such as by conjugation with a labeling component. The terms "isolated nucleic acid" and "isolated polynucleotide" are used interchangeably; a nucleic acid or polynucleotide is considered "isolated" if it: (1) is not associated with all or a portion

of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is linked to a polynucleotide to which it is not linked in nature, or (3) does not occur in nature as part of a larger sequence.

[0048] The term "vector," as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby be replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors").

[0049] The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polynucleotide or polypeptide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and which has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring. The term "naturally-occurring" may be used interchangeably herein with the term "native".

[0050] "Leukocyte rolling," as used herein, includes weak adhesion of leukocytes to endothelial cells of blood vessels and rolling of leukocytes along endothelial cells of blood vessels prior to firm adhesion and transmigration of leukocytes into endothelial tissue. Following leukocyte rolling, these adherent leukocytes can migrate through the endothelium and destroy ischemic tissue during reperfusion. Accordingly, reduction of leukocyte rolling results in a reduction of damage to tissues and organs caused by acute inflammatory responses.

[0051] As used herein, a "P-selectin antagonist" includes any agent which is capable of antagonizing P-selectin, e.g., by inhibiting interaction between P-selectin and a P-selectin glycoprotein ligand-1, e.g., by inhibiting interactions of P-selectin expressing endothelial cells and activated platelets with PSGL-1 expressing leukocytes.

[0052] The term "isolated" or "purified" refers to a molecule that is substantially free of its natural environment and is the predominant species present (e.g., on a molar basis) such as more than 50% of the composition. For instance, an isolated protein is substantially free of cellular material or other proteins from the cell or tissue source from which it was derived. The term also refers to preparations where the isolated protein is at least 60% (w/w) pure, or at least 70% (w/w) pure; or at least 75% (w/w) pure; or at least 80% (w/w) pure; or at least 85% (w/w) pure, or at least 90% (w/w) pure, or at least 92% (w/w) pure, or at least 95% (w/w) pure, or at least 96% (w/w) pure, or at least 97% (w/w) pure, or at least 98% (w/w) pure, or at least 99% (w/w) pure, or 100% (w/w) pure. In some embodiments, the isolated molecule is sufficiently pure for pharmaceutical compositions.

[0053] "Inhibitory" activity refers to a reduction in an activity of P-selectin by a P-selectin inhibitor (such as an antibody or fragment thereof), relative to the activity of P-selectin in the absence of the same inhibitor. A neutralizing antibody may reduce one or more P-selectin activities. For example, the reduction in activity (e.g., P-selectin binding to PSGL-1) is preferably at least about 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, or at least 95%, or higher. In another example, the dissociative activity of a dual function antibody or fragment (i.e., the percentage of preformed P-selectin/PSGL-1 complex which may be caused to dissociate) may be at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 75%, at least 80%, at least 85%, at least 90%, at least 95%, or higher.

[0054] The term "P-selectin inhibitor" when used herein includes any agent, such as, e.g., a neutralizing antibody, capable of inhibiting activity, expression, processing, binding, or cell surface localization of P-selectin. Such inhibitors are said to "inhibit," "neutralize," or "reduce" the biological activity of P-selectin.

[0055] The term "effective amount" refers to an amount of a biologically active molecule or conjugate or derivative thereof sufficient to exhibit a detectable therapeutic effect preferably without undue adverse side effects (such as toxicity, irritation and allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of the presently disclosed inventive concepts. The term "pharmaceutically acceptable" refers to compounds and compositions which are suitable for administration to humans and/or animals without undue adverse side effects such as toxicity, irritation and/or allergic response commensurate with a

reasonable benefit/risk ratio. The compounds of the presently disclosed inventive concepts may be designed to provide delayed, controlled or sustained release using formulation techniques which are well known in the art.

[0056] The term "epitope" refers to an antigenic determinant in a polypeptide that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. Epitopes may be either linear or conformational. A conformational epitope is produced by spatially juxtaposed amino acids from different segments of a linear polypeptide chain.

[0057] The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, generally being directed against a single epitopic site. Furthermore, in contrast to conventional polyclonal antibody preparations that typically include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant. In addition to their specificity, the monoclonal antibodies are advantageous in that, in one embodiment, they are synthesized by the hybridoma culture, uncontaminated by other immunoglobulins. The modifier "monoclonal" indicates the character of the antibody as being obtained from a substantially homogeneous population of antibodies, and is not to be construed as requiring production of the antibody by any particular method.

[0058] Antibodies

[0059] Antibody molecules belong to a family of plasma proteins called immunoglobulins, whose basic building block, the immunoglobulin fold or domain, is used in various forms in many molecules of the immune system and other biological recognition systems. A typical immunoglobulin has four polypeptide chains, containing an antigen binding region known as a variable region and a non-varying region known as the constant region.

[0060] Native antibodies and immunoglobulins are usually heterotetrameric glycoproteins of about 150,000 daltons, composed of two identical light (L) chains and two identical heavy (H) chains. Each light chain is linked to a heavy chain by one covalent disulfide bond, while the number of disulfide linkages varies between the heavy chains of different immunoglobulin isotypes. Each heavy and light chain also has regularly spaced intrachain disulfide bridges. Each heavy chain has at one end a

variable domain (VH) followed by a number of constant domains. Each light chain has a variable domain at one end (VL) and a constant domain at its other end. The constant domain of the light chain is aligned with the first constant domain of the heavy chain, and the light chain variable domain is aligned with the variable domain of the heavy chain.

[0061] Depending on the amino acid sequences of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are at least five major classes of immunoglobulins: IgA, IgD, IgE, IgG and IgM, and several of these may be further divided into subclasses (isotypes), e.g. IgG_1, IgG_2, IgG_3 and IgG_4 and IgA_1 and IgA_2. The constant domains of the heavy chains that correspond to the different classes of immunoglobulins are called alpha (α), delta (δ), epsilon (ε), gamma (γ) and mu (μ), respectively. The light chains of antibodies can be assigned to one of two clearly distinct types, called kappa (κ) and lambda (λ), based on the amino sequences of their constant domain. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known.

[0062] The term "variable" in the context of variable domain of antibodies, refers to the fact that certain portions of the variable domains differ extensively in sequence among antibodies. The variable domains are for binding and determine the specificity of each particular antibody for its particular antigen. However, the variability is not evenly distributed through the variable domains of antibodies. It is concentrated in three segments per chain called complementarity determining regions (CDRs), also known as hypervariable regions, both in the light chain and the heavy chain variable domains. In most instances, three CDRs are present in a light chain variable region (CDRL1, CDRL2 and CDRL3) and three CDRs are present in a heavy chain variable region (CDRH1, CDRH2 and CDRH3). CDRs contribute to the functional activity of an antibody molecule and are separated by amino acid sequences that comprise scaffolding or framework regions. Among the various CDRs, the CDR3 sequences, and particularly CDRH3, are the most diverse and therefore have the strongest contribution to antibody specificity. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al., Sequences of Proteins of Immunological Interest (National Institute of Health, Bethesda, Md. (1987), incorporated by reference in its entirety); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Chothia et al., Nature, 342:877 (1989), incorporated by reference in its entirety).

[0063] The more highly conserved portions of variable domains are called the framework (FR). The variable domains of native heavy and light chains each comprise four FR regions, largely adopting a β-sheet configuration, connected by three CDRs, which form loops connecting, and in some cases forming part of, the β-sheet structure. The CDRs in each light and heavy chain are held together in close proximity by the FR regions and contribute to the formation of the antigen-binding site of the antibody. The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody-dependent cellular toxicity.

[0064] An antibody of the presently disclosed inventive concepts thus can be in any of a variety of forms, including a whole immunoglobulin, an antibody fragment such as Fv, Fab, and similar fragments, a single chain antibody which includes the variable domain complementarity determining regions (CDRs), and the like forms, all of which fall under the broad term "antibody", as used herein. In preferred embodiments, in the context of both the therapeutic and screening methods described below, an antibody or fragment thereof is used that is immuno-specific for an antigen or epitope of the presently disclosed inventive concepts as described herein.

[0065] The term "antibody fragment" as used herein refers to a portion of a full-length antibody, generally the antigen binding or variable region. Examples of antibody fragments include Fab, Fab', $F(ab')_2$ and Fv fragments. Papain digestion of antibodies produces two identical antigen binding fragments, called the Fab fragment, each with a single antigen binding site, and a residual "Fc" fragment, so-called for its ability to crystallize readily. Pepsin treatment yields an $F(ab')_2$ fragment that has two antigen binding fragments that are capable of cross-linking antigen, and a residual other fragment (which is termed pFc'). Additional fragments can include diabodies, linear antibodies, single-chain antibody molecules, and multispecific antibodies formed from anti-body fragments. As used herein, "functional fragment" with respect to antibodies, refers to Fv, F(ab) and $F(ab')_2$ fragments. Fragments of the antibodies of the presently disclosed inventive concepts may be as small as about 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, or 30 to 35, to 40, to 45, to 50, to 75, to 100, or to 150 to 200 to 250 (all inclusive) or more amino acids, for example.

[0066] Some types of antibody fragments are defined as follows:

[0067] Fab is the fragment that contains a monovalent antigen-binding fragment of an antibody molecule. A Fab fragment can be produced by digestion of whole antibody with the enzyme papain to yield an intact light chain and a portion of one heavy chain.

[0068] Fab' is the fragment of an antibody molecule can be obtained by treating whole antibody with pepsin, followed by reduction, to yield an intact light chain and a portion of the heavy chain. Two Fab' fragments are obtained per antibody molecule.

[0069] Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxyl terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge region.

[0070] $(Fab')_2$ is the fragment of an antibody that can be obtained by treating whole antibody with the enzyme pepsin without subsequent reduction. $F(ab')_2$ is a dimer of two Fab' fragments held together by two disulfide bonds.

[0071] Fv is the minimum antibody fragment that contains a complete antigen recognition and binding site. This region consists of a dimer of one heavy and one light chain variable domain in a tight, non-covalent association (VH-VL dimer). It is in this configuration that the three CDRs of each variable domain interact to define an antigen binding site on the surface of the VH-VL dimer. Collectively, the six CDRs confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

[0072] A single chain antibody (SCA) is defined herein as a genetically engineered molecule containing the variable region of the light chain, the variable region of the heavy chain, linked by a suitable polypeptide linker as a genetically fused single chain molecule. Such single chain antibodies are also referred to as "single-chain Fv" or "sFv" or "scFv" antibody fragments. Generally, the Fv polypeptide further comprises a polypeptide linker between the VH and VL domains that enables the sFv to form the desired structure for antigen binding.

[0073] The presently disclosed inventive concepts in one embodiment are directed to antibodies that specifically bind to human P-selectin. CDRs in such antibodies are not limited to the specific sequences of VH and VL and may include variants of these sequences that retain the ability to block and dissociate P-selectin binding to PSGL-1. Such variants may be produced by a skilled artisan using techniques well known in the art. For example, amino acid substitutions, deletions, or

additions, can be made in the FRs and/or in the CDRs as described elsewhere herein. While changes in the FRs are usually designed to improve stability and decrease immunogenicity of the antibody, changes in the CDRs are typically designed to increase affinity of the antibody for its target. Variants of FRs also include naturally occurring immunoglobulin allotypes. Such affinity-increasing changes may be determined empirically by routine techniques that involve altering the CDR and testing the affinity antibody for its target.

[0074] For example, conservative amino acid substitutions can be made within any one of the disclosed CDRs. Various alterations can be made according to methods well known to those skilled in the art (78). These include but are not limited to nucleotide sequences that are altered by the substitution of different codons that encode an identical or a functionally equivalent amino acid residue ("conservative substitutions") within the sequence, thus producing a "silent" change. For example, the nonpolar amino acids which may be conservatively substituted for each other include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan, and methionine. The polar neutral amino acids which may be conservatively substituted for each other include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids which may be conservatively substituted for each other include arginine, lysine, and histidine. The negatively charged (acidic) amino acids which may be conservatively substituted for each other include aspartic acid and glutamic acid. Substitutes for an amino acid within the sequence may also be selected from other members of the class to which the amino acid belongs.

[0075] Derivatives and analogs of antibodies of the presently disclosed inventive concepts can be produced by various techniques well known in the art, including recombinant and synthetic methods (79, 80). Antibodies in which CDR sequences differ only insubstantially and conservatively from those of the variable regions of anti-P-selectin antibodies such as hSel001, discussed in further detail below, are also encompassed within the scope of this invention. As noted above, typically, an amino acid is substituted by a related amino acid having similar charge, hydrophobic, or stereochemical characteristics. Such substitutions would be within the ordinary skills of an artisan. Further, a skilled artisan would appreciate that changes can be made in FRs without adversely affecting the binding properties of an antibody. Changes to FRs include, but are not limited to, humanizing a non-human derived or engineering certain framework residues that are important for antigen contact or for stabilizing

the binding site, e.g., changing the class or subclass of the constant region, changing specific amino acid residues which might alter the effector function such as Fc receptor binding.

[0076] The presently disclosed inventive concepts in one embodiment are directed to antibodies that specifically bind to P-selectin wherein the CDRs of a parental nonhuman antibody are grafted into FRs of human acceptor antibodies, a process called antibody humanization. The humanization process is designed to reduce the immunogenicity of a nonhuman antibody while maintaining as much of the original affinity as possible. In one embodiment, the human heavy and/or light chain acceptor FRs are unmutated amino acid sequences of the germline sequences from which they were derived. Such germline FRs would be expected to be nonimmunogenic considering that these sequences are present in all humans prior to antibody rearrangement and affinity maturation. Furthermore, amino acid residues of such antibody FRs, particularly residues adjacent to or positioned near the CDRs, may require amino acid substitutions to better preserve the antibody binding affinity. For example, when key amino acids differ between a parental murine monoclonal antibody variable FR and the human variable FR acceptor, the human FR amino acids may be substituted by the mouse amino acid residues at those positions. Nonetheless, it is anticipated that the FRs of the heavy and/or light chain may contain no amino acid substitutions and antibodies derived from such humanization may still possess much of if not all the binding affinity of the parental antibody. Further, antibodies of the invention may contain human VH and/or VL FRs that are of purely germline sequence and also lack substitutions in one or both of these FR sequences.

[0077] As used herein, the "affinity" of the antibody for P-selectin or the conformational epitope thereof is characterized by its K_d, or dissociation constant. A stronger affinity is represented by a lower K_d while a weaker affinity is represented by a higher K_d. As such, an antibody of the present invention preferably has an affinity for a P-selectin conformational epitope represented by a $K_d \leq 1000$nM, or ≤ 500nM, or ≤ 100nM, or ≤ 50nM, or more preferably by a $K_d \leq 25$nM, and still more preferably by a $K_d \leq 10$nM, and even more preferably by a $K_d \leq 5$nM, or ≤ 1nM, or ≤ 0.1nM.

[0078] An antibody or antibody fragment "homolog," as used herein, means that a relevant amino acid sequence (preferably for example in the CDRs and/or variable domains VH and/or VL) of a protein or a peptide is at least 50% identical, at least 60% identical, at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 91% identical, at

least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical, at least 99.5% identical, or 100% identical to a given sequence. By way of example, such sequences may be variants derived from various species, or the homologous sequence may be recombinantly produced. The sequence may be derived from the given sequence by truncation, deletion, amino acid substitution, or addition. Percent identity between two amino acid sequences is determined by standard alignment algorithms such as, for example, Basic Local Alignment Tool (BLAST) and other alignment algorithms and methods of the art (81-84).

[0079] The preparation of monoclonal antibodies is conventional and well known to persons of ordinary skill in the art. Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. In an alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal anti-P-selectin antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the conformational epitopes described herein respectively to thereby isolate immunoglobulin library members that bind P-selectin in accordance with the present invention. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurJZAP™. Phage Display Kit, Catalog No. 240612).

[0080] Methods of *in vitro* and *in vivo* manipulation of monoclonal antibodies are well known to those skilled in the art. For example, the monoclonal antibodies to be used in accordance with the present invention may be made by the hybridoma method first described by Kohler and Milstein (85), or may be made by recombinant methods, e.g., as described in U.S. Pat. No. 4,816,567, for example.

[0081] Another method involves humanizing a monoclonal antibody by recombinant means to generate antibodies containing, for example, human or primate specific and recognizable sequences.

[0082] Methods of making antibodies of the presently disclosed inventive concepts which bind with high affinity to human P-selectin or to the conformational epitopes thereof as described herein may comprise transfecting a cell with a DNA construct, the construct comprising a DNA sequence encoding at least a portion of the neutralizing P-selectin specific antibodies of the invention, culturing the cell under

conditions such that the antibody protein is expressed by the cell, and isolating the antibody protein.

[0083] Preferably, the constant region has been modified to modulate (i.e. reduce or enhance) effector function as noted elsewhere as compared to the effector function of a wild-type immunoglobulin heavy chain Fc region. In various embodiments, the IgG constant region has reduced effector function, or alternatively it has increased effector fuction. Fc effector function includes, for example, antibody-dependent cellular cytotoxicity (ADCC), phagocytosis, complement-dependent cytotoxicity, and half-life or clearance rate function. The IgG amino acid sequence of the Fc domain can be altered to affect binding to Fc gamma receptors (and thus ADCC or phagocytosis functions), or to alter interaction with the complement system (complement-dependent cytotoxicity function).

[0084] In one embodiment, the antibody comprises a constant region or Fc portion that has low or no affinity for at least one Fc receptor. In an alternative embodiment, the second polypeptide has low or no affinity for complement protein C1q. In general, an effector function of an antibody can be altered by altering the affinity of the antibody for an effector molecule such as an Fc receptor. Binding affinity will generally be varied by modifying the effector molecule binding site. Disclosure of IgG modifications that alter interaction with effector molecules such as Fc receptors can be found for example in U.S. Patent Nos. 5,624,821 and 5,648,260.

[0085] Antibody proteins of the presently disclosed inventive concepts can be produced using techniques well known in the art. For example, the antibody proteins can be produced recombinantly in cells (79, 86).

[0086] For recombinant production, a polynucleotide sequence encoding the antibody protein is inserted into an appropriate expression vehicle, such as a vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. The expression vehicle is then transfected into a suitable target cell which will express the peptide. Transfection techniques known in the art include, but are not limited to, calcium phosphate precipitation (87) and electroporation (88). A variety of host-expression vector systems may be utilized to express the antibody proteins described herein preferably including eukaryotic cells.

[0087] The presently disclosed inventive concepts further provide isolated nucleic acids encoding the antibodies disclosed or otherwise enabled herein. The nucleic acids may comprise DNA or RNA and may be wholly or partially synthetic or recombinant. Reference to a nucleotide sequence as set out herein encompasses a

DNA molecule with the specified sequence, and encompasses a RNA molecule with the specified sequence in which U is substituted for T, unless context requires otherwise.

[0088] In another embodiment, the nucleic acid molecules which encode the antibodies of the presently disclosed inventive concepts also comprise nucleotide sequences that are, for example, at least 50% identical to the sequences disclosed herein. Also contemplated are embodiments in which a sequence is at least 60% identical, at least 70% identical, at least 75% identical, at least 80% identical, at least 85% identical, at least 90% identical, at least 91% identical, at least 92% identical, at least 93% identical, at least 94% identical, at least 95% identical, at least 96% identical, at least 97% identical, at least 98% identical, at least 99% identical, or at least 99.5% identical, to a sequence disclosed herein and/or which hybridize to a sequence of the presently disclosed inventive concepts under conditions of high or moderate stringency. The percent identity may be determined by visual inspection and mathematical calculation.

[0089] Stringency, including "high stringency," as used herein, includes conditions readily determined by the skilled artisan based on, for example, the length of the DNA. Generally, such conditions are defined as hybridization conditions of 50% formamide, 6xSSC at 42°C (or other similar hybridization solution, such as, e.g., Stark's solution, in 50% formamide at 42°C), and with washing at approximately 68°C with 0.2xSSC, 0.1% SDS. The skilled artisan will recognize that the temperature and wash solution salt concentration can be adjusted as necessary according to factors such as the length of the probe.

[0090] "Moderate stringency," as used herein, includes conditions that can be readily determined by those having ordinary skill in the art based on, for example, the length of the DNA. The basic conditions are set forth by Sambrook et al. (79) and include use of a prewashing solution for the nitrocellulose filters 5xSSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization conditions of 50% formamide, 6xSSC at 42°C (or other similar hybridization solution, such as Stark's solution, in 50% formamide at 42°C), and washing conditions of 60°C, 0.5xSSC, 0.1% SDS.

[0091] The monoclonal antibodies herein specifically include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as

well as fragments of such antibodies, so long as they exhibit the desired biological activity (U.S. Patent No. 4,816,567).

[0092] Methods of making antibody fragments are also known in the art (89) (incorporated herein by reference). Antibody fragments of the present invention can be prepared by proteolytic hydrolysis of the antibody or by expression in E. coli of DNA encoding the fragment. Antibody fragments, as noted above, can be obtained by pepsin or papain digestion of whole antibodies conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5S fragment denoted $F(ab')_2$. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5S Fab' monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab' fragments and an Fc fragment directly. These methods are described, for example, in U.S. Patent No. 4,036,945 and U.S. Patent No. 4,331,647, and references contained therein, which are hereby expressly incorporated in their entireties by reference.

[0093] Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical, or genetic techniques may also be used, so long as the fragments bind to the conformational epitope that is recognized by the intact antibody. For example, Fv fragments comprise an association of VH and VL chains. This association may be noncovalent or the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. Preferably, the Fv fragments comprise VH and VL chains connected by a peptide linker. These single-chain antigen binding proteins (sFv) are prepared by constructing a structural gene comprising DNA sequences encoding the VH and VL domains connected by an oligonucleotide. The structural gene is inserted into an expression vector, which is subsequently introduced into a host cell such as E. coli. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Another form of an antibody fragment is a peptide coding for a single CDR. CDR peptides ("minimal recognition units") are often involved in antigen recognition and binding. CDR peptides can be obtained by cloning or constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells.

[0094] The presently disclosed inventive concepts comprise engineered antibodies including fully human and humanized forms of non-human (e.g., primate or murine) antibodies. Such humanized antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$ or other antigen-binding subsequences of antibodies) that contain minimal sequences derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins in which residues from CDRs of the human acceptor antibody are replaced by residues from the donor antibody CDRs of a nonhuman species such as mouse, rat or rabbit having the desired specificity, affinity and capacity. An example of a humanized antibody of the presently disclosed inventive concepts is a humanized antibody comprising the CDRs of the G4 antibody and comprising human framework sequences which are homologous to the framework sequences of the G4 antibody.

[0095] In making an engineered antibody, a DNA sequence encoding an antibody molecule of the presently disclosed inventive concepts is prepared synthetically by established standard methods. For example, according to the phosphoamidine method, oligonucleotides are synthesized, e.g. in an automatic DNA synthesizer, purified, annealed, ligated and cloned in suitable vectors.

[0096] The DNA sequence may then be inserted into a recombinant expression vector, which may be any vector, which may conveniently be subjected to recombinant DNA procedures. The choice of vector will often depend on the host cell into which it is to be introduced. Thus, the vector may be an autonomously replicating vector, i.e., a vector that exists as an extrachromosomal entity, the replication of which is independent of chromosomal replication, e.g., a plasmid. Alternatively, the vector may be one which, when introduced into a host cell, is integrated into the host cell genome and replicated together with the chromosome(s) into which it has been integrated.

[0097] In the vector, the DNA sequence encoding the protein should be operably connected to a suitable promoter sequence. The promoter may be any DNA sequence, which shows transcriptional activity in the host cell of choice and may be derived from genes encoding proteins either homologous or heterologous to the host cell. Examples of suitable promoters for directing the transcription of the coding DNA sequence in mammalian cells include, but are not limited to, the LTR promoter, SV 40 promoter, the MT-1 (metallothionein gene) promoter or the adenovirus 2 major late promoter. A suitable promoter for use in insect cells is the polyhedrin promoter.

Suitable promoters for use in yeast host cells include promoters from yeast glycolytic genes or alcohol dehydrogenase genes or the TPI1 or ADH2-4c promoters. Suitable promoters for use in filamentous fungus host cells are, for instance, the ADH3 promoter or the tpiA promoter.

[0098] The DNA coding sequence may also be operably connected to a suitable terminator, such as the human growth hormone terminator or (for fungal hosts) the TPI1 or ADH3 promoters. The vector may further comprise elements such as polyadenylation signals (e.g. from SV 40 or title adenovirus 5 Elb region), transcriptional enhancer sequences (e.g. the SV 40 enhancer) and translational enhancer sequences (e.g., ones encoding adenovirus VA RNAs).

[0099] The recombinant expression vector may further comprise a DNA sequence enabling the vector to replicate in the host cell in question. An example of such a sequence (when the host cell is a mammalian cell) is the SV 40 origin of replication. The vector may also comprise a selectable marker, e.g. a gene the product of which complements a defect in the host cell, such as the gene coding for dihydrofolate reductase (DHFR) or one which confers resistance to a drug, e.g. neomycin, hydromycin or methotrexate.

[0100] The procedures used to ligate the DNA sequences coding the proteins, the promoter and the terminator, respectively, and to insert them into suitable vectors containing the information necessary for replication, are well known to persons skilled in the art.

[0101] To obtain recombinant proteins of the presently disclosed inventive concepts the coding DNA sequences may be usefully fused with a second peptide coding sequence and a protease cleavage site coding sequence, giving a DNA construct encoding the fusion protein, wherein the protease cleavage site coding sequence positioned between the HBP fragment and second peptide coding DNA, inserted into a recombinant expression vector, and expressed in recombinant host cells. In one embodiment, said second peptide selected from, but not limited by the group comprising glutathion-S-reductase, calf thymosin, bacterial thioredoxin or human ubiquitin natural or synthetic variants, or peptides thereof. In another embodiment, a peptide sequence comprising a protease cleavage site may be the Factor Xa, with the amino acid sequence IEGR, enterokinase, with the amino acid sequence DDDDK, thrombin, with the amino acid sequence LVPR/GS, or Acharombacter lyticus, with the amino acid sequence XKX, cleavage site.

[0102] The host cell into which the expression vector is introduced may be any

cell which is capable of expression of the peptides or full-length proteins, and is preferably a eukaryotic cell, such as invertebrate (insect) cells or vertebrate cells, e.g. Xenopus laevis oocytes or mammalian cells, in particular insect and mammalian cells. Examples of suitable mammalian cell lines include, but are not limited to, the HEk293 (ATCC CRL-1573), COS (ATCC CRL-1650), BHK (ATCC CRL-1632, ATCC CCL-10) or CHO (ATCC CCL-61) cell lines. Methods of transfecting mammalian cells and expressing DNA sequences introduced in the cells are well known in the art.

[0103] Alternatively, fungal cells (including yeast cells) may be used as host cells. Examples of suitable yeast cells include cells of *Saccharomyces* spp. or *Schizosaccharomyces* spp., in particular strains of *Saccharomyces cerevisiae*. Examples of other fungal cells are cells of filamentous fungi, e.g. *Aspergillus* spp. or *Neurospora* spp., in particular strains of *Aspergillus oryzae* or *Aspergillus niger*. The use of *Aspergillus* spp. for the expression of proteins is described in, e.g., EP 238 023.

[0104] The medium used to culture the cells may be any conventional medium suitable for growing mammalian cells, such as a serum-containing or serum-free medium containing appropriate supplements, or a suitable medium for growing insect, yeast or fungal cells, or any cell used to express the proteins. Suitable media are available from commercial suppliers or may be prepared according to published recipes.

[0105] The proteins recombinantly produced by the cells may then be recovered from the culture medium by conventional procedures including separating the host cells from the medium by centrifugation or filtration, precipitating the proteinaceous components of the supernatant or filtrate by means of a salt, e.g. ammonium sulphate, purification by a variety of chromatographic procedures, e.g. HPLC, ion exchange chromatography, affinity chromatography, or the like.

[0106] Once the antibodies have been obtained, for example once individual B cells have been identified and/or monoclonal antibodies have been produced, the sequences encoding the variable regions of these antibodies can be obtained. The variable region sequences can for example be obtained by first sequencing the antibody protein produced by the hybridoma, B-cell or phage and determining the encoding nucleic acid sequence. In one embodiment, the immunoglobulin variable region (VH and VL) DNA or cDNA may be sequenced instead. Where the antibody is derived from a hybridoma cell line or isolated B-cell, the cDNAs encoding the variable regions may be amplified using PCR by for example the methods described in Babcook et al. (Proc. Natl. Acad. Sci. USA, 93:7843-7848 (1996)), and in PCT

Publication No. WO 92/02551. The contents of both references are expressly incorporated herein by reference in their entirety.

[0107] A "chimeric" antibody refers to an antibody made up of components from at least two different sources. In certain embodiments, a chimeric antibody comprises a portion of an antibody derived from a first species fused to another molecule, e.g., a portion of an antibody derived from a second species. In certain such embodiments, a chimeric antibody comprises a portion of an antibody derived from a non-human animal fused to a portion of an antibody derived from a human. In certain such embodiments, a chimeric antibody comprises all or a portion of a variable region of an antibody derived from one animal fused to a portion of an antibody from a second animal. For example but not by way of limitation, a chimeric antibody may comprise all or portion of a variable region of an antibody derived from a non-human animal fused to a constant region of an antibody derived from a human.

[0108] Utilization of the monoclonal antibodies of the presently disclosed inventive concepts may require administration thereof to a subject, such as but not limited to, a human. However, when the monoclonal antibodies are produced in a non-human animal, such as a rodent, administration of such antibodies to a human patient will normally elicit an immune response, wherein the immune response is directed towards the sequence of the antibodies. Such reactions limit the duration and effectiveness of such a therapy. In order to overcome such problem, the monoclonal antibodies of the presently disclosed inventive concepts are "humanized", that is, the antibodies are engineered such that one or more antigenic portions thereof are removed and like portions of a human antibody are substituted therefore, while the antibodies' affinity for the desired epitope is retained. This engineering may only involve a few amino acids, or may include entire framework regions of the antibody, leaving only the complementarity determining regions of the antibody intact. Several methods of humanizing antibodies are known in the art and are disclosed in US Patent Nos. 6,180,370, issued to Queen et al. on January 30, 2001; 6,054,927, issued to Brickell on April 25, 2000; 5,869,619, issued to Studnicka on February 9, 1999; 5,861,155, issued to Lin on January 19, 1999; 5,712,120, issued to Rodriquez et al. on January 27, 1998; and 4,816,567, issued to Cabilly et al. on March 28, 1989, the Specifications of which are all hereby expressly incorporated herein by reference in their entirety.

[0109] As mentioned above, a "humanized" antibody refers to a non-human antibody that has been modified so that it more closely matches (in amino acid

sequence) a human antibody. As described above, antibodies interact with target antigens predominantly through amino acid residues that are located in the heavy and light chain complementarity determining regions (CDRs). For this reason, the amino acid sequences within CDRs may be more diverse between individual antibodies than sequences outside of CDRs. Because CDR sequences are responsible for most antibody-antigen interactions, it is possible to express recombinant antibodies that mimic the properties of specific, naturally occurring antibodies by constructing expression vectors in which the CDR sequences from the naturally occurring antibody are grafted into framework sequences from a different antibody with different properties, such as human antibody framework regions. Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences for human heavy and light chain variable region genes can be found in the "VBase" human germline sequence database (available on the Internet at mrc-cpe.cam.ac.uk/vbase), as well as in Kabat, E. A., et al. (1991) Sequences of Proteins of Immunological Interest, Fifth Edition, U.S. Department of Health and Human Services, NIH Publication No. 91-3242; Tomlinson, I. M., et al. (1992) "The Repertoire of Human Germline VH Sequences Reveals about Fifty Groups of VH Segments with Different Hypervariable Loops" J. Mol. Biol. 227:776-798; and Cox, J. P. L. et al. (1994) "A Directory of Human Germ-line VH Segments Reveals a Strong Bias in their Usage" Eur. J. Immunol. 24:827-836; the contents of each of which are expressly incorporated herein by reference.

[0110] Humanized forms of antibodies are immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', $F(ab')_2$, or other antigen-binding subsequences of antibodies) that are principally comprised of the sequence of a human immunoglobulin, and contain minimal sequence derived from a non-human immunoglobulin. Humanization can be performed following the method of Winter and co-workers (Jones et al., 1986; Riechmann et al., 1988; Verhoeyen et al., 1988), by substituting rodent CDR sequences for the corresponding sequences of a human antibody. (See also U.S. Patent No. 5,225,539.) In some instances, F_v framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies can also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions

correspond to those of a non-human immunoglobulin and all or substantially all of the framework regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin (Jones et al., 1986; Riechmann et al., 1988; and Presta, 1992).

[0111] The presently disclosed inventive concepts further include the use of fully human monoclonal antibodies. Fully human antibodies essentially relate to antibody molecules in which the entire sequence of both the light chain and the heavy chain, including the CDRs, arise from human genes. Such antibodies are termed "human antibodies" or "fully human antibodies" herein. "Human antibodies" contain human antibody sequences and do not contain antibody sequences from a non-human animal. In certain embodiments, a human antibody may further contain synthetic sequences not found in native antibodies. The term is not limited by the manner in which the antibodies are made.

[0112] Human monoclonal antibodies may be prepared by the trioma technique; the human B-cell hybridoma technique (see Kozbor et al., Hybridoma, 2:7 (1983)) and the EBV hybridoma technique to produce human monoclonal antibodies (see Cole et al., PNAS, 82:859 (1985)). Human monoclonal antibodies may be utilized in the practice of the presently disclosed and claimed inventive concept(s) and may be produced by using human hybridomas (see Cote et al. PNAS, 80:2026 (1983)) or by transforming human B-cells with Epstein Barr Virus in vitro (see Cole et al., 1985).

[0113] In addition, human antibodies can be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example but not by way of limitation, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in Marks et al., J Biol. Chem., 267:16007 (1992); Lonberg et al., Nature, 368:856 (1994); Morrison, 1994; Fishwild et al., Nature Biotechnol., 14:845 (1996); Neuberger, Nat. Biotechnol., 14:826 (1996); and Lonberg and Huszar, Int Rev Immunol., 13:65 (1995).

[0114] Human antibodies may additionally be produced using transgenic nonhuman animals which are modified so as to produce fully human antibodies rather than the animal's endogenous antibodies in response to challenge by an antigen. (See

PCT Publication No. WO 94/02602). The endogenous genes encoding the heavy and light immunoglobulin chains in the nonhuman host have been incapacitated, and active loci encoding human heavy and light chain immunoglobulins are inserted into the host's genome. The human genes are incorporated, for example, using yeast artificial chromosomes containing the requisite human DNA segments. An animal which provides all the desired modifications is then obtained as progeny by crossbreeding intermediate transgenic animals containing fewer than the full complement of the modifications. One embodiment of such a nonhuman animal is a mouse, and is termed the XENOMOUSE™ as disclosed in PCT Publication Nos. WO 96/33735 and WO 96/34096. This animal produces B cells which secrete fully human immunoglobulins. The antibodies can be obtained directly from the animal after immunization with an immunogen of interest, as, for example, a preparation of a polyclonal antibody, or alternatively from immortalized B cells derived from the animal, such as hybridomas producing monoclonal antibodies. Additionally, the genes encoding the immunoglobulins with human variable regions can be recovered and expressed to obtain the antibodies directly, or can be further modified to obtain analogs of antibodies such as, for example, single chain Fv molecules.

[0115] An example of a method of producing a nonhuman host, exemplified as a mouse, lacking expression of an endogenous immunoglobulin heavy chain is disclosed in U.S. Patent No. 5,939,598, issued to Kucherlapati et al. on August 17, 1999, and incorporated herein by reference. It can be obtained by a method including deleting the J segment genes from at least one endogenous heavy chain locus in an embryonic stem cell to prevent rearrangement of the locus and to prevent formation of a transcript of a rearranged immunoglobulin heavy chain locus, the deletion being effected by a targeting vector containing a gene encoding a selectable marker; and producing from the embryonic stem cell a transgenic mouse whose somatic and germ cells contain the gene encoding the selectable marker.

[0116] A method for producing an antibody of interest, such as a human antibody, is disclosed in U.S. Patent No. 5,916,771, issued to Hori et al. on June 29, 1999, and incorporated herein by reference. It includes introducing an expression vector that contains a nucleotide sequence encoding a heavy chain into one mammalian host cell in culture, introducing an expression vector containing a nucleotide sequence encoding a light chain into another mammalian host cell, and fusing the two cells to form a hybrid cell. The hybrid cell expresses an antibody containing the heavy chain and the light chain.

[0117] The term "neutralizing antibody" or "antibody that neutralizes" refers to an antibody that reduces at least one activity of a polypeptide comprising the epitope to which the antibody specifically binds. In certain embodiments, a neutralizing antibody reduces an activity in vitro and/or in vivo. The term "antigen-binding site" refers to a portion of an antibody capable of specifically binding an antigen. In certain embodiments, an antigen-binding site is provided by one or more antibody variable regions.

[0118] The antibodies of the present invention preferably include one or more modifications which inactivate complement. The term "complement activity" broadly encompasses the biochemical and physiological activities associated with activation of the complement system, individual complement pathway associated molecules, as well as genes encoding these molecules. Therefore, complement activities include, e.g., structure and expression of a gene encoding a complement pathway molecule, biochemical activity (e.g., enzymatic or regulatory) of a complement pathway molecule, cellular activities that initiate or result from activation of the complement system, and presence of serum autoantibodies against complement pathway molecules. In the hSel001 antibody the preferred modification to inactivate complement is a replacement of a lysine residue with alanine at position 342 in the heavy chain constant region CH2. Other substitutions at the same position may include for example any of gly, leu, trp, tyr, pro, thr, ser, met, asp, asn, glu, gln, phe, ile, val, thr, and cys with the proviso that the substitution is also effective in eliminating the ability of the constant region to activate complement.

[0119] The terms "complement pathway associated molecules," "complement pathway molecules," and "complement pathway associated proteins" are used interchangeably and refer to the various molecules that play a role in complement activation and the downstream cellular activities mediated by, responsive to, or triggered by the activated complement system. They include initiators of complement pathways (i.e., molecules that directly or indirectly triggers the activation of complement system), molecules that are produced or play a role during complement activation (e.g., complement proteins/enzymes such as C3, C5, C5b-9, Factor B, MASP-1, and MASP-2), complement receptors or inhibitors (e.g., clusterin, vitronectin, CR1, or CD59), and molecules regulated or triggered by the activated complement system (e.g., membrane attack complex-inhibitory factor, MACIF). Thus, in addition to complement proteins noted above, complement pathway associated molecules also include, e.g., C3/C5 convertase regulators (RCA) such as

complement receptor type 1 (also termed CR1 or CD35), complement receptor type 2 (also termed CR2 or CD21), membrane cofactor protein (MCP or CD46), and C4bBP; MAC regulators such as vitronectin, clusterin (also termed "SP40,40"), CRP, CD59, and homologous restriction factor (HRF); immunoglobulin chains such as Ig kappa, Ig lambda, or Ig gamma; C1 inhibitor; and other proteins such as CR3, CR4 (CD11b/18), and DAF (CD55).

[0120] Dual Function Anti-P-selectin Antibodies

[0121] The presently disclosed inventive concepts are directed to "dual function" antibodies and fragments thereof which bind specifically to P-selectin and not only block the binding of PSGL-1 to P-selectin, but also dissociate preformed P-selectin/PSGL-1 complexes. The present disclosure describes a heretofore unrecognized antibody binding domain (a conformational epitope) within the lectin domain (e.g., carbohydrate recognition domain, CRD) of P-selectin to which the dual function antibodies (which may be chimeric, human or humanized antibodies, or fragments thereof for example) bind. The presently disclosed inventive concepts are also directed to anti-P-selectin antibodies which bind to the conformational epitope described herein and which have a dual function in (1) blocking binding of PSGL-1 to P-selectin and (2) causing dissociation of preformed P-selectin/PSGL-1 complexes. The presently disclosed inventive concepts in particular are directed to using such dual function anti-P-selectin antibodies or antibody fragments thereof in treatments of inflammatory, thrombotic or other conditions or disorders in primates (including humans) which involve platelet, sickled red cell, leukocyte, lymphocyte, and/or endothelial cell adhesion, wherein the condition or disorder comprises or is associated with (but not limited to) at least one of sickle cell vasoocclusive pain crisis, inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis, and enteritis), arthritis (e.g., rheumatoid arthritis, osteoarthritis, and psoriatic arthritis), graft rejection, graft versus host disease, asthma, chronic obstructive pulmonary disease, psoriasis, dermatitis, sepsis, nephritis, lupus erythematosis, scleroderma, rhinitis, anaphylaxis, diabetes, multiple sclerosis, atherosclerosis, thrombosis, tumor metastasis, allergic reactions, thyroiditis, ischemic reperfusion injury (e.g., due to myocardial infarction, stroke, or organ transplantation), and conditions associated with extensive trauma, or chronic inflammation, such as for example, type IV delayed hypersensitivity, associated for example with infection by Tubercle bacilli, or systematic inflammatory response syndrome, or multiple organ failure.

[0122] Importantly, the use of such dual function antibodies in treating these

inflammatory diseases will allow not only the prevention, reduction, or inhibition of inflammation, but will also provide a mechanism to treat ongoing inflammatory disease processes in that the antibodies can dissociate preformed P-selectin/PSGL-1. For example, in the case of sickle cell vasoocclusive pain crisis, the dual function antibody is able to not only prevent future vasoocclusive events, but can also be used in the treatment of ongoing vasoocclusion. The presently disclosed inventive concepts are also directed to screening assays for the detection of anti-P-selectin antibodies which bind to the conformational epitope of P-selectin newly described here, and which not only block binding of PSGL-1 to P-selectin but also cause reversal of the binding of PSGL-1 to P-selectin (i.e., dissociation of the preformed complex).

[0123] As noted herein, the presently disclosed inventive concepts are directed to purified antibodies (including but not limited to chimeric, human, or humanized antibodies and fragments thereof), which recognize (i.e., bind to) P-selectin (SEQ ID NO:1) and which block binding of P-selectin to PSGL-1 (or PSGL-1-like receptors) and further cause dissociation of preformed adhesions or cell complexes that were mediated through PSGL-1/P-selectin interactions, and therapeutic methods of using such antibodies (or binding fragments thereof)

[0124] More particularly, the presently disclosed inventive concepts are directed to purified antibodies (or fragments thereof), against P-selectin, host cells that produce such anti-P-selectin antibodies (or fragments thereof), screening assays to identify anti-P-selectin antibodies (or fragments thereof) which block leukocytes, sickled erythrocytes, lymphocyte, platelet and endothelial cell P-selectin-mediated adhesion and additionally cause dissociation of preformed adhesions or cell complexes that were mediated through PSGL-1/P-selectin interactions, and therapeutic methods using such antibodies (or binding fragments thereof). The presently disclosed inventive concepts include novel antibodies against primate (including human) P-selectin and binding fragments thereof, particularly including, but not limited to, G4, humanized forms of G4, and hSel001 antibodies. Preferred antibodies of the disclosure are capable of specifically binding primate (particularly human) P-selectin, and inhibiting one or more P-selectin activities in vitro and/or in vivo. Where used herein, the term "PSGL-1" is also intended to include "PSGL-1-like receptor" on sickled red cells (erythrocytes).

[0125] In general, an antibody or antibody fragment of the presently disclosed inventive concepts can have any upper size limit so long as it is has similar or immunological properties relative to antibody that binds with specificity to the P-

selectin-binding site described herein and which blocks binding of PSGL-1 to P-selectin and dissociates preformed P-selectin/PSGL-1 complexes. Where used herein the term "inclusive" is intended to refer to all integers between any two numbers listed herein.

[0126] As noted elsewhere herein, antibody fragments of the presently disclosed inventive concepts retain the ability to selectively bind to all of or a portion of the P-selectin binding epitope described herein. Preferably, an antibody or binding fragment of an antibody of the present invention is capable of binding to an epitope comprising one or more of amino acid residues 1-35, or, more particularly, 4-23, of the sequence set forth in SEQ ID NO:1.

[0127] As noted above, the antibodies or antibody fragments of the presently disclosed inventive concepts in preferred embodiments comprise immunoglobulins of the isotypes IgG_1, IgG_2, IgG_3, IgG_4 or IgG_2/G_4 chimeras, preferably binds to P-selectin with a high affinity (for example wherein the K_d is $\leq$ 1000nM) and preferably comprises a human constant region, and preferably inhibits binding of P-selectin to PSGL-1 and more preferably also caused reversal of binding of P-selectin to PSGL-1 in a preformed complex. Further, the anti-P-selectin antibody or binding fragment thereof preferably does not activate complement via the classical pathway by interacting with C1q and preferably does not bind Fc receptors, collectively called antibody effector function. The presently disclosed inventive concepts in particular are directed to using such dual function anti-P-selectin antibodies or antibody fragments as described and identified herein in treatments for inflammatory, thrombotic or other conditions or disorders in primates (including humans) which involve platelet, sickled red cell, leukocyte, lymphocyte, and/or endothelial cell adhesion, wherein the condition or disorder comprises or is associated with (but not limited to) at least one of sickle cell vasoocclusive pain crisis, inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis, and enteritis), arthritis (e.g., rheumatoid arthritis, osteoarthritis, and psoriatic arthritis), graft rejection, graft versus host disease, asthma, chronic obstructive pulmonary disease, psoriasis, dermatitis, sepsis, nephritis, lupus erythematosis, scleroderma, rhinitis, anaphylaxis, diabetes, multiple sclerosis, atherosclerosis, thrombosis, tumor metastasis, allergic reactions, thyroiditis, ischemic reperfusion injury (e.g., due to myocardial infarction, stroke, or organ transplantation), and conditions associated with extensive trauma, or chronic inflammation, such as for example, type IV delayed hypersensitivity, associated for example with infection by Tubercle bacilli, or systematic inflammatory response syndrome, or multiple organ failure.

[0128] As noted elsewhere herein, P-selectin plays a central role in recruitment of leukocytes and lymphocytes to inflammatory and thrombotic sites by binding to a surface ligand (PSGL-1) on these cells and in the binding of sickled red cells to endothelium having activated endothelial cells. PSGL-1 is constitutively expressed on leukocytes, including neutrophils and monocytes, and on some endothelial cells. A PSGL-1-like receptor is expressed on sickled red cells and enables these cells to bind P-selectin on activated endothelial cells.

[0129] Without wanting to be bound by theory, it is believed that the treatment of vasoocclusive sickle cell pain crisis, for example by the anti-P-selectin antibody of the present invention, is effective by inhibiting any one or more of the following interactions: (1) PSGL-1 on leukocytes binding to P-selectin on activated endothelium; (2) a PSGL-1-like ligand on sickled red cells binding to P-selectin on activated endothelium; (3) P-selectin on the surface of activated platelets binding PSGL-1 on endothelial cells; (4) sickled red cells binding leukocytes through an uncharacterized ligand-receptor interaction; (5) P-selectin on activated platelets binding the PSGL-1 like receptor on sickled red cells, and/or; (6) P-selectin on the surface of activated platelets binding PSGL-1 on leukocytes. It is believed that the dual function anti-P-selectin antibody blocks the initiation and propagation of vasoocclusion at multiple levels of cell-cell interactions in the microvasculature. Further, as noted elsewhere herein, the dual function anti-P-selectin antibody dissociates P-selectin/PSGL-1 complexes and thereby can be used therapeutically to intervene in ongoing vasoocclusion.

[0130] P-selectin mediates interactions of activated platelets or endothelial cells with blood cells including certain red blood cells (i.e. sickled red cells) and leukocytes including monocytes, neutrophils, eosinophils, $CD4^+$T cells, $CD8^+$T cells, B cells and natural killer (NK) cells. As noted herein, it is known that P-selectin is involved in a number of cellular responses to inflammation resulting from injury, infection, or physicochemical assaults. Atherosclerosis, characterized by atherosclerotic lesions on the inner surfaces of blood vessels, is one example of a condition involving the binding of certain leukocytes to P-selectin-bearing endothelial cells on the inner lining of blood vessel walls.

[0131] As indicated above, therapies directed to blocking P-selectin function, for example, using antibodies to P-selectin to prevent the tethering and rolling of leukocytes and adherence of red blood cells (i.e. sickled red cells), could have a profound effect on numerous types of inflammatory and thrombotic diseases. Given

its pivotal roll in the initiation of rolling and tethering of leukocytes to the endothelium and platelets, P-selectin is a primary target for therapeutic development to treat inflammatory and thrombotic disorders. For example, the transient nature of the acute phase of sickle cell anemia coupled with the recurrent chronic effects of organ damage and associated complications and morbidity suggests that a therapeutic intervention that exhibits both blocking initial adhesion due to binding of P-selectin and PSGL-1, and inducing dissociation of prior, ongoing or pre-established adhesion, would have novel application to this and other inflammatory and thrombotic diseases. The presently disclosed inventive concepts thus encompasses a method of using a conformational antibody binding epitope of P-selectin to screen for and identify "dual function" antibodies to P-selectin which not only block P-selectin-PSGL-1 binding, but which also cause dissociation of preformed P-selectin/PSGL-1 complex (and thus cell-cell complex), and the use of such antibodies for therapeutic treatment of diseases, such as, but not limited to, inflammatory and thrombotic diseases.

[0132] As noted above, novel conformational binding epitopes of P-selectin have been discovered as described herein. The discovery of these conformational binding epitopes have further led to the discovery of dual function anti-P-selectin antibodies (thus the antibodies may be referred to herein as "dual function" antibodies) which bind with high specificity to the conformational epitope and which not only block the binding of P-selectin and PSGL-1, but which also induce the dissociation of preformed P-selectin/PSGL-1 complexes (i.e., induce the reversal of P-selectin-PSGL-1 binding) thereby causing the dissociation of cell complexes such as leukocyte/endothelial cell, leukocyte/platelet, lymphocyte/endothelial cell, lymphocyte/platelet, sickled red cell/endothelial cell or sickled red cell/platelet complexes.

[0133] The binding regions for some antibodies to P-selectin have been previously mapped using constructs of large functional domains encompassing the lectin, epidermal growth factor (EGF) and consensus repeat (CR) regions of the native protein P-selectin in mouse and human (90, 70, 91-95). These results indicated the primary binding areas for some function-blocking antibodies to P-selectin were in the lectin binding domain, a region that spans amino acid residues 1-120 of the native P-selectin protein, or in the EGF domain spanning amino acids 121-154.

[0134] Examples are provided herein below. However, the presently disclosed inventive concepts are to be understood to not be limited in the applications in these specific experiments, results and laboratory procedures. Rather, the Examples are

simply provided as among various embodiments and are meant to be exemplary, not exhaustive.

[0135] The present disclosure describes the discovery of novel nonlinear (e.g., conformational) epitopes by using mouse/human chimeras containing the lectin, EGF, CR1 and CR2 domains of P-selectin that were probed with function-blocking test antibodies to P-selectin. Previous work has shown that, at a minimum, expression of the lectin and EGF domains are required for proper folding and conformation of P-selectin constructs (91). A comparison of the amino acid sequences of human and mouse P-selectin indicated that there is homology in the lectin domain with a specific number of amino acid residue differences between human and mouse. Herein, three-dimensional (3-D) homology was used to compare the human and mouse lectin, EGF, CR1 and CR2 domains of P-selectin (Fig. 1) to identify amino acid differences between human and mouse P-selectins (sequences and numbering according to the mature proteins).

[0136] The method used 3-D modeling of P-selectin to compare the positions of amino acid differences between human and mouse P-selectin on the exposed surface of the protein and to identify clusters of amino acid differences between human and mouse in the lectin and EGF domains which are located on the surface of the folded protein. This 3-D method represents clusters of amino acid differences which result from juxtaposition of discontinuous amino acids brought into proximity to one another by folding of the protein. For example, some amino acids will form conformational epitopes by virtue of being on the same surface, e.g. face, of helical structures. Homology comparison of such clusters allowed for selection of amino acid substitutions to test the effect of such changes on the binding of function-blocking (PSGL-1 blocking) antibodies to human P-selectin.

[0137] The method further involved mapping of conserved restriction sites in the open reading frames of the cDNA to identify a strategy for constructing chimeric proteins that span the lectin, EGF, CR1 and CR2 domains and would enable substitution of single or multiple amino acids at specific sites in the human or mouse P-selectin to identify those amino acids which optimize antibody binding to human P-selectin. Chimeras were constructed with known molecular cloning techniques, using human and mouse P-selectin N-terminal regions spanning the ATG through CR2 domain with a suitable vector such as pBluescript (pBS-hPsel and pBS-mPsel). The chimeras were inserted into another suitable vector such as pIG1 (pIG-hPsel and pIG-mPsel) where the constructs were fused to the Fc region of human IgG1 containing

the hinge, CH2 and CH3 region. These constructs preserved structures that are consistent with the native conformation of P-selectin. Thus domains that were exposed on the surface of the native protein were also present on the chimera constructs and thus served as putative epitopes for binding of test antibodies. Such constructs could be transfected and transiently expressed using molecular and cell expression techniques known to persons having ordinary skill in the art.

[0138] Using this method, test antibodies, can be evaluated for binding to the human/mouse chimeras using a method such as, but not limited to, fluorescence-activated cell sorting (FACS) and surface plasmon resonance (BIACORE) methods known to persons having ordinary skill in the art. The effects of changes in amino acids in various positions in the chimera constructs by substitution of mouse amino acids, for example, into the human sequence, conversely, or human amino acids into the mouse sequence, for example, that abrogated or enabled binding of antibodies directed to human P-selectin were evaluated and thus enabled identification of particular amino acids for optimal binding.

[0139] *Characterization of Chimera Constructs*

[0140] Amino acids of mouse P-selectin which have been substituted into the human P-selectin sequence are indicated in boldface in the chimeras described below. Amino acids of human P-selectin which have been substituted into the mouse sequence are indicated in italicized boldface. Substitution of glutamine for histidine is indicated as underlined boldface.

[0141] **Native Protein Constructs**

[0142] SEQ ID NO:1

[0143] Human P-selectin lectin, EGF, CR1, CR2 domains

```
1    WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61   TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121  SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181  FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
241  FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---
```

[0144] SEQ ID NO:2

[0145] Mouse P-selectin lectin, EGF, CR1, CR2 domains– Amino acid differences from human in boldface.

```
 42  WTY**N**YSTKAYSWN**N**SR**V**F**C**R**RH**F**T**DLVAIQNKNEI**A**HLN**D**V**I**P**FF**N**SYYWIGIRK**I**N**NK**W
102  TWVGI**N**K**T**LT**E**EAENWADNEPNNK**K**NN**Q**DCVEIYIKS**N**SAPGKWNDE**P**C**F**K**R**K**R**ALCYTA
162  SCQDMSCS**N**QGEC**I**ETIG**S**YTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS
```

222 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**QCLASGIWTN**N**PP**K**C**D**A**V**QC**Q**S**L**E**A**P**P**H**G**T**M**A**C**M**H**PIA**A

282 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**N**TLH**CT**G**SG**Q**W**SE**P**L**P**T**C**EAIA**

[0146] **Human/Mouse Chimera Constructs**

[0147] SEQ ID NO:3

[0148] *Chimera-1*

[0149] (mouse substitutions in human cluster A - $\mathbf{N_4N_{14}V_{17}F_{18}R_{20}R_{21}H_{22}F_{23}}$)

1 WTY**N**YSTKAYSWN**N**SR**VF**C**RRHF**TDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0150] SEQ ID NO:4

[0151] *Chimera-2*

[0152] (human cluster A to I_{35} - mouse thereafter)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEI**AH**LN**D**V**I**P**FFN**SYYWIGIRK**I**N**NK**W

61 TWVGT**N**K**T**LT**E**EAENWADNEPNNK**K**NN**Q**DCVEIYIKS**N**SAPGKWNDE**P**C**F**K**R**K**R**ALCYTA

121 SCQDMSCS**N**QGEC**I**ETIG**S**YTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS

181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**QCLASGIWTN**N**PP**K**C**D**A**V**QC**Q**S**L**E**A**P**P**H**G**T**M**A**C**M**H**PIA**A

241 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**N**TLH**CT**G**SG**Q**W**SE**P**L**P**T**C**EAIA**

[0153] SEQ ID NO:5

[0154] *Chimera-3*

[0155] (substitutions in human cluster A – to mouse $\mathbf{N_4N_{14}V_{17}F_{18}}$)

1 WTY**N**YSTKAYSWN**N**SR**VF**CQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0156] SEQ ID NO:6

[0157] *Chimera-4*

[0158] (substitutions in human cluster A – to mouse $\mathbf{R_{20}R_{21}H_{22}F_{23}}$)

1 WTYHYSTKAYSWNISRKYC**RRHF**TDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0159] SEQ ID NO:7

[0160] *Chimera-5*

[0161] (single amino acid change – human H_4 to mouse N_4)

1 WTY**N**YSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0162] SEQ ID NO:8

[0163] *Chimera-5Q*

[0164] (substitution of **Q** for H_4 in cluster A – removes putative glycosylation site)

1 WTY**Q**YSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0165] SEQ ID NO:9

[0166] *Chimera-6*

[0167] (human sequence to EGF – S_{121} – mouse EGF, CR1 and CR2)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCS**N**QGEC**I**ETIG**S**YTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS

181 FNSQC**T**FS**C**A**E**GY**ELD**GP**GE**L**Q**CLASGIWTN**N**PP**K**C**D**AV**Q**C**QS**L**EA**PP**H**GTM**A**C**MH**PIA**A

241 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**N**TLH**CT**G**SG**Q**W**SE**P**L**P**TCEAIA**

[0168] SEQ ID NO:10

[0169] *Chimera-7*

[0170] (human sequence to G_{177} – mouse thereafter)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLG**E**FS

181 FNSQC**T**FS**C**A**E**GY**ELD**GP**GE**L**Q**CLASGIWTN**N**PP**K**C**D**AV**Q**C**QS**L**EA**PP**H**GTM**A**C**MH**PIA**A

241 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**N**TLH**CT**G**SG**Q**W**SE**P**L**P**TCEAIA**

[0171] SEQ ID NO:11

[0172] *Chimera-7B*

[0173] (human sequence to end of EGF – V_{156} – mouse thereafter)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS
181 FNSQC**TFS**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTN**N**PP**K**C**D**AVQC**QS**L**EAPPH**GT**MA**C**MH**PIA**A
241 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**NTLH**CTGSGQWSEPLPTCEAIA**

[0174] SEQ ID NO:12

[0175] *Chimera-8*

[0176] (single amino acid change – human I_{14} to mouse $\mathbf{N}_{14}$)

1 WTYNYSTKAYSWN**N**SRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0177] SEQ ID NO:13

[0178] *Chimera-9*

[0179] (single amino acid change - human K_{17} to mouse $\mathbf{V}_{17}$)

1 WTYHYSTKAYSWNISR**V**YCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0180] SEQ ID NO:14

[0181] *Chimera-10*

[0182] (single amino acid change – human Y_{18} to mouse $\mathbf{F}_{18}$)

1 WTYHYSTKAYSWNISRK**F**CQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0183] SEQ ID NO:15

[0184] *Chimera-11*

[0185] (single amino acid change – human Q_{20} to mouse $\mathbf{R}_{20}$)

1 WTYHYSTKAYSWNISRKYC**R**NRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0186] SEQ ID NO:16

[0187] *Chimera-12*

[0188] (single amino acid change – human N_{21} to mouse $\mathbf{R}_{21}$)

1 WTYHYSTKAYSWNISRKYCQ**R**RYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0189] SEQ ID NO:17

[0190] *Chimera-13*

[0191] (single amino acid change – human R_{22} to mouse $\mathbf{H}_{22}$)

1 WTYHYSTKAYSWNISRKYCQN**H**YTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0192] SEQ ID NO:18

[0193] *Chimera-14*

[0194] (single amino acid change – human Y_{23} to mouse $\mathbf{F}_{23}$)

1 WTYHYSTKAYSWNISRKYCQNR**F**TDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

241 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0195] SEQ ID NO:19

[0196] *Chimera-15*

[0197] (human sequence to cluster C2 – S_{97} – mouse thereafter)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKS**N**SAPGKWNDE**P**C**F**K**R**K**R**ALCYTA

121 SCQDMSCS**N**QGEC**I**ETIG**S**YTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS

181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTN**NP**P**K**C**D**AVQC**QS**L**EA**PP**H**GT**M**A**C**M**H**P**IA**A

241 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**NTLH**CTG**SGQ**W**S**E**P**L**P**T**C**EAIA**

[0198] SEQ ID NO:20

[0199] *Chimera-16*

[0200] (substitution of human $H_4I_{14}K_{17}N_{21}R_{22}$ into mouse Cluster A)

1 WTY***H***YSTKAYSWN***I***SR***K***FCR***NR***FTDLVAIQNKNEIAHLNDVIPFFNSYYWIGIRKINNKW

61 TWVGTNKTLTEEAENWADNEPNNKKNNQDCVEIYIKSNSAPGKWNDEPCFKRKRALCYTA

121 SCQDMSCSNQGECIETIGSYTCSCYPGFYGPECEYVKECGKVNIPQHVLMNCSHPLGEFS

181 FNSQCTFSCAEGYELDGPGELQCLASGIWTNNPPKCDAVQCQSLEAPPHGTMACMHPIAA

242 FAYDSSCKFECQPGYRARGSNTLHCTGSGQWSEPLPTCEAIA

[0201] SEQ ID NO:21

[0202] *Chimera-17*

[0203] (human sequence to Cluster B to I_{35} – mouse Cluster B to I_{42} – human to CR1 to E_{154} – mouse CR1, CR2)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEI**AH**LN**D**V**I**PYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS

181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTNN**PP**K**C**D**A**VQC**QS**L**EA**P**PH**GT**MA**C**MH**PIA**A

242 F**AYD**SSC**K**F**E**C**QP**G**YRAR**G**SNTLH**CTG**SG**Q**W**SE**P**L**P**T**C**EAIA**

[0204] SEQ ID NO:22

[0205] *Chimera-17B*

[0206] (human sequence to Cluster B to I_{35} – mouse Cluster B to I_{42} – human thereafter)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEI**AH**LN**D**V**I**PYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

242 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0207] SEQ ID NO:23

[0208] *Chimera-18*

[0209] (human sequence with mouse cluster C (C1, C2, C3) and mouse CR1, CR2)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLP**FFN**SYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKS**N**SAPGKWNDEHCLKKK**R**ALCYTA

121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS

181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTNN**PP**K**C**D**A**VQC**QS**L**EA**P**PH**GT**MA**C**MH**PIA**A

242 F**AYD**SSC**K**F**E**C**QP**G**YRAR**G**SNTLH**CTG**SG**Q**W**SE**P**L**P**T**C**EAIA**

[0210] SEQ ID NO:24

[0211] *Chimera-18B*

[0212] (human sequence with mouse cluster C (C1, C2, C3)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLP**FFN**SYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKS**N**SAPGKWNDEHCLKKK**R**ALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
242 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0213] SEQ ID NO:25

[0214] *Chimera-19*

[0215] (human sequence with mouse Cluster D and mouse CR1, CR2)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRK**I**N**NK**W
61 TWVGT**NK**T**L**T**E**EAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS
181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTN**N**PP**K**C**D**A**V**QC**Q**S**L**E**A**P**PH**GT**MA**C**MH**PIA**A
242 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**NTLH**CT**G**S**GQ**W**S**E**P**L**P**T**C**EAIA**

[0216] SEQ ID NO:26

[0217] *Chimera-19B*

[0218] (human sequence with mouse Cluster D)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRK**I**N**NK**W
61 TWVGT**NK**T**L**T**E**EAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS
181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA
242 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0219] SEQ ID NO:27

[0220] *Chimera-20*

[0221] (human sequence with mouse Cluster E and mouse CR1, CR2)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDE**P**C**F**K**R**KHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYV**K**ECG**KVNI**PQHVLMNCSHPLG**E**FS
181 FNSQC**T**F**S**C**AE**GY**ELD**GP**GE**L**Q**CLASGIWTN**N**PP**K**C**D**A**V**QC**Q**S**L**E**A**P**PH**GT**MA**C**MH**PIA**A
242 F**AYD**SSC**K**F**E**C**QP**G**YRAR**GS**NTLH**CT**G**S**GQ**W**S**E**P**L**P**T**C**EAIA**

[0222] SEQ ID NO:28

[0223] *Chimera-20B*

[0224] (human sequence with mouse Cluster E)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW
61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDE**P**C**F**K**R**KHALCYTA
121 SCQDMSCSKQGECLETIGNYTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

242 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0225] SEQ ID NO:29

[0226] *Chimera-21*

[0227] (human sequence with mouse Cluster F)

1 WTYHYSTKAYSWNISRKYCQNRYTDLVAIQNKNEIDYLNKVLPYYSSYYWIGIRKNNKTW

61 TWVGTKKALTNEAENWADNEPNNKRNNEDCVEIYIKSPSAPGKWNDEHCLKKKHALCYTA

121 SCQDMSCS**N**QGEC**I**ETIG**S**YTCSCYPGFYGPECEYVRECGELELPQHVLMNCSHPLGNFS

181 FNSQCSFHCTDGYQVNGPSKLECLASGIWTNKPPQCLAAQCPPLKIPERGNMTCLHSAKA

242 FQHQSSCSFSCEEGFALVGPEVVQCTASGVWTAPAPVCK---

[0228] *FACS analysis of anti-P-selectin antibodies to human/mouse chimeras*

[0229] Antibody binding to human/mouse chimeras of P-selectin was analyzed using FACS analysis on a system such as a BD BIOSCIENCES FACS ARIA CELL SORTER to measure binding of anti-P-selectin antibodies to human/mouse chimeras which were coupled to beads coated with a goat anti-human Fc antibody. Such beads coated with chimeras were incubated with test anti-P-selectin antibodies that were then detected with anti-mouse Fc or isotype specific antibodies labeled with reporters, such as FITC, suitable for detection by the FACS system.

[0230] *One-step Surface Plasmon Resonance (BIACORE)*

[0231] In one aspect of the presently disclosed inventive concepts, BIACORE chips were used to capture a test anti-P-selectin antibody. Human-mouse P-selectin chimeras described herein were disposed onto the chip and test antibodies were added to the prebound chip. Binding of the chimeras to test antibodies was measured by resonance response units.

[0232] *Two-Step Surface Plasmon Resonance (BIACORE) Analysis*

[0233] In another aspect of the presently disclosed inventive concepts, a capture chip, such as a BIACORE chip was provided with a goat anti-human IgG Fc polyclonal antibody covalently attached to its surface. P-selectin chimeric human/mouse constructs of the lectin, EGF, CR1 and CR2 domain on a human IgG Fc were injected onto the chip and captured at concentrations that achieve a standardized level of surface coating as measured by the resonance response. The resonance response level achieved after loading each P-selectin chimera construct was designated as a new "secondary baseline" level. Test anti-P-selectin antibodies (e.g., mouse or humanized monoclonal anti-P-selectin antibodies, including G1, G3, G4, G5 and hSel001) were then injected onto the BIACORE chip and incubated for

binding to the P-selectin chimera construct already captured on the surface. The method could be modified to test humanized antibodies by creating P-selectin constructs on mouse IgG Fc and capturing with a goat anti-mouse IgG Fc polyclonal antibody and then probing with test humanized anti-P-selectin antibodies. Antibodies which bind to the P-selectin constructs cause an increase of the resonance response level from the secondary baseline. The resulting increase in resonance response may be measured as "added resonance units (RUs)" and thus indicate the level of binding to the P-selectin construct pre-coated onto the capture chip of the test antibody. Using these methods, optimal requirements for the binding of anti-P-selectin antibodies to P-selectin chimeras were precisely mapped to particular conformational epitopes.

[0234] *Identification of dual function anti-P-selectin antibodies (antibodies that both block and dissociate binding of P-selectin to PSGL-1)*

[0235] BIACORE analysis was also used to discover dual functionality of specific anti-P-selectin antibodies, i.e., as discussed above, they can both block and dissociate (reverse) binding interactions between P-selectin and PSGL-1. In this method, PSGL-1, or small molecule mimetics of the binding epitope of PSGL-1 such as a biotinylated glycosulfopeptide mimetic (e.g., GSP-6), or chimeric proteins containing the N-terminus of PSGL-1, are captured on a BIACORE chip, such as a streptavidin chip, using methods known to persons having ordinary skill in the art (GSP-6 is a glycosylated, sulfated 18 amino acid peptide mimetic of amino acids 42-60 of the exposed N-terminus of PSGL-1 described in detail in U.S. Patent No. 6,593,459, for example). First, to demonstrate "function-blocking" ability, in one embodiment, an anti-P-selectin antibody is pre-mixed with soluble P-selectin and incubated for a period to allow formation of the P-selectin/antibody complex. The resulting anti-P-selectin antibody/P-selectin complex is introduced onto the chip or other substrate bearing the PSGL-1 (or PSGL-1 mimetic) and binding to the PSGL-1 or its mimetic is measured. Anti-P-selectin antibodies, which prevent binding of P-selectin to the PSGL-1 or PSGL-1 mimetic on the chip, are designated herein as function-blocking antibodies.

[0236] Second, anti-P-selectin antibodies which have been shown (by the above-method or another similar method) to be function-blocking antibodies (i.e., which block PSGL-1 binding to P-selectin), can be tested for an additional function, that is, having the ability to dissociate (reverse) binding between preformed P-selectin PSGL-1 complex. Such antibodies can be tested for "dual function" properties

using the method of BIACORE analysis discussed herein. In one embodiment, to demonstrate the dual function property, PSGL-1, or a mimetic thereof such as GSP-6, is coupled to a BIACORE chip. P-selectin is then disposed on the chip and allowed to bind to the PSGL-1, or the mimetic. After equilibrium binding of P-selectin to PSGL-1, or the mimetic, is indicated by the sensogram, function-blocking anti-P-selectin antibodies are introduced and the dissociation of P-selectin binding to PSGL-1, or the mimetic is measured by any appropriate method. Such antibodies that are shown to dissociate (i.e., reverse), P-selectin/PSGL-1 binding are designated as "dissociating antibodies" and are characterized as dual function antibodies, i.e., they possess both function-blocking and dissociating properties in disrupting binding of P-selectin to PSGL-1. Such dual function antibodies are a particularly preferred embodiment of the invention as they are especially suitable for therapeutic application as treatments of acute and chronic inflammatory and thrombotic diseases such as are described elsewhere herein.

[0237] *Discovery of Conformational Epitopes*

[0238] The three-dimensional (3-D) structure of the mature human and mouse P-selectin proteins were analyzed and compared as to amino acid differences in the lectin and EGF domains. Six clusters of conformational amino acid differences were identified on exposed surfaces of the proteins. These were designated as clusters A, B, C, D, E and F (Fig. 1). The N-termini of human and mouse P-selectins spanning residues 1-35 contain 8 amino acid differences. Cluster A was arbitrarily defined by the boundary of the first amino acid difference (H_4) and the last amino acid difference (Y_{23}). Cluster A contains 20 amino acids and forms a rigid alpha helix with a cysteine bond near the N-terminus of the protein (see region "1" in Fig. 5). Cluster B (Fig. 1) is a conformational epitope spanning amino acid residues 36-42 and contains 4 amino acid differences between human and mouse P-selectin. Where used herein, the term "conformational epitope" is intended to refer to an epitope which is not recognized under reducing conditions. Clusters C and E (Fig. 1) are conformational and discontinuous and are brought into proximity by folding of the native P-selectin protein. Cluster C has three conformational regions (C1, C2, C3) containing 5 amino acid differences between human and mouse P-selectin. Cluster C1 is separated from C2 by 51 amino acids and cluster C2 is separated from C3 by 15 amino acids. Likewise cluster E has two conformational epitopes (E1, E2) containing five amino acid differences between human and mouse P-selectin with cluster E1 being separated from E2 by 19 amino acids. Clusters A, B, C, D and E lie within the consensus lectin

domain of P-selectin (Fig. 1). Cluster F resides in the EGF domain and has 3 amino acid differences out of 11 amino acids. Clusters C1, E1, C2, E2 and C3 encompass key contact residues which have previously been identified for interaction of P-selectin with its physiological ligand PSGL-1 (Somers et al). Clusters A and B are distal to (upstream of) these contact residues.

[0239] The open reading frames of cDNAs for human and mouse P-selectin were analyzed to identify common restriction sites that could be used to assemble chimeras spanning the clusters. PCR and chemical DNA synthesis was used to generate cDNAs coding for specific protein or chimera constructs such as SEQ ID NO: 1-29 (described above, and in the Sequence Listing). Restriction cloning was used to construct plasmids coding for the human/mouse chimeras. The chimeras were transiently expressed in COS-7 cells and utilized for FACS and BIACORE analysis. P-selectin chimeras were tested for binding function using BIACORE by analyzing their binding to GSP-6 bound to a BIACORE chip. As noted above, GSP-6 is a small molecule that mimics the N-terminus of human PSGL-1. All tested chimeras bound to the GSP-6 on the chip, though to varying degrees, as mouse P-selectin has a lower binding affinity to human PSGL-1 than does human P-selectin. This indicated that chimeras had maintained function after expression and purification.

[0240] *FACS Analysis*

[0241] The results of FACS analysis of anti-P-selectin antibodies, using the constructs or chimeras corresponding to SEQ ID NOs.:1-29 are summarized in Table 1. Four anti-P-selectin test antibodies (G1, G3, G4 and G5) were isolated from hybridomas generated by immunization of mice with a human recombinant P-selectin containing the lectin and EGF domains (90, and unpublished data). These studies had shown that these antibodies were specific to human P-selectin and that G1, G3 and G4 are function-blocking antibodies while G5 is non-blocking (90, and unpublished data). G1, G3 and G5 were analyzed by FACS analysis. Using this method, G1, G3 and G5 all bound to human P-selectin (SEQ ID NO:1) but not to mouse P-selectin (SEQ ID NO:2). When the corresponding eight mouse amino acids were substituted in cluster A of the human sequence (Chimera 1, SEQ ID NO:3), binding by G1 but not G3 or G5 was abolished, indicating that at least one or more of the corresponding eight amino acid positions in cluster A was essential for binding of G1 to P-selectin and that the substitution with the "mouse" amino acids in those one or more positions abolished the binding. To confirm the importance of these residues, the eight different human amino acids in positions 1-23 were substituted in cluster A of the

mouse sequence (SEQ ID NO:4, chimera-2). These substitutions conferred G1 binding to the mouse protein. Chimeras containing the human P-selectin lectin domain with mouse amino acid substitutions in the EGF, CR1 and CR2 domains (SEQ ID NO:9, chimera-6), and human sequence through the EGF domain and into the CR1 domain with mouse sequence in the remainder of CR1 domain and the entire CR2 domain (SEQ ID NO:10, chimera-7), were bound by G1 and G3 indicating that the primary binding epitopes remained intact after substitution of these mouse amino acids and that the conformation of the antibody binding epitopes were not adversely affected. These data confirmed that the binding epitopes for G1 and G3 resided in the lectin domain.

[0242] Using the FACS method, the test antibody G3 was shown to bind human P-selectin but not mouse P-selectin and in contrast to G1, bound to SEQ ID NO:3 (chimera-1), indicating that G3 binds to an epitope distinct from the epitope bound by G1. Specifics of the G3 epitope mapping are outlined in Table 1 below.

[0243] The test antibody G5, previously shown to be non-blocking, was also analyzed using this method. G5 was also shown to bind human P-selectin but not mouse P-selectin. G5 bound to SEQ ID NO:3 and SEQ ID NO:10 that spans the EGF domain and includes the first part of CR1 to N_{178}, but G5 did not bind to SEQ ID NO:9 that spans to S_{128}. These results indicate that antibody G5 binds to the first part of CR1 and requires at least amino acids R_{128} through N_{178}.

[0244] Table 1. Results of binding of various antibodies (G1, G3, G4, G5, hSel001) to human and mouse P-selectin and chimera constructs thereof. [1]By FACS, [2]By BIACORE 1-step, [3]By BIACORE 2-step, [W]Weak binding

Human/Mouse Chimeras								
SeqID	Mouse Domains Inserted in Human P-selectin	Human	Mouse	G1	G3	G5	G4	hSel001
1	None	1-279	0	$+^{1,2,3}$	$+^{1,2,3}$	$+^{1,3}$	$+^{3}$	$+^{2}$
2	all	0	1-282	$-^{1,2,3}$	$-^{1,2,3}$	$-^{1,3}$	$-^{3}$	$-^{2}$
3	$A_{4,14,17,18,20,21,22,23}$	1-3, 24-279	4-23	$-^{1,2,3}$	$+^{1,3}$	$+^{1}$	$-^{3}$	
4	B,C,D,E,F	1-35	36-282	$+^{1,2,3}$	$-^{3}$		$+^{3}$	
5	$A_{4,14,17,18}$	19-279	1-18	$-^{2}$				
6	$A_{20,23}$	1-19, 24-279	20-23	$-^{2}$				
7	A_4	1-3, 5-279	4	$+^{2w,3w}$	$+^{3}$		$+^{3w}$	
8	none	1-3, 5-279	0	$+^{2,3}$	$+^{3}$		$+^{3}$	
9	F, CR1, CR2	1-128	129-282	$+^{1,2,3}$	$+^{1,3}$	$-^{1,3}$	$+^{3}$	
10	CR1, CR2	1-177	178-282	$+^{1,2,3}$	$+^{1,3}$	$+^{1,3}$	$+^{3}$	
11	CR1, CR2	1-156	157-282	$+^{2}$	$+^{2}$	$-^{2}$		
12	A_{14}	1-13, 15-279	14	$-^{2}$				
13	A_{17}	1-16, 18-279	17	$-^{2}$				
14	A_{18}	1-17, 19-279	18	$+^{2}$				
15	A_{20}	1-19, 21-279	20	$+^{2}$				
16	A_{21}	1-20, 22-279	21	$+^{2w}$				
17	A_{22}	1-21, 23-279	22	$-^{2}$				
18	A_{23}	1-22, 24-270	23	$+^{2}$				
19	C2,E2,C3, F,CR1,CR2	1-97	98-282	$+^{2,3}$	$-^{3}$		$+^{3}$	
20	B,C,D,E,F	1-35 H/M hybrid	36-282	$+^{2,3}$	$-^{2,3}$		$+^{3}$	$+^{2}$
21	B,CR1,CR2	1-35, 43-156	36-42, 157-282	$+^{3}$	$+^{3}$	$-^{3}$		
22	B	1-35, 43-279	36-42		$+^{3}$	$+^{3}$		
23	C1,C2,C3,CR1,CR2	1-43, 47-97, 99-113, 115-156	44-46, 98, 114, 157-282	$+^{3}$	$-^{3}$	$-^{3}$		
24	C1,C2,C3	1-43, 47-97, 99-113, 115-279	44-46, 98, 114		$-^{3}$	$+^{3}$		
25	D,CR1,CR2	1-55, 72-156	56-71, 157-282	$+^{3}$	$+^{3}$			
26	D	1-55, 72-279	56-71		$+^{3}$	$+^{3}$		
27	E1,E2,CR1, CR2	1-84, 89-107, 113-156	85-88, 108-112, 157-282	$+^{3}$	$+^{3}$			
28	E1,E2	1-84, 89-107, 113-279	85-88, 108-112		$+^{3}$	$+^{3}$		
29	F	1-128, 140-279	129-139		$+^{3}$	$+^{3}$		
			Critical Amino Acid Positions:	A (4,14,17, 21,22)	C	First part of CR1 (157-164)	A (4,14,17,21,22)	A (4,14,17, 21,22)

[0245] *One-step Surface Plasmon Resonance (BIACORE)*

[0246] To further investigate the importance of the cluster A domain (amino acids 4-23) to the binding of the G1 antibody to P-selectin, several chimeric constructs were made in which single or multiple mouse amino acids were inserted into the human P-selectin sequence and binding was analyzed using the surface plasmon resonance ("one-step" BIACORE) methods disclosed herein. The one-step BIACORE binding results are presented in Table 1. The G1 test antibody was captured on a BIACORE chip and the binding of various chimeras was measured as response units. A representative sensogram showing binding of G1 to constructs of human P-selectin (SEQ ID NO:1), mouse P-selectin with human cluster A (SEQ ID NO:4) and mouse P-selectin (SEQ ID NO:2) is shown in Figure 2. Using this method, it was shown that G1 bound to human P-selectin and to SEQ ID NO:4 (where human amino acids were substituted in cluster A of mouse P-selectin), but did not bind to mouse P-selectin (SEQ ID NO:2). These results demonstrated that this method is consistent with the FACS results.

[0247] Mouse P-selectin (SEQ ID NO:2) has a putative glycosylation site (N) at position 4 whereas human P-selectin (SEQ ID NO:1) does not. To test the importance of this difference, position 4 of human P-selectin SEQ ID NO:1 was substituted with an N (forming SEQ ID NO:7) or a Q (forming SEQ ID NO:8) were and the effect of these substitutions on G1 antibody binding was measured. Inserting asparagine (N) into human P-selectin at position 4 diminished G1 binding suggesting that glycosylation at this site in human P-selectin would interfere with antibody binding. Substitution of glutamine (Q) at this position did not prevent G1 binding.

[0248] To further identify amino positions in cluster A that are optimal or essential for G1 antibody binding, single amino acid substitutions of mouse sequence amino acids into the human P-selectin (SEQ ID NO:1) were made, and binding of the resulting chimeras to G1 was measured using the one-step BIACORE method disclosed herein (Table 1). The chimeras tested (with specific substitutions indicated in parentheses) were: SEQ ID NO:7 (H_4N); SEQ ID NO:12 ($I_{14}N$); SEQ ID NO:13 ($K_{17}V$); SEQ ID NO:14 ($Y_{18}F$); SEQ ID NO:15 ($Q_{20}R$); SEQ ID NO:16 ($N_{21}R$); SEQ ID NO:17 ($R_{22}H$); and SEQ ID NO:18 ($Y_{23}F$). The G1 antibody bound to SEQ ID NO:14, 15 and 18, but did not bind SEQ ID NO:12, 13, and 17 and only weakly to SEQ ID NO:7 and SEQ ID NO:16. This result indicated that amino acid positions 4, 14, 17, 21, and 22 are each individually required positions for G1 binding. In a preferred embodiment, these amino acids are H_4, I_{14}, K_{17}, N_{21} and R_{22}, respectively.

[0249] To confirm that the humanized form of G1 (hSel001) maintained the identical epitope specificity of the parental antibody, the binding of hSel001 to SeqID:1, 2 and 20 was tested using this method. The binding pattern of hSel001 was identical to that of G1 confirming that the epitope specificity was maintained during the humanization process.

[0250] *Two-step Surface Plasmon Resonance (BIACORE)*

[0251] To assess G1, G3, G4 and G5 (G5 is non-blocking) binding to additional chimeras, the two-step surface plasmon resonance ("two-step" BIACORE) assay described herein was used. The results of the "two-step" assays for the test antibodies are presented in Table 1, and in Fig. 2. Using this method, none of the test antibodies investigated bound to mouse P-selectin and all bound to human P-selectin demonstrating their specificity to human P-selectin. G1, G3, G4 and G5 test antibodies all bound to SEQ ID NO:10 indicating they all bind to a region spanning the N-terminus through the lectin and EGF domains of human P-selectin. The G5 non-blocking antibody did not bind to SEQ ID NO:9, but did bind SEQ ID NO:10 confirming that G5 binds to the CR1 domain.

[0252] Further analysis using this method showed that G3 did not bind SEQ ID NO:23, which has mouse amino acids inserted in cluster C1, C2, C3, CR1, and CR2, nor did it bind SEQ ID NO:24 which has mouse amino acids in C1, C2, and C3. G3 also did not bind to other chimeras that had mouse sequence in cluster C, that is SEQ ID NO:19 and SEQ ID NO:20. These results indicate that the blocking G3 antibody requires cluster C for binding and demonstrates the novel finding that conformational clusters of amino acids brought into proximity by protein folding can serve as binding domains (conformational epitopes) for anti-P-selectin antibodies. The method also confirmed that G3 can block binding of PSGL-1 and P-selectin and thus has function-blocking properties (Fig. 3). However, the method also showed that G3 did not bind to or dissociate (reverse) the binding of P-selectin/PSGL-1 complex (Fig. 4) and thus does not have the dual function properties of the preferred antibodies of the presently disclosed inventive concepts.

[0253] Amino acid positions which contribute to the binding of G1 and G4 to P-selectin were identified by generating a human/mouse hybrid in cluster A. The hybrid cluster A chimera (SEQ ID NO:20) contains human P-selectin amino acids at positions 4, 14, 17, 21 and 22 (H, I, K, N, and R, respectively) and mouse P-selectin amino acids at positions 18, 20, and 23 (Y, Q, and Y, respectively). As indicated in Table 1, both G1 and G4 bound SEQ ID NO:20. This result when taken with the previous data

indicates that amino acid positions 4, 14, 17, 21, and 22 comprise positions which are each required for optimal binding of G1, G4 and the humanized form of G1 (hSel001) to P-selectin. These results comprise a novel finding that a group of antibodies including G1, G4 and hSel001 bind the same or similar epitope and that this epitope is found in the helix structure of cluster A that is distal to the lectin-ligand binding domain contact residues previously identified for P-selectin (71). In a preferred embodiment the amino acids at positions 4, 14, 17, 21, and 22 are H, I, K, N, and R, respectively. 3-D analysis of this epitope revealed a rigid helical structure with the required amino acids occupying sites on the same face of the helix; thus cluster A is designated as comprising a conformational epitope (Fig. 5). BIACORE analysis shown in Figs. 3 and 4 confirmed that G1, G4 and hSel001 can block and also dissociate the binding of P-selectin and PSGL-1 and thus binding of the herewithin described epitope by this group of antibodies has the dual function properties of the preferred embodiments of the presently disclosed inventive concepts.

[0254] These results indicate that antibodies that bind to a conformational epitope located within amino acids 1-35, and more particularly within amino acids 4-23, of SEQ ID NO:1 which is distal to the lectin-ligand binding domain in human P-selectin, will have unique dual function properties. Without being be bound by theory, it is contemplated that the antibodies which bind to this epitope act by contributing allosteric forces that exert on the lectin-ligand binding interface to induce a conformational change that dissociates P-selectin binding to PSGL-1. Thus G1 is able to bind the distal epitope at cluster A and block and dissociate the complex by binding and disrupting the molecular interactions at the lectin-ligand binding site on P-selectin. In contrast, antibodies such as G3, that bind to an epitope in the lectin-ligand binding domain of P-selectin can block P-selectin binding to PSGL-1 by allosteric hindrance, but cannot cause dissociation of the P-selectin/PSGL-1 complex since the antibody cannot bind to the conformational epitope of Cluster C when it is occupied by the ligand. The test antibody G5 bound to the cluster of P-selectin CR1 and was shown to be non-blocking (Fig. 3).

[0255] In summary, antibodies which bind to P-selectin have been characterized as having three possible activities in regard to the interaction of P-selectin, and its ligand, PSGL-1.

[0256] First, P-selectin antibodies can bind to P-selectin but not interfere with the binding of PSGL-1 to P-selectin ("non-blocking"). For example, as shown herein, the antibody G5 binds amino acids 157-164 and requires R_{157}, E_{161}, L_{162}, E_{163} and L_{164}

of CR1 for binding but this binding does not block P-selectin from binding to PSGL-1.

[0257] Second, P-selectin antibodies can bind to P-selectin and interfere with the binding of PSGL-1 to P-selectin ("function-blocking"), but not bind to or dissociate a preformed P-selectin/PSGL-1 complex. For example, the results described herein show that antibody G3 binds to conformational clusters in a different part of P-selectin that span the lectin-ligand binding domain. G3 binds cluster C and requires C1 amino acids Y_{44}, Y_{45}, S_{46} and C2 amino acid P_{98} and C3 amino acid H_{114} and thus requires a conformational epitope. This antibody blocks the interaction between P-selectin and PSGL-1 but cannot bind to or dissociate preformed P-selectin/PSGL-1 complexes.

[0258] Third, we have discovered P-selectin antibodies with specific specificity that can bind to P-selectin and not only block the binding of PSGL-1 to P-selectin (function-blocking antibody) but can also cause reversal of preformed P-selectin/PSGL-1 binding (dissociative binding). Such antibodies are referred to herein as "dual function" antibodies. The results disclosed herein demonstrate, for example, that G1 binds a conformational epitope in cluster A, and that this binding had an absolute requirement for a conformational epitope comprising amino acid positions 4, 14, 17, 21, and 22, preferably wherein those amino acids are H, I, K, N, and R, respectively. As discussed elsewhere herein, substitution of the "human" amino acid (H, I, K, N, and R) at any one of these positions, respectively, with the corresponding "mouse" amino acid (N, N, V, R, and H) will result in the abrogation of binding by the dual function antibodies described herein.

[0259] In another embodiment of the presently disclosed inventive concepts, a previously uncharacterized mouse monoclonal anti-P-selectin antibody clone designated G4, generated using standard hybridoma methods, was tested for binding to the conformational epitope of cluster A, and was tested for dual function capabilities using the methods described herein. G4 was tested for binding to human/mouse chimeras SEQ ID NOs.:1-4, 7-10, 19 and 20. G4 was shown to bind SEQ ID NO:20 and had similar binding specificity as described for G1 (see Table 1). G4 was then shown to block binding of P-selectin to PSGL-1 (Fig. 3) and also to cause dissociation of preformed P-selectin/PSGL-1 complexes (Fig. 4), thus characterizing G4 as a dual function P-selectin antibody which binds an epitope (in cluster A) which is distal to the lectin-ligand binding domain of P-selectin and blocks and dissociates binding of P-selectin to PSGL-1. The G1 and G4 antibodies thus both bound to an epitope in cluster A and both demonstrated dual function properties. This result also demonstrates the use of cluster A or specific binding positions or amino acids thereof

as an epitope able to be used to screen anti-P-selectin antibodies for dual function capabilities. Such dual function antibodies possess unique properties for therapeutic applications where initiation of P-selectin-mediated adhesion and/or ongoing P-selectin-mediated adhesion in acute or chronic settings may be treated. Using the methods described herein, other antibodies having dual function properties can be identified using the method of screening using the cluster A epitope or specific positions or amino acids thereof.

[0260] The humanized IgG2 anti-P-selectin antibody lacking effector function called hSel001 (a humanized P-selectin binding antibody comprising CDRs of mouse antibody G1 grafted into human framework regions as previously characterized in Publication No. WO 2008/069999) was also screened using the screening method described herein. A summary of the data (Table 1) shows that hSel001 antibody bound to the same chimeras (SEQ ID NO:1 and 20) as antibody G1. hSel001 binding was specific to the conformational epitope described herein located within cluster A. Results showed that antibody hSel001 possesses dual function properties enabling it to both block binding of P-selectin to PSGL-1 (Fig. 3) and dissociate preformed P-selectin/PSGL-1 complexes (Fig. 4). Thus hSel001 is another antibody optionally encompassed by the presently disclosed inventive concepts and can be used as a therapeutic treatment for inflammatory and thrombotic diseases as described herein, and wherein P-selectin binding to PSGL-1 is blocked, and dissociation of preformed P-selectin/PSGL-1 complex is promoted.

[0261] *Cell-based in vitro rolling assays under flow with human neutrophils*

[0262] To further evaluate the blocking and dissociative properties of antibodies G1, G4 and hSel001, cell-based *in vitro* rolling assays were performed with freshly isolated human neutrophils that were introduced under a flow of 1.0 dyn/cm^2 in a flow chamber coated with low and high levels of membrane P-selectin. The low density P-selectin was coated at 0.25μg/ml and the high density P-selectin was coated at 2μg/ml. Site densities were determined using I^{125}-labeled G1 mAb to be 50 sites/mm^2 (low) and 380 sites/mm^2 (high). On low density P-selectin, neutrophils rolled at an average velocity of either 5μm/s or 6.5μm/s. On high density P-selectin, neutrophils rolled at an average velocity of 1μm/s. Neutrophils are introduced in buffer under flow and allowed to begin rolling and tethering. Once equilibrated, test antibodies (G1, G3, G4 and hSel001) were introduced in cell-free buffer under flow. There is a dead volume of about 1 minute interval before the antibody reaches the chamber. At 1 minute intervals thereafter, cells remaining bound are counted and

expressed as % cells bound. Results were recorded on video microscopy for approximately 0-20 minutes and the data analyzed post run.

[0263] Results in Figure 6 panels (A) and (C) showed that neutrophils rolled at a higher velocity on low density P-selectin. Thus as the P-selectin/PSGL-1 complex released due to normal on/off kinetics of the lectin/ligand binding, neutrophils traveled greater distances at higher velocity to the next P-selectin binding site. As the complex releases, the previously occupied P-selectin becomes available for binding by anti-P-selectin antibodies. Thus all four antibodies, G1, G3, G4 and hSel001, showed equivalent blocking functionality over the course of 1-4 minutes.

[0264] Results in Figure 6 panels (B) and (D) on high density P-selectin showed that neutrophils roll much slower (1μm/s) as a greater number of P-selectin binding sites are available. Many neutrophils come to a rolling stop on P-selectin at this density. Under these conditions the murine antibodies G1 and G4 and the humanized antibody hSel001 were able to release rolling and tethering neutrophils by dissociating the P-selectin/PSGL-1 complex immediately and over the course of 1-8 minutes. In contrast the G3 anti-P-selectin antibody required up to 16-20 minutes to block rolling neutrophils. This indicated that the G3 antibody was only able to bind unoccupied P-selectin sites and thus block P-selectin/PSGL-1 complexes, but was not able to bind and dissociate the pre-formed complex. These cell-binding assays under flow confirm the BIACORE results reported previously herein which demonstrate that murine antibodies G1 and G4 and humanized antibody hSel001 all have dual function properties causing both blockage and dissociation of preformed P-selectin/PSGL-1 complexes.

[0265] *hSel001 has enhanced binding versus mouse antibody G1*

[0266] The P-selectin binding affinities of G1 and hSel001 were analyzed in vitro and compared using surface plasmon resonance (Biacore). Soluble human P-selectin was covalently attached to a Biacore CM5 chip and the mouse antibody G1 and humanized antibody hSel001 were independently tested by introduction to the chip.

[0267] In order to further assess the interaction of the anti-P-selectin antibodies with P-selectin (antigen), kinetic analysis using surface plasmon resonance (SensiQ) was performed. The mouse monoclonal anti-P-selectin antibody G1 and the humanized hSel001 antibody were analyzed by surface plasmon resonance on SensiQ. To analyze the kinetics of binding of these two antibodies, the sensor chip was functionalized by covalently attaching recombinant protein G. The mouse antibody G1 was introduced and captured on the chip by injecting a 20nM solution for 1

minute. The humanized antibody hSel001 was introduced and captured on a similarly functionalized separate channel by injecting a 10nM solution for 1 minute. Concentrations of soluble human P-selectin (100nM-1.56nM) were introduced and binding measured as response units (RU). The data for binding of each was analyzed using Qdat analysis software.

[0268] Figure 7 shows binding results for both antibodies at a single P–selectin concentration.

[0269] Based on these results, the K_d (dissociation constant) for hSel001 was measured to be 5.89nM compared to a K_d of 8.94nM for the mouse antibody G1 (Table 2). This represents a 34% improvement in the binding affinity of the humanized anti-P-selectin antibody hSel001 when compared to the mouse monoclonal anti-P-selectin antibody G1. In addition the K_a (association constant) for hSel001 was higher by 64.7% than G1, meaning hSel001 binds more quickly to P-selectin. Both of these results indicate that the humanized hSel001 antibody has improved K_d (affinity) and K_a (speed of initial binding) versus G1.

Table 2 – Kinetic Constants for P-Selectin

Antibody	ka ($x10^6$ $M^{-1}s^{-1}$)	kd ($x10^{-2}$ s^{-1})	KD (nM)	Res. SD (RU)
G1	6.3±2	5.6±2	8.94±3	3.39
hSel001	2.22±1	1.306±6	5.89±2	4.48

[0270] Antibodies of the presently disclosed inventive concepts provided by any of the above described methods are preferably used in the manufacture of a pharmaceutical composition for use in the therapeutic treatment of a pathological condition, wherein such treatment comprises administering the pharmaceutical composition for mitigating, reversing, or inhibiting an inflammatory response or thrombosis or other condition.

[0271] It is an important objective of the presently disclosed inventive concepts to use the antibodies, or functionally active fragments or variants of said antibodies for the manufacture of a pharmaceutical composition and its use in the prevention and/or treatment of inflammatory responses or diseases or thrombosis such as, but not limited to, those described herein.

[0272] For example, the presently disclosed inventive concepts in particular are directed to, but not limited to, using such dual function anti-P-selectin antibodies or antibody fragments as described and identified herein in treatments for inflammatory,

thrombotic or other conditions or disorders in primates (including humans) which involve platelet, sickled red cell, leukocyte, lymphocyte, and/or endothelial cell adhesion, wherein the condition or disorder comprises or is associated with (but not limited to) at least one of sickle cell vasoocclusive pain crisis, inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis, enteritis), arthritis (e.g., rheumatoid arthritis, osteoarthritis, psoriatic arthritis), graft rejection, graft versus host disease, asthma, chronic obstructive pulmonary disease, psoriasis, dermatitis, sepsis, nephritis, lupus erythematosis, scleroderma, rhinitis, anaphylaxis, diabetes, multiple sclerosis, atherosclerosis, thrombosis, tumor metastasis, allergic reactions, thyroiditis, ischemic reperfusion injury (e.g., due to myocardial infarction, stroke, or organ transplantation), and conditions associated with extensive trauma, or chronic inflammation, such as for example, type IV delayed hypersensitivity, associated for example with infection by Tubercle bacilli, or systematic inflammatory response syndrome, or multiple organ failure. The term "primate" as used herein refers to humans, monkeys, including baboons and cynomolgus monkeys, and apes, the latter including chimpanzees, gorillas, gibbons and orangutans, for example. Other pathologic conditions not listed herein but which relate to inflammatory or thrombotic conditions or disclosures may also be treated using the antibodies and compositions described herein.

[0273] In the pharmaceutical composition of a medicament according to the presently disclosed inventive concepts, the antibodies may be formulated by any of the established methods of formulating pharmaceutical compositions, e.g. as described in the latest edition of Remington's Pharmaceutical Sciences or described elsewhere herein. The composition may typically be in a form suited for local or systemic injection or infusion and may, as such, be formulated with sterile water or an isotonic saline or glucose solution. The compositions may be sterilized by conventional sterilization techniques, which are well known in the art. The resulting aqueous solutions may be packaged for use or filtered under aseptic conditions and lyophilized, the lyophilized preparation being combined with the sterile aqueous solution prior to administration. The composition may contain pharmaceutically acceptable auxiliary substances as required to approximate physiological conditions, such as buffering agents, tonicity adjusting agents and the like, for instance sodium acetate, sodium lactate, sodium chloride, potassium chloride, calcium chloride, etc. The concentration of proteins may vary widely, for example, from less than about .01% to as much as 15-20% or more by weight. A unit dosage of the composition

may contain for example from about 1 μg to about 1000 mg of an antibody or antibody fragment.

[0274] The antibodies or antibody fragments of the presently disclosed inventive concepts may be administered topically or by injection. Dosages will be prescribed by the physician according to the particular condition and the particular individual to be treated. Dosages and frequency is carefully adapted and adjusted according to parameters determined by the physician in charge. Preferred administration routes may be oral, via inhalation, subcutaneous, intravenous, intramuscular, intratracheal, intravesical, or intraperitoneal injections and may be given per 24 to 48 hours, or per week, every 14 days, every 4 weeks for example in the range of from 0.01-1000 mg, especially 0.1 mg to 100 mg, in particular 1-10 mg per kg body weight. The dose may be administered continuously through a catheter or in individual boluses. The antibody of the invention may be administered in an efficacious quantity such as, but not limited to, the ranges between 1 ng/kg to 1 μg/kg, 0.01 μg/kg to 50 μg/kg, 0.1 μg/kg to 1 μg/kg, 1 μg/kg to 5 μg/kg, 5 μg/kg to 10 μg/kg, 10 μg/kg to 50 μg/kg, 50 μg/kg to 100 μg/kg, 100 mg/kg to 1 mg/kg, 1 mg/kg to 10 mg/kg, or 10 mg/kg to 100 mg/kg body weight.

[0275] Pharmaceutical compositions used in the presently disclosed inventive concepts comprising antibodies described herein may additionally be supplemented by other therapeutic compounds which are routinely prescribed by the physician according to the particular condition and the particular individual to be treated such as an anti-inflammatory drug, wherein said drugs are prescribed by the physician according to the particular condition and the particular individual to be treated.

[0276] As noted elsewhere herein, the phenomenon of P-selectin/PSGL-1 binding has functional importance in sickled red cell, endothelial cell leukocyte and platelet interactions, and/or microvesicle adhesion, leukocyte rolling, recruitment, aggregation; leukocyte secretion of cytokines; promotion of coagulation; and other aspects of inflammation, thrombosis, coagulation, immune response, and signal transduction including , but not limited to, sickle cell vasoocclusive pain crisis, inflammatory bowel disease (e.g., Crohn's Disease, ulcerative colitis, enteritis), arthritis (e.g., rheumatoid arthritis, osteoarthritis, psoriatic arthritis), graft rejection, graft versus host disease, asthma, chronic obstructive pulmonary disease, psoriasis, dermatitis, sepsis, nephritis, lupus erythematosis, scleroderma, rhinitis, anaphylaxis, diabetes, multiple sclerosis, atherosclerosis, thrombosis, tumor metastasis, allergic reactions, thyroiditis, ischemic reperfusion injury (e.g., due to myocardial infarction,

stroke, or organ transplantation), and conditions associated with extensive trauma, or chronic inflammation, such as for example, type IV delayed hypersensitivity, associated for example with infection by Tubercle bacilli, or systematic inflammatory response syndrome, or multiple organ failure. A neutralizing antibody (or fragment thereof) to P-selectin as described herein will inhibit one or more of these activities in a patient as mediated through P-selectin/PSGL-1 receptor binding (or in the case of sickled red cells, P-selectin/PSGL-1 like receptor binding), in vivo or in vitro, for example. Thus, the inhibition of P-selectin/PSGL-1 binding with a neutralizing antibody (or fragment thereof) described herein is useful in the treatment in a patient of various conditions and disorders including but not limited to, those described herein.

[0277] The P-selectin specific antibodies or binding fragments described herein can be linked to another molecule. For example, antibodies may be linked to another peptide or protein, toxin, radioisotope, cytotoxic or cytostatic agents. The antibodies can be linked covalently by chemical cross-linking or by recombinant methods. The antibodies may also be linked to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol, polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; or 4,179,337. The antibodies can be chemically modified by covalent conjugation to a polymer, for example, to increase their stability or half-life. Exemplary polymers and methods to attach them are also shown in U.S. Pat. Nos. 4,766,106; 4,179,337; 4,495,285; and 4,609,546.

[0278] The antibodies (or fragments thereof) may also be tagged with a detectable label. A detectable label is a molecule which, by its chemical nature, provides an analytically identifiable signal which allows the detection of a molecular interaction. A protein, including an antibody, has a detectable label if it is covalently or non-covalently bound to a molecule that can be detected directly (e.g., by means of a chromophore, fluorophore, or radioisotope) or indirectly (e.g., by means of catalyzing a reaction producing a colored, luminescent, or fluorescent product). Detectable labels include a radiolabel such as 131I or 99Tc, a heavy metal, or a fluorescent substrate, such as Europium, for example, which may also be attached to antibodies using conventional chemistry. Detectable labels also include enzyme labels such as horseradish peroxidase or alkaline phosphatase. Detectable labels further include chemical moieties such as biotin, which may be detected via binding to a specific cognate detectable moiety, e.g., labeled avidin.

[0279] The presently disclosed inventive concepts are also directed to methods of screening for anti-P-selectin antibodies and binding fragments thereof which block both P-selectin/PSGL-1 binding and/or which cause dissociation of preformed P-selectin/PSGL-1 complexes.

[0280] As noted above, the presently disclosed inventive concepts are directed to antibodies against P-selectin, host cells that produce such anti-P-selectin antibodies, vectors that contain DNA which encode such anti-P-selectin antibody expression and screening methods to identify anti-P-selectin antibodies which block P-selectin/PSGL-1 binding and in a further embodiment has a "dual function" in also causing dissociation of preformed P-selectin/PSGL-1 complex. Thus, in one embodiment the presently disclosed inventive concepts is directed to methods of identifying anti-P-selectin antibodies that specifically bind to a conformational epitope in amino acids 1-35, and more preferably in amino acids 4-23, of human P-selectin (SEQ ID NO:1) (such as the conformational epitope described herein) and which block PSGL-1, or mimetics thereof, from binding to P-selectin, and which can reverse such binding thereto, thus exhibiting a dual function in blocking selectin-mediated adhesion due to P-selectin/PSGL-1 binding and in causing dissociation of preformed P-selectin/PSGL-1 complexes.

[0281] The screening method in preferred embodiments comprises *in vitro* fluid-based and/or substrate-based assays that can be used to identify anti-P-selectin antibodies or fragments thereof that inhibit or abolish P-selectin/PSGL-1 binding and preferably also cause dissociation of preformed P-selectin/PSGL-1 complexes. Test antibodies can be screened for dual function capability with a series of assays such as, but not limited to, those described herein which will identify those antibodies that bind to a conformational epitope within amino acids 1-35, and more particularly within amino acids 4-23, of P-selectin, and that block the binding of the PSGL-1 ligand to P-selectin, and which preferably cause dissociation of preformed P-selectin/PSGL-1 complexes. No anti-P-selectin antibodies have heretofore been shown to have the ability to both block PSGL-1 binding to P-selectin and to cause dissociation of preformed P-selectin/PSGL-1 complexes. Where used herein, the term "test antibody" refers to entire antibodies or fragments of antibodies. The test antibody can be a member of a library (e.g. phage, yeast, or bacteria) or an antibody fragment in a library. The library could be subtracted by eliminating all members that bound nondesired epitopes.

[0282] In a first step of the screening method, for example, test antibodies

generated against P-selectin are assayed for the ability to block binding of PSGL-1 to P-selectin. Test antibodies which block binding of PSGL-1 to P-selectin are screened to determine their ability to cause dissociation of preformed P-selectin/PSGL-1 complexes. Test antibodies identified as having dual function of blocking both PSGL-1 binding to P-selectin, and causing dissociation of P-selectin/PSGL-1 complex comprise particularly preferred embodiments of the presently disclosed inventive concepts and can be used in the methods of the presently disclosed inventive concepts. Examples of fluid-based embodiments of the assays include, but are not limited to, (1) cell based FACS assays with leukocytes or HL60/activated platelets which measure cell aggregates which have or have not been exposed to an antibody able to bind to P-selectin (e.g., hSel001) or to a test antibody to demonstrate dissociation of the PSGL-1/P-selectin complex, (2) a liquid-based assay based on a P-selectin/GSP-6-streptavidin-biotin complex which has or has not been exposed to an antibody able to bind to P-selectin (e.g., hSel001) or to a test antibody, and measured with SEC (size exclusion chromatography), and (3) use of an AlphaLisa bead as a substrate but used in a liquid based assay.

[0283] In one embodiment of the method, test antibodies which block binding of PSGL-1 to P-selectin are first identified using a screening assay. For example, in a preferred embodiment of the screening assay, PSGL-1 or a synthetic PSGL-1 mimetic such as GSP-6, or a terminal epitope portion of PSGL-1 able to bind to P-selectin is provided (and optionally is bound to a support substrate such as a BIACORE chip), in a method known to persons having ordinary skill in the art. The PSGL-1 (or the PSGL-1 mimetic) (which may be bound to the substrate) is then exposed to an anti-P-selectin test antibody/P-selectin complex. The degree of binding of the complex to the PSGL-1-substrate is then evaluated. If the test antibody/P-selectin complex does not bind to the PSGL-1, the test antibody is identified as a "function-blocking" antibody. The GSP-6 or PSGL-1 mimetic, in one embodiment, is bound to biotin. The GSP-6/mimetic-biotin complex itself may be bound to a streptavidin coating on the substrate for example.

[0284] In another embodiment of the screening assay, P-selectin, or a portion thereof which maintains the integrity of the conformational epitope, is provided, and as above, is optionally bound to the support substrate. For example, a portion of P-selectin which maintains the conformational epitope includes, but is not limited to, the sequence comprising the lectin and EGF binding domains of P-selectin (e.g., amino acids 1-153 of SEQ ID NO:1). In this embodiment, the P-selectin or portion thereof

with the conformational epitope is exposed to the test antibody, which binds to form the P-selectin-antibody complex. Then PSGL-1, or a high molecular weight mimetic thereof such as a GSP-6/biotin/avidin complex, is exposed to the P-selectin/test antibody complex and the degree of binding thereto of PSGL-1 (or the mimetic) is evaluated. An antibody which prevents or inhibits the binding of PSGL-1 to the P-selectin/antibody complex is identified as a "function-blocking" antibody.

[0285] In another embodiment of the screening assay, either PSGL-1 or a mimetic thereof is bound, as described above, to a support substrate (such as a bead or BIACORE chip). P-selectin is then applied to the PSGL-1/substrate to form the P-selectin/PSGL-1 (or mimetic) complex. The test antibody is then applied and dissociation of the complex is measured as a decrease in mass or as Response Units (RU) since P-selectin is being dissociated away. A function-blocking anti-P-selectin antibody, which induces dissociation of the P-selectin/PSGL-1 complex, is designated as a dual function anti-P-selectin antibody.

[0286] In an alternate embodiment of this screening assay, P-selectin or a portion of P-selectin comprising a conformational epitope may be bound to a support substrate rather than the PSGL-1. PSGL-1 or a high molecular weight mimetic thereof such as a GSP-6/biotin/avidin complex is then exposed to the P-selectin on the support substrate and allowed to form a PSGL-1/P-selectin complex. The PSGL-1/P-selectin complex is then exposed to a function-blocking anti-P-selectin antibody and dissociation of the complex is evaluated, for example using a BIACORE method as described elsewhere herein.

[0287] In yet another embodiment of the assay, the anti-P-selectin antibody itself is bound to the support substrate, and a P-selectin/PSGL-1 complex is exposed to it, and dissociation thereof is measured as above.

[0288] Although the presently disclosed inventive concepts and the advantages thereof have been described in detail, it should be understood that various changes, substitutions and alterations can be made herein without departing from the spirit and scope of the presently disclosed inventive concepts as defined herein. Moreover, the scope of the present application is not intended to be limited to the particular embodiments of the process, items of manufacture, compositions of matter, means, methods and steps described in the specification. As one having ordinary skill in the art will readily appreciate from the present disclosure, processes, items of manufacture, compositions of matter, means, methods, or steps, presently existing or later to be developed that perform substantially the same function or achieve

substantially the same result as the corresponding embodiments described herein may be utilized according to the presently disclosed inventive concepts. Accordingly, the invention described herein is intended to include within their scope such processes, items of manufacture, compositions of matter, means, methods, or steps.

[0289] Each of the references, patents or publications cited herein, including but not limited to U.S. Serial No. 12/974,539; 12/974,739; 12/516,987; and WO 2008/069999, is expressly incorporated herein by reference in its entirety.

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What is claimed is:

1. An isolated antibody or binding fragment thereof which specifically binds to a conformational epitope of P-selectin, wherein the conformational epitope is within amino acid positions 1-35 of SEQ ID NO:1.

2. The isolated antibody or binding fragment of claim 1 wherein the conformational epitope is within amino acids 4-23 of SEQ ID NO:1.

3. The isolated antibody or binding fragment of claim 2 wherein the conformational epitope comprises amino acid positions 4, 14, 17, 21, and 22 of SEQ ID NO:1.

4. The isolated antibody or binding fragment of claim 3 wherein the amino acids in amino acid positions 4, 14, 17, 21, and 22 are H, I, K, N, and R, respectively.

5. The isolated antibody or binding fragment of claim 4 wherein binding is abrogated when any one or more of amino acid positions 4, 14, 17, 21, or 22 is substituted with N, N, V, R, or H, respectively.

6. The isolated antibody or binding fragment of claim 1 comprising the ability to block the binding of P-selectin glycoprotein ligand-1 (PSGL-1) to P-selectin.

7. The isolated antibody or binding fragment of claim 1 further comprising the ability to cause dissociation of a preformed P-selectin-PSGL-1 complex.

8. The isolated antibody or binding fragment of claim 1 comprising the ability to block the function of P-selectin by inhibiting the binding of activated endothelial cells to leukocytes, lymphocytes, sickled red cells, and/or platelets.

9. The isolated antibody or binding fragment of claim 1 comprising the ability to block the function of P-selectin by inhibiting the binding of activated platelets to leukocytes, lymphocytes, sickled red cells, and/or platelets.

10. The isolated antibody or binding fragment of claim 1 comprising the ability to cause dissociation of cell-cell binding between activated endothelial cells and leukocytes, lymphocytes, sickled red cells, and/or platelets.

11. The isolated antibody or binding fragment of claim 1 comprising the ability to cause dissociation of cell-cell binding between activated platelets and leukocytes, lymphocytes, sickled red cells, and/or platelets.

12. The isolated antibody or binding fragment of claim 1 wherein the antibody or fragment thereof is monoclonal.

13. The isolated antibody or binding fragment of claim 1 wherein the antibody or fragment thereof is chimeric, human, or humanized.

14. The isolated antibody or binding fragment of claim 1 comprising an immunoglobulin selected from the class consisting of IgA, IgD, IgE, IgG, and IgM.

15. The isolated antibody or binding fragment of claim 14 wherein the isolated antibody or binding fragment thereof is an IgG selected from an isotype consisting of IgG1, IgG2, IgG3, IgG4, or an IgG2/G4 chimera.

16. The binding fragment of claim 1 comprising at least one of a Fab, Fab', F(ab)2, or scFv fragment.

17. The isolated antibody or binding fragment of claim 1 which binds to the conformational epitope with a $K_d \leq 1000$ nM, a $K_d \leq 500$ nM, a $K_d \leq 100$ nM, a $K_d \leq 50$ nM, a $K_d \leq 25$ nM, a $K_d \leq 10$ nM, a $K_d \leq 5$ nM, a $K_d \leq 1$ nM, or a $K_d \leq 0.1$ nM.

18. The isolated antibody of claim 1 which is designated as the monoclonal antibody derived from the hybridoma having ATCC Designation No. PTA 12154 or a humanized antibody comprising the CDRs of said monoclonal antibody.

19. A composition comprising the isolated antibody or binding fragment of claim 1 disposed within a pharmaceutically-acceptable carrier, vehicle, or diluent.

20. A cell line which expresses the antibody or binding fragment of claim 1.

21. The cell line of claim 20 comprising the hybridoma having ATCC Designation No. PTA 12154.

22. An isolated monoclonal antibody produced by the hybridoma of claim 21.

23. The isolated monoclonal antibody of claim 22 wherein the monoclonal antibody is designated as G4.

24. An isolated humanized antibody comprising the CDRs of the monoclonal antibody produced by the hybridoma of claim 21.

25. A method of treating or inhibiting an inflammatory or thrombotic condition or disorder in a subject in need of such therapy, comprising: administering to the subject a therapeutically-effective amount of an antibody or binding fragment thereof which specifically binds to a conformational epitope of P-selectin which is within amino acid positions 1-35 of SEQ ID NO:1.

26. The method of claim 25 wherein the conformational epitope is within amino acid positions 4-23 of SEQ ID NO:1.

27. The method of claim 25 wherein the conformational epitope comprises amino acid positions 4, 14, 17, 21, and 22 of SEQ ID NO:1.

28. The method of claim 27 wherein the amino acids in amino acid positions 4, 14, 17, 21, and 22 are H, I, K, N, and R, respectively.

29. The method of claim 28 wherein binding is abrogated when any one or more of amino acid positions 4, 14, 17, 21 or 22 is substituted with N, N, V, R, or H, respectively.

30. The method of claim 25 wherein the antibody or binding fragment thereof comprises the ability to block the binding of P-selectin glycoprotein ligand-1 (PSGL-1) to P-selectin.

31. The method of claim 25 wherein the antibody or binding fragment thereof further comprises the ability to cause dissociation of a preformed P-selectin-PSGL-1 complex.

32. The method of claim 25 wherein the antibody or binding fragment of claim 1 comprises the ability to cause dissociation of cell-cell binding between activated endothelial cells and leukocytes, lymphocytes, sickled red cells, and/or platelets.

33. The method of claim 25 wherein the antibody or binding fragment of claim 1 comprises the ability to cause dissociation of cell-cell binding between activated platelets and leukocytes, lymphocytes, sickled red cells, and/or platelets.

34. The method of claim 25 wherein the antibody or binding fragment thereof comprises the ability to block the function of P-selectin by inhibiting the binding of activated endothelial cells to leukocytes, lymphocytes, sickled red cells and/or platelets.

35. The method of claim 25 wherein the antibody or binding fragment thereof comprises the ability to block the function of P-selectin by inhibiting the binding of activated platelets to leukocytes, lymphocytes, sickled red cells and/or platelets.

36. The method of claim 25 wherein the antibody or binding fragment thereof is monoclonal.

37. The method of claim 25 wherein the antibody or fragment thereof is chimeric, human, or humanized.

38. The method of claim 25 wherein the antibody or binding fragment thereof comprises an immunoglobulin selected from the class consisting of IgA, IgD, IgE, IgG, and IgM.

39. The method of claim 38 wherein the antibody or binding fragment thereof is an IgG1, IgG2, IgG3, IgG4, or an IgG2/G4 chimera.

40. The method of claim 25 wherein the binding fragment comprises at least one of a Fab, Fab', F(ab)2, or scFv fragment.

41. The method of claim 25 wherein the antibody or binding fragment thereof binds to the conformational epitope with a $K_d \leq 1000$ μM, a $K_d \leq 500$ nM, a $K_d \leq 100$ nM, a

$K_d \leq 50$ nM, a $K_d \leq 25$ nM, a $K_d \leq 10$ nM, a $K_d \leq 5$ nM, a $K_d \leq 1$ nM, or a $K_d \leq .1$ nM.

42. The method of claim 25 wherein the inflammatory, thrombotic condition or other condition or disorder is related to at least one or more of platelet, sickled red cell, leukocyte, lymphocyte or endothelial cell adhesion, vasoocculsive sickle cell pain crisis, thrombosis, atherosclerosis, tumor metastasis, allergic reactions, thyroiditis, psoriasis, dermatitis, nephritis, lupus erythematosis, scleroderma, sepsis, rhinitis, anaphylaxis, diabetes, multiple sclerosis, graft rejection, graft vs. host disease, asthma, chronic obstructive pulmonary disease, inflammatory bowel disease, arthritis, and ischemic reperfusion injury, conditions associated with extensive trauma, or chronic inflammation, systematic inflammatory response syndrome, and multiple organ failure.

43. The method of claim 42 wherein the ischemic reperfusion injury is caused by at least one of myocardial infarction, stroke, and organ transplantation.

44. The method of claim 25 wherein said antibody is administered to the subject parenterally, intramuscularly, intraperitoneally, epidurally, or orally, intravenously, subcutaneously, or in a nebulized form.

45. The method of claim 25 wherein said antibody or binding fragment is administered to the subject an amount of 1 ng/kg to 100 mg/kg.

46. The method of claim 25 wherein the antibody is a monoclonal antibody designated herein as G1, hSel001, G4, or a humanized antibody comprising the CDRs of said monoclonal antibody.

47. A method of blocking cell-to-cell binding of P-selectin glycoprotein ligand-1 (PSGL-1) to P-selectin, comprising: administering to activated platelets, leukocytes, lymphocytes, and/or sickled red cells an antibody or binding fragment thereof which specifically binds to a conformational epitope of P-selectin which is within amino acid positions 1-35 of SEQ ID NO:1.

48. The method of claim 47 wherein the antibody or binding fragment thereof further comprises the ability to cause dissociation of a preformed P-selectin-PSGL-1 complex.

49. The method of claim 47 wherein the antibody or binding fragment of claim 1 comprises the ability to cause dissociation of cell-cell binding between activated endothelial cells and leukocytes, lymphocytes, sickled red cells, and/or platelets.

50. The method of claim 47 wherein the antibody or binding fragment of claim 1 comprises the ability to cause dissociation of cell-cell binding between activated platelets and leukocytes, lymphocytes, sickled red cells, and/or platelets.

51. The method of claim 47 wherein the antibody or binding fragment thereof comprises the ability to block the function of P-selectin by inhibiting the binding of activated endothelial cells to leukocytes, lymphocytes, sickled red cells and/or platelets.

52. The method of claim 47 wherein the antibody or binding fragment thereof comprises the ability to block the function of P-selectin by inhibiting the binding of activated platelets to leukocytes, lymphocytes, sickled red cells and/or platelets.

53. The method of claim 47 wherein the antibody is a monoclonal antibody designated herein as G1, hSel001, G4, or a humanized antibody comprising the CDRs of said monoclonal antibody.

54. A screening method, comprising: exposing a conformational epitope of P-selectin to a test antibody able to bind to the conformational epitope, forming an epitope-test antibody complex; exposing the epitope-test antibody complex to a PSGL-1 or a PSGL-1 mimetic able to bind to P-selectin; and concluding that the test antibody blocks the binding of PSGL-1 to P-selectin when the PSGL-1 or PSGL-1 mimetic is not able to bind to the epitope-test antibody complex.

55. The screening method of claim 54 wherein the conformational epitope is within amino acids 1-35 of SEQ ID NO:1.

56. The screening method of claim 54 wherein the conformational epitope is within amino acids 4-23 of SEQ ID NO:1.

57. The screening method of claim 54 wherein the conformational epitope comprises amino acid positions 4, 14, 17, 21, and 22 of SEQ ID NO:1.

58. The screening method of claim 57 wherein the conformational epitope further comprises amino acid positions 20 and 23 of SEQ ID NO:1.

59. The screening method of claim 57 wherein the amino acids in amino acid positions 4, 14, 17, 21, and 22 of SEQ ID:NO:1 are H, I, K, N, and R, respectively.

60. The screening method of claim 54 wherein the conformational epitope is provided as a component of an intact P-selectin protein which is bound to the substrate.

61. The screening method of claim 54 wherein the conformational epitope is provided as a component of a portion of P-selectin protein which is bound to the substrate.

62. The screening method of claim 54 wherein the conformational epitope is bound to a support substrate.

63. The screening method of claim 54 wherein the PSGL-1 or PSGL-1 mimetic is

bound to a support substrate.

64. A method of characterizing an anti-P-selectin antibody, comprising: providing a preformed P-selectin/PSGL-1 complex comprising an intact PSGL-1 protein, a PSGL-1 fragment, or a PSGL-1 mimetic which is bound to a P-selectin protein or fragment thereof which comprises a conformational epitope to which a function-blocking anti-P-selectin antibody can bind; exposing the preformed P-selectin/PSGL-1 complex to the anti-P-selectin antibody under conditions suitable for enabling the anti-P-selectin antibody to bind to the conformational epitope; and characterizing the anti-P-selectin antibody as to its ability to cause dissociation of the preformed P-selectin/PSGL-1 complex.

65. The method of claim 64 wherein the conformational epitope is within amino acids 1-35 of SEQ ID NO:1.

66. The method of claim 64 wherein the conformational epitope is within amino acids 4-23 of SEQ ID NO:1.

67. The method of claim 64 wherein the conformational epitope comprises amino acid positions 4, 14, 17, 21, and 22 of SEQ ID NO:1.

68. The method of claim 67 wherein the amino acids in amino acid positions 4, 14, 17, 21, and 22 are H, I, K, N, and R, respectively.

69. The method of claim 67 wherein the conformational epitope further comprises amino acid positions 20 and 23 of SEQ ID NO:1.

70. The method of claim 64 wherein the P-selectin protein or fragment thereof comprising the conformational epitope is bound to a support substrate.

71. The method of claim 64 wherein the intact PSGL-1 protein, PSGL-1 fragment thereof, or PSGL-1 mimetic is bound to a support substrate.

72. A testing substrate, comprising a support substrate and a conformational epitope bound to the support substrate and to which conformational epitope a function-blocking anti-P-selectin antibody can bind, wherein the conformational epitope is within amino acids 1-35 of SEQ ID NO:1.

73. The testing substrate of claim 72 wherein the conformational epitope is within amino acids 4-23 of SEQ ID NO:1.

74. The testing substrate of claim 72 wherein the conformational epitope comprises amino acid positions 4, 14, 17, 21, and 22 of SEQ ID NO:1.

75. The testing substrate of claim 72 wherein the conformational epitope further comprises amino acid positions 20 and 23 of SEQ ID NO:1.

76. The testing substrate of claim 72 wherein the amino acids in amino acid

positions 4, 14, 17, 21, and 22 of SEQ ID:NO:1 are H, I, K, N, and R, respectively.

77. The testing substrate of claim 72 wherein the conformational epitope is provided as a component of an intact P-selectin protein which is bound to the support substrate.

78. The testing substrate of claim 72 wherein the conformational epitope is provided as a component of a portion of P-selectin protein which is bound to the support substrate.

Human/Mouse P-selectin

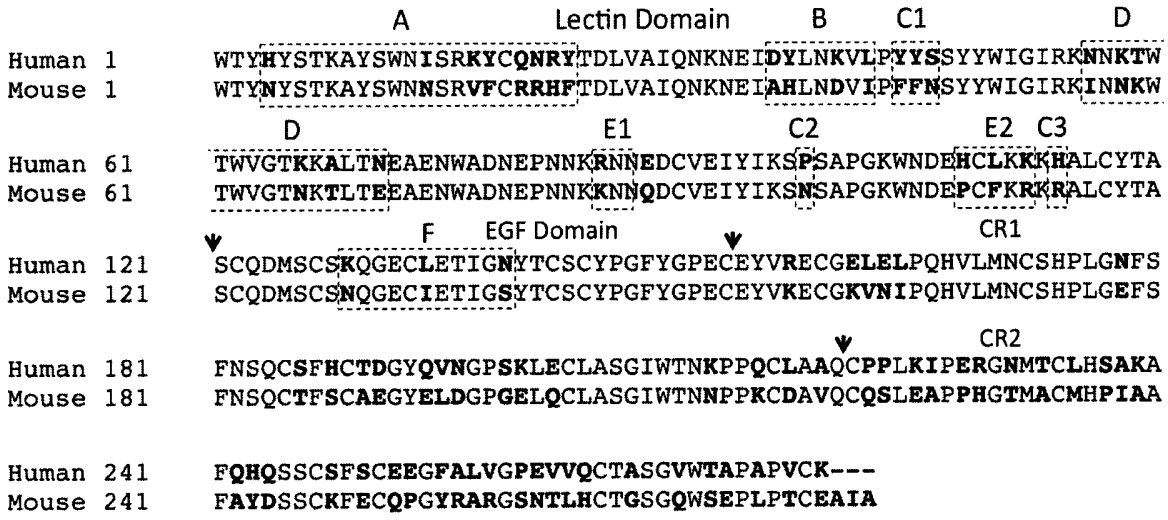


Figure 1

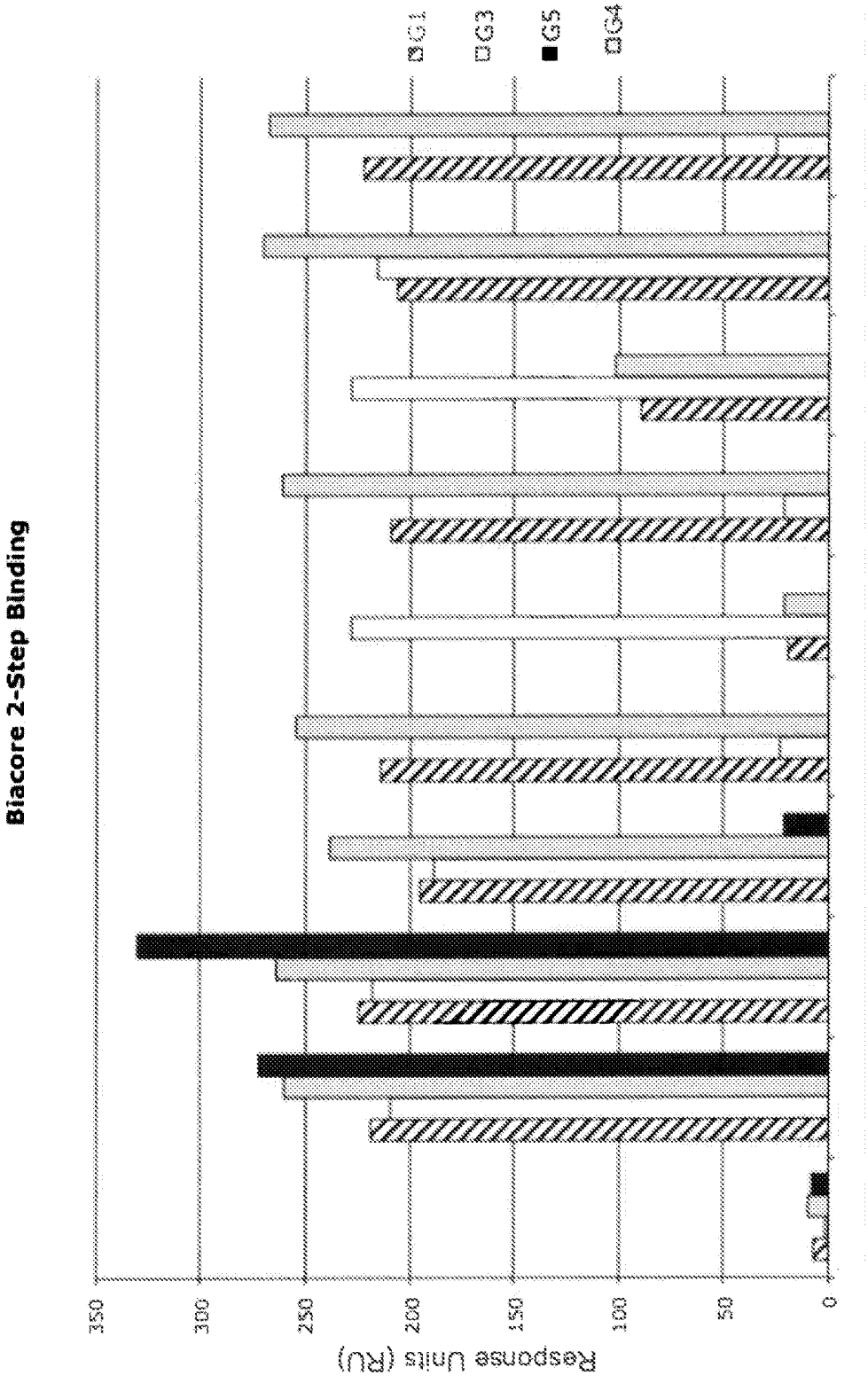

Biacore 2-Step Binding
Response Units (RU)
0
50
100
150
200
250
300
350
G1
G3
G5
G4
2
1
10
9
18
3
4
7
8
19
P-selectin Construct SeqID

Figure 2

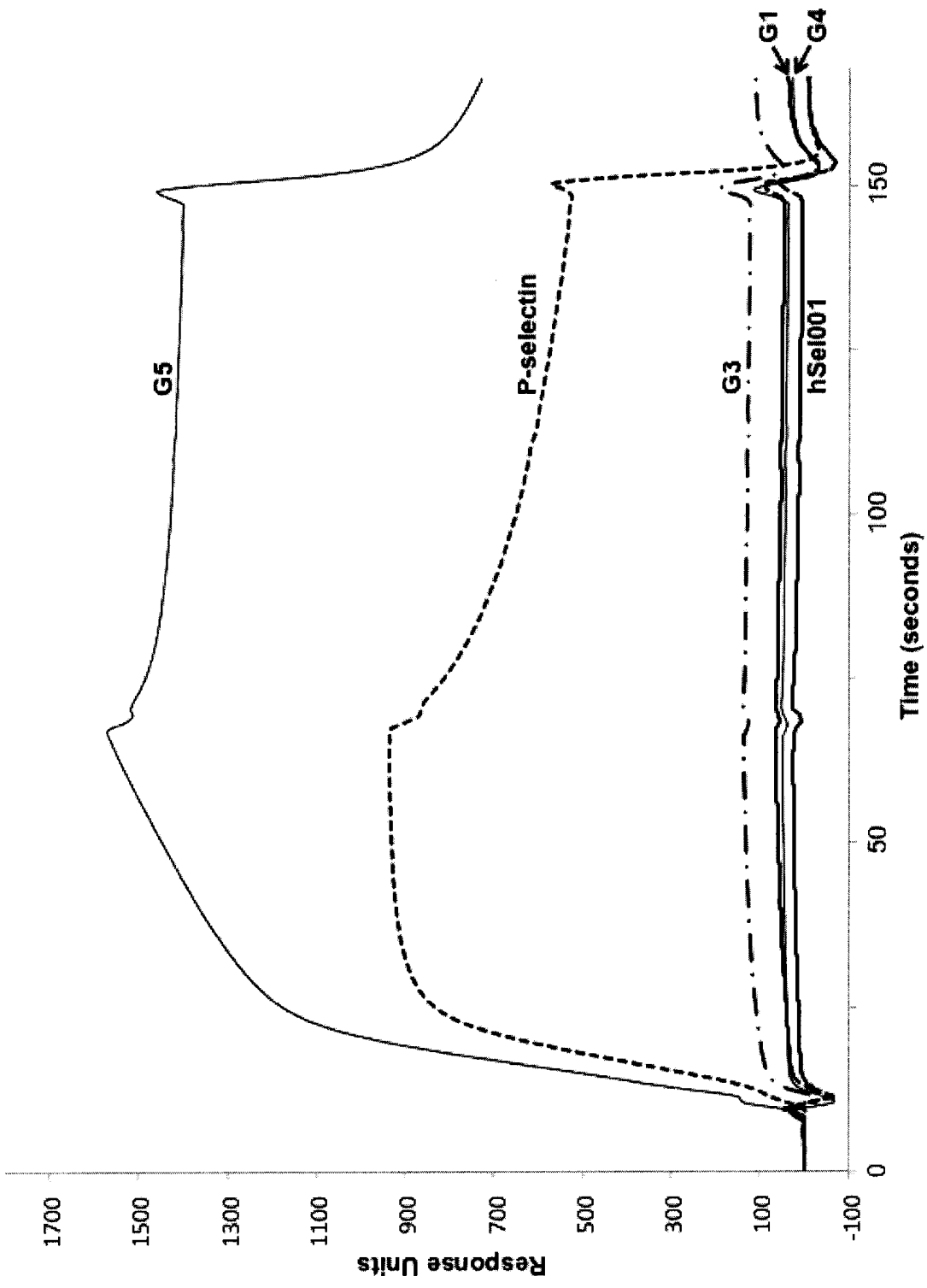

Response Units
1700
1500
1300
1100
900
700
500
300
100
-100
0
50
100
150
Time (seconds)
G5
P-selectin
G3
hSel001
G1
G4

Figure 3

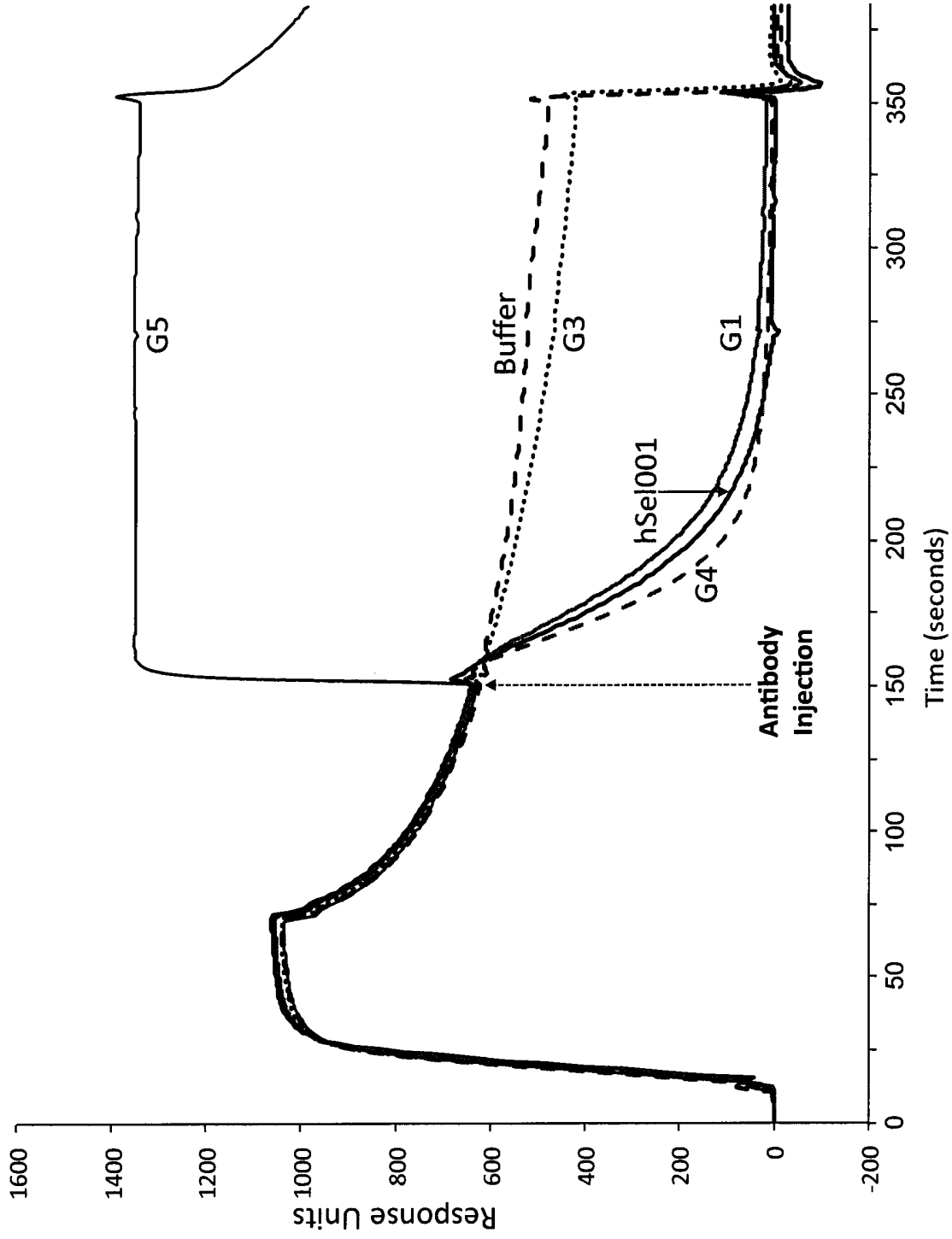

Response Units
1600
1400
1200
1000
800
600
400
200
0
-200
0
50
100
150
200
250
300
350
Time (seconds)
G5
Buffer
G3
G1
hSe|001
G4
Antibody
Injection

Figure 4

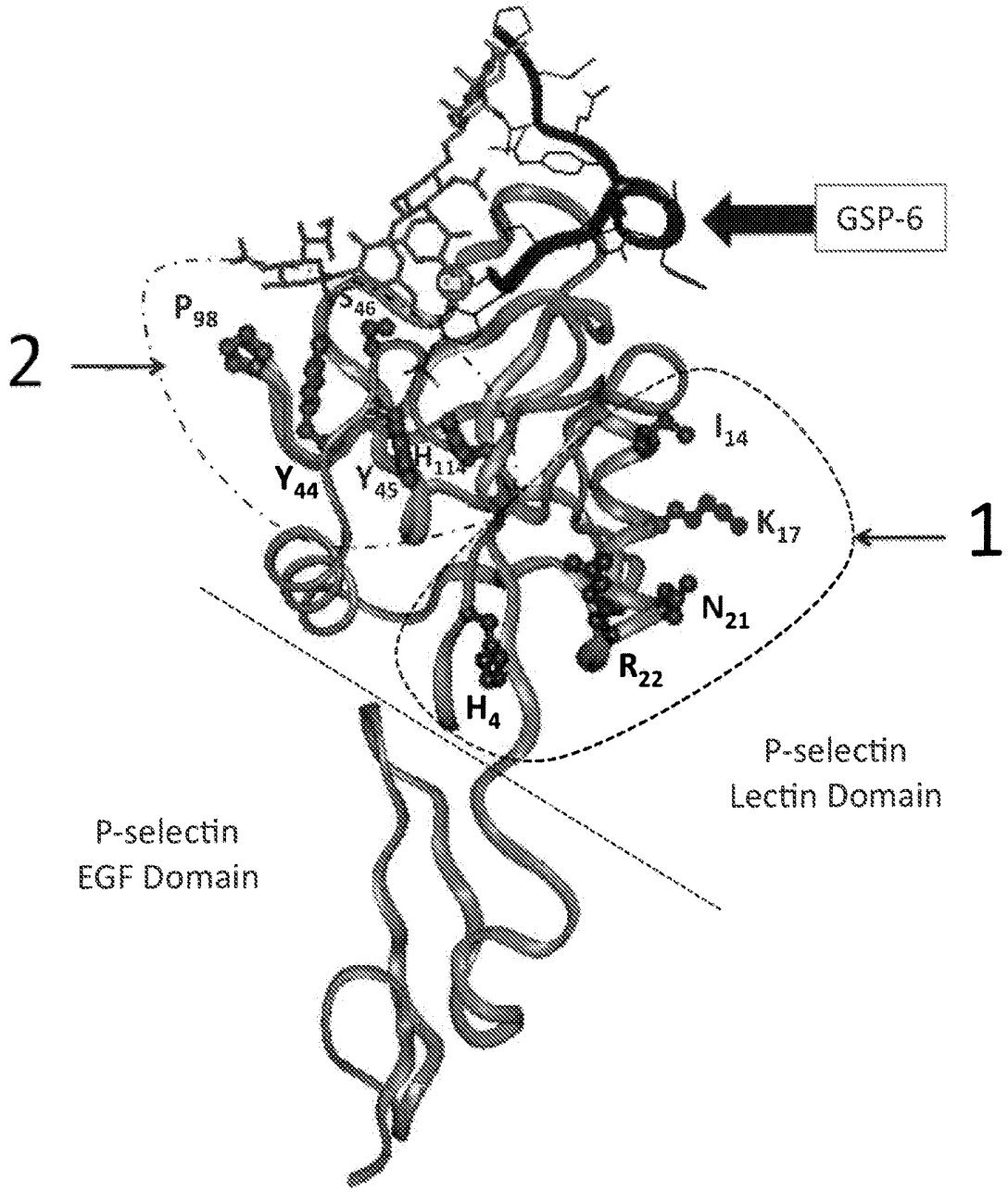

GSP-6
2
1
P_{98}
S_{46}
I_{14}
H_{11}
Y_{44}
Y_{45}
K_{17}
N_{21}
R_{22}
H_4
P-selectin
Lectin Domain
P-selectin
EGF Domain

Figure 5

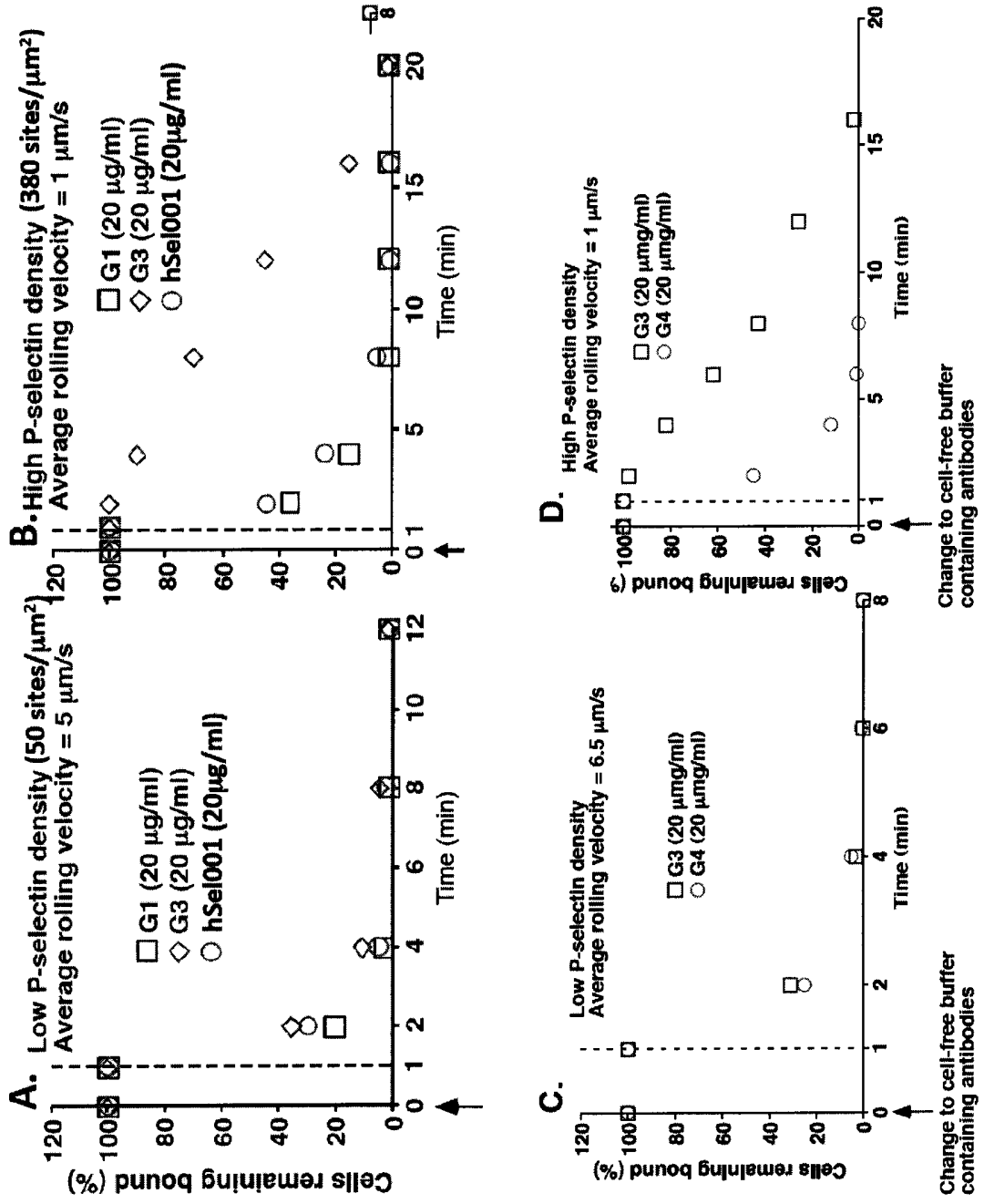

A.
Low P-selectin density (50 sites/μm²)
Average rolling velocity = 5 μm/s
Cells remaining bound (%)
Time (min)
G1 (20 μg/ml)
G3 (20 μg/ml)
hSel001 (20μg/ml)
B.
High P-selectin density (380 sites/μm²)
Average rolling velocity = 1 μm/s
Time (min)
G1 (20 μg/ml)
G3 (20 μg/ml)
hSel001 (20μg/ml)
C.
Low P-selectin density
Average rolling velocity = 6.5 μm/s
Cells remaining bound (%)
Time (min)
G3 (20 μmg/ml)
G4 (20 μmg/ml)
Change to cell-free buffer containing antibodies
D.
High P-selectin density
Average rolling velocity = 1 μm/s
Cells remaining bound (%)
Time (min)
G3 (20 μmg/ml)
G4 (20 μmg/ml)
Change to cell-free buffer containing antibodies

Figure 6

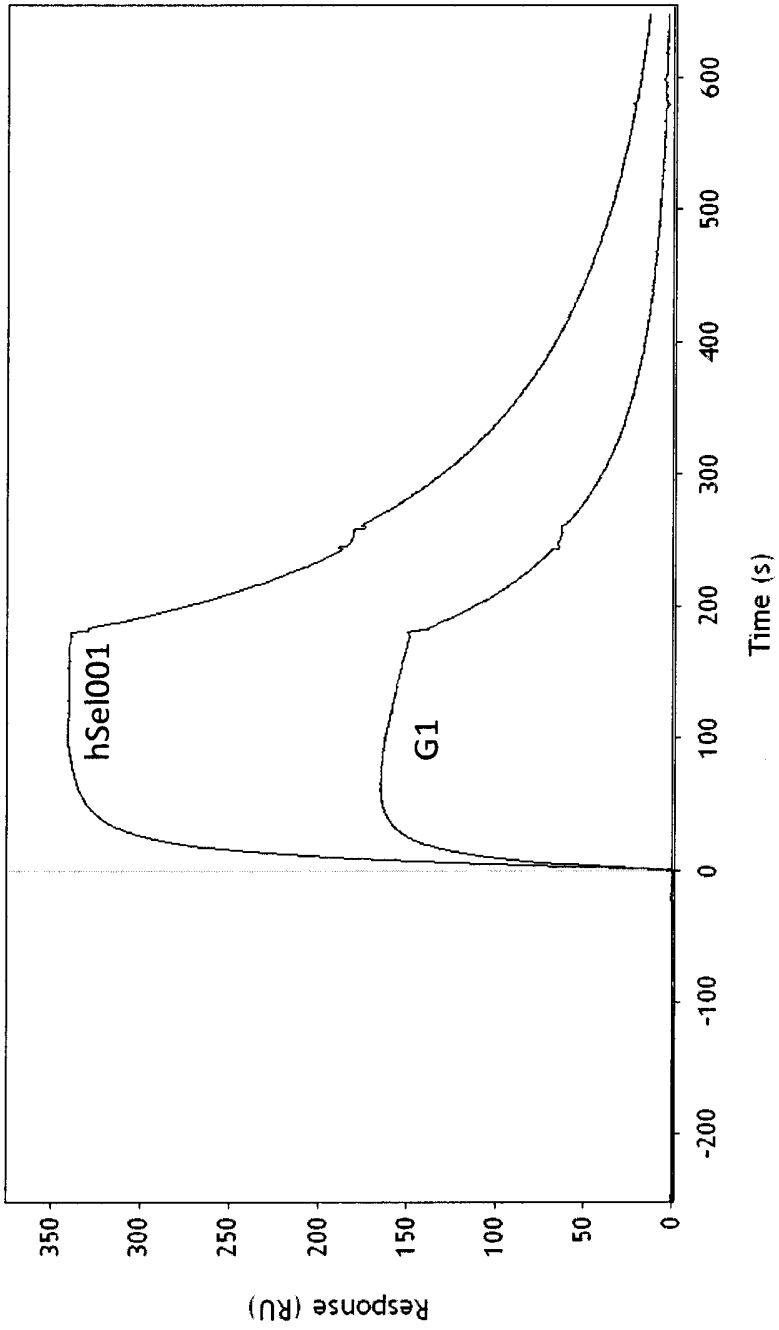

Response (RU)
350
300
250
200
150
100
50
0
-200
-100
0
100
200
300
400
500
600
Time (s)
hSel001
G1

Figure 7

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 11/66470

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 39/00 (2012.01)
USPC - 424/139.1; 424/142.1
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC(8) - A61K 39/00 (2012.01)
USPC - 424/139.1; 424/142.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 530/388.15; 530/395

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST(USPT, PGPB, EPAB, JPAB); Google Scholar: P-selectin, P-selectin glycoprotein ligand-1, PSGL-1, antibody, monoclonal, conformational, epitope, platelet, endothelial cell, pharmaceutical, hybridoma, reperfusion, myocardial infarction, stroke, organ transplant, screen, lectin, chimeric, human, humanized, complex, G1, hSe1001,G4

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2010/0209423 A1 (GRAUS, et al.) 19 August 2010 (19.08.2010) para [0015]-[0018], [0023], [0029], [0051], [0055], [0056], [0058], [0065]-[0067], [0073], [0080], [0083], [0088], [0117], [0121], [0124], [0127]; claim 1	1-20, 25-53, 64-78
Y	US 5,593,882 A (ERBE, et al.) 14 January 1997 (14.01.1997) col 3, ln 61-66; col 4, ln 10-65; col 9, ln 22-42; col 12, ln 30-35; SEQ ID NO:39	1-20, 25-78
Y	US 2009/0285812 A1 (ALVAREZ et al.) 19 November 2009 (19.11.2009) para [0134]-[0136], claim 14	54-63
Y	MOORE, et al. P-selectin glycoprotein ligand-1 mediates rolling of human neutrophils on P-selectin. J Cell Biol, February 1995, 128(4):661-671; pg 662, left col, para 3	46, 53
X,P	US 2011/0293617 A1 (ROLLINS, et al.) 1 December 2011 (01.12.2011)	1-78
X,P	US 2011/0287017 A1 (ROLLINS, et al.) 24 November 2011 (24.11.2011)	1-78
X,P	US 2011/0212096 A1 (ROLLINS, et al.) 1 September 2011 (01.09.2011)	1-78

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2012 (04.04.2012)	24 APR 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 September 2011 (09.09.2011)

PCT

(10) International Publication Number
WO 2011/107480 A1

(51) International Patent Classification:
A61K 39/395 (2006.01) *C07K 16/18* (2006.01)
A61P 25/28 (2006.01)

(21) International Application Number:
PCT/EP2011/053038

(22) International Filing Date:
1 March 2011 (01.03.2011)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/309,957 3 March 2010 (03.03.2010) US

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford Middlesex UB6 0NN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **BHINDER, Tejinder, Kaur** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **FORD, Susannah, Karen** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **GERMASCHEWSKI, Volker** [DE/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **LEWIS, Alan, Peter** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage Hertfordshire SG1 2NY (GB). **PEPYS, Mark, Brian** [GB/GB]; Pentraxin Therapeutics Ltd, UCL Business PLC, Network Building, 97 Tottenham Court Road, London W1T 4TP (GB).

(74) Agent: **REDDISH, Anna**; GlaxoSmithKline, Global Patents (CN925.1), 980 Great West Road, Brentford Middlesex TW8 9GS (GB).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2011/107480 A1

(54) **Title**: ANTIGEN BINDING PROTEINS SPECIFIC FOR SERUM AMYLOID P COMPONENT

(57) **Abstract**: The present invention relates to antigen binding proteins, such as antibodies, which bind to serum amyloid P component (SAP), polynucleotides encoding such antigen binding proteins, pharmaceutical compositions comprising said antigen binding proteins and methods of manufacture. The present invention also concerns the use of such antigen binding proteins in the treatment or prophylaxis of diseases associated with amyloid deposition including systemic amyloidosis, local amyloidosis, Alzheimer's disease, and type 2 diabetes.

FIELD OF INVENTION

The present invention relates to antigen binding proteins, such as antibodies, which bind to serum amyloid P component (SAP), polynucleotides encoding such antigen binding proteins, pharmaceutical compositions comprising said antigen binding proteins and methods of manufacture. The present invention also concerns the use of such antigen binding proteins in the treatment or prophylaxis of diseases associated with amyloid deposition including systemic amyloidosis, local amyloidosis, Alzheimer's disease, and type 2 diabetes.

BACKGROUND OF THE INVENTION

Amyloidosis is a serious and usually fatal disease caused by the extracellular accumulation in the tissues of abnormal insoluble protein fibres known as amyloid fibrils. These are derived from more than 20 different proteins in different forms of the disease but all amyloid fibrils share a common cross-β core structure and all are derived by misfolding of normally soluble precursor proteins (Pepys, M.B. (2006) Annu. Rev. Med., 57: 223-241). A normal non-fibrillar plasma protein, serum amyloid P component (SAP), is also always present in amyloid deposits by virtue of its avid specific calcium dependent binding to all types of amyloid fibrils (Pepys et al. (1979) Clin. Exp. Immunol., 38: 284-293; Pepys et al. (1997) Amyloid: Int. J. Exp. Clin. Invest., 4: 274-295).

Human SAP is a constitutive protein in the plasma, at a concentration of around 20-40 mg/l (Nelson et al. (1991) Clin. Chim. Acta, 200:191-200) and with a total of about 50-100 mg of SAP in the combined plasma and extravascular compartments both of normal individuals and patients with diseases other than amyloidosis (Hawkins et al. (1990) J. Clin. Invest., 86: 1862-1869). In patients with amyloidosis, SAP is also specifically concentrated in the amyloid deposits and in an individual with extensive systemic amyloidosis there may be as much as 20,000 mg of SAP in the amyloid (Pepys et al. (1994) PNAS, 91: 5602-5606), reversibly bound to the fibrils and in equilibrium with the fluid phase SAP pool. The normal physiological function of circulating SAP is poorly understood, but animal experiments and *in vitro* studies suggest a role in host defence (Noursadeghi et al. (2000) PNAS, 97: 14584-14589)). SAP is also a normal tissue matrix constituent associated with elastic fibres and the glomerular basement membrane although its function there is not known.

In amyloidosis, the extracellular amyloid deposits cause disease by progressive accumulation until they damage the structure and thus the function of whatever tissue they occupy (Pepys, M.B. (2006) Annu. Rev. Med., 57: 223-241). There is very rarely any inflammatory or 'foreign body' response to amyloid deposition, either seen locally in the tissues or suggested by systemic markers of inflammation. Systemic amyloidosis can involve any organ, is usually fatal and causes ~1 per thousand deaths in developed countries. Localised amyloid, confined to a single anatomical location or tissue type, can also be very serious, for example cerebral amyloid angiopathy is an important cause of haemorrhagic stroke. The clinical presentations of amyloidosis are extremely diverse and the diagnosis is rarely made before significant organ damage is present. Over 20 different amyloid fibril proteins are responsible for different forms of amyloidosis, but treatments that substantially reduce the abundance of the respective amyloid fibril precursor protein do halt amyloid accumulation and the deposits may regress. Unfortunately effective measures are not always available and, when they do exist, are toxic or hazardous and slow to act (Pepys, M.B (2006) Annu. Rev. Med., 57: 223-241). There is therefore a major unmet medical need for therapy which safely promotes the clearance of established amyloid deposits. Furthermore, there are other conditions in which amyloid deposits are always present, most importantly Alzheimer's disease (AD) and type 2 diabetes mellitus, in which the contribution of amyloid deposition to the pathogenesis of disease, specifically loss of cognitive and pancreatic islet function, respectively, is not known (Pepys, M.B. (2006) Annu. Rev. Med., 57: 223-241). However, amyloid deposits anywhere else in the body are demonstrably pathogenic and it is likely that the cerebral deposits of AD and the islet amyloid deposits of type 2 diabetes are also harmful. Since treatment which clears amyloid deposits in systemic amyloidosis will certainly be therapeutic (Pepys, M.B. (2006) Annu. Rev. Med., 57: 223-241), removal of the amyloid deposits in AD and type 2 diabetes should also be clinically beneficial.

Binding of SAP stabilises amyloid fibrils, protects them from proteolysis *in vitro* (Tennent et al., (1995) PNAS, 92: 4299-4303), can enhance amyloid fibrillogenesis *in vitro* (Myers et al., (2006), Biochemistry, 45: 2311-2321) and contributes to pathogenesis of systemic amyloidosis *in vivo* (Botto et al., (1997) Nature Med., 3: 855-859). Coupled with its universal

presence in all amyloid deposits, these properties of SAP make it an attractive therapeutic target.

European patent application EP 0915088 discloses D-proline derivative compounds that are competitive inhibitors of binding of SAP to amyloid fibrils, as well as methods for their manufacture. A preferred compound disclosed in EP 0915088 is (R)-1-[6-[(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo oxohexanoyl] pyrrolidine-2-carboxylic acid (CPHPC).

International patent application WO 03/051836 discloses prodrugs for D-proline derivative compounds.

International patent application WO 2004/099173 discloses glycerol cyclic pyruvate derivatives that are competitive inhibitors of binding of SAP to amyloid fibrils.

International patent application WO 04/059318 describes methods which are asserted to enhance fibrocyte formation which comprise the provision of compositions which bind SAP. Such compositions include anti-SAP antibodies and CPHPC. WO 04/059318 does not disclose the treatment of disease associated with amyloid deposition. Furthermore, there is compelling clinical and *in vivo* evidence that neither SAP nor its depletion have any effect on fibrosis in humans (Tennent et al., (2007) Arthritis Rheum., 56: 2013-2017; Pepys, M.B., Tennent, G.A. and Denton, C.P. (2007) Reply to Letter from Pilling, D., Buckley, C.D., Salmon, M. and Gomer, R.G., Serum amyloid P and fibrosis in systemic sclerosis: comment on the article by Tennent et al. *Arthritis Rheum.,* 56**:** 4229-4230).

The bis-D-proline compound, CPHPC, disclosed in the patents listed above, is bound with high affinity by human SAP and was intended as a drug to remove SAP from amyloid deposits *in vivo* and thereby facilitate their clearance. Binding of CPHPC by SAP triggers rapid clearance of the complex by the liver, depletes almost all circulating SAP for as long as the drug is administered, and removes much but not all amyloid bound SAP (Pepys et al., (2002) Nature, 417: 254-259). In initial clinical studies (Gillmore et al., (2010) Brit. J. Haematol., doi:10.1111/j.1365-2141.2009.08036.x), administration of CPHPC seemed to

arrest amyloid accumulation but it did not produce amyloid regression and since CPHPC does not completely remove all SAP from amyloid deposits, another approach is needed.

International patent application WO 2009/000926 discloses the use of compounds which deplete SAP from the circulation, such as D-proline derivatives, in particular CPHPC, in combination with an antibody specific for SAP for the treatment or prophylaxis of amyloidosis.

Related International patent application PCT/EP2008/011135 concerns various mouse monoclonal antibodies which may be used in combination with compounds which deplete SAP from the circulation, such as D-proline derivatives, in particular CPHPC, for the treatment or prophylaxis of amyloidosis.

Accordingly, there is a need in the art for antibodies, particularly humanised or human antibodies, which specifically target SAP and provide improved therapeutic efficacy in patients, particularly human patients, with diseases associated with amyloid deposition in order to preserve organ function and prolong life.

SUMMARY OF THE INVENTION

The present invention provides, in a first aspect, an antigen binding protein which specifically binds to SAP and competes for binding to SAP with a reference antibody which comprises a heavy chain variable region sequence of SEQ ID NO:7, and a light chain variable region sequence of SEQ ID NO:9.

In a second aspect of the invention, there is provided an antigen binding protein which binds to SAP and comprises CDRH3 set forth in SEQ ID NO: 3 or a functional variant of CDRH3.

In a third aspect of the invention, there is provided an antigen binding protein which specifically binds to SAP, wherein the antigen binding protein is a chimeric or a humanised antibody comprising the corresponding CDRH3 of the variable domain sequence of SEQ ID NO:7, or a functional variant of CDRH3.

In a fourth aspect of the invention, there is provided an antigen binding protein which specifically binds to SAP, and comprises a binding unit H3 comprising Kabat residues 95-101 of SEQ ID NO:7, or a functional variant of binding unit H3.

In a fifth aspect of the invention, there is provided an antigen binding protein which specifically binds to SAP and comprises a heavy chain variable region selected from SEQ ID NO:27-31; and/or a light chain variable region selected from SEQ ID NO:34-36; or a variant heavy chain variable region or light chain variable region with 75% or greater sequence identity.

In a sixth aspect of the invention, there is provided an antigen binding protein which specifically binds to SAP and comprises a heavy chain of SEQ ID NO:62; and/or a light chain of SEQ ID NO:64; or a variant heavy chain or light chain with 75% or greater sequence identity.

The present invention also provides a nucleic acid molecule encoding an antigen binding protein of the invention, expression vectors comprising the same, and host cells capable of producing antigen binding proteins of the invention.

In a further aspect of the invention a pharmaceutical composition comprising an antigen binding protein as defined herein is provided. The present invention also provides methods of preventing and/or treating a subject susceptible to or afflicted with a disease associated with amyloid deposition, which method comprises the step of administering a prophylactically or therapeutically effective amount of an antigen binding protein to said subject. The use of an antigen binding protein as defined herein for preventing and/or treating a subject susceptible to or afflicted with a disease associated with amyloid deposition is provided. The use of an antigen binding protein as defined herein for the manufacture of a medicament for preventing and/or treating a subject susceptible to or afflicted with a disease associated with amyloid deposition is also provided.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows the binding curves for murine antibodies SAP-E and SAP-K at a 1 μg/mL coating concentration of human SAP.

Figure 2 shows the binding curves for murine antibodies SAP-E and SAP-K at a 5 μg/mL coating concentration of human SAP.

Figure 3 shows the binding curves for chimeric antibodies cSAP-E and cSAP-K. The profile of the curves for the chimeric antibodies is the same as that of the equivalent hybridomas.

Figure 4 shows the binding curves for SAP-K H0L0, SAP-K H1L0, SAP-K H2L0 and SAP-K H3L0 compared to the SAP-K chimera and the SAP-E H1L1 compared to the SAP-E chimera. An irrelevant human IgG1 kappa antibody was also tested as a negative control.

Figure 5 shows purified SAP-K and SAP-E murine monoclonal antibodies in a competition ELISA with the SAP-E chimera.

Figure 6 shows purified SAP-K and SAP-E murine monoclonal antibodies in a competition ELISA with the SAP-K chimera.

Figure 7 shows an immunoradiometric assay for binding of monoclonal mouse antibodies SAP-E and SAP-K to human SAP captured by immobilised sheep polyclonal anti-human SAP antibody.

Figure 8 shows epitope mapping for monoclonal anti-human SAP antibody SAP-E.

Figure 9 shows the location of the epitopes on human SAP recognised by SAP-K (A, highlighted in black) and SAP-E (B, shown in white).

Figure 10 shows C3 activation by humanised monoclonal anti-human SAP antibodies in whole human serum.

Figure 11 shows C3 activation by low dose humanised monoclonal anti-human SAP antibodies in whole human serum.

Figure 12 shows C3 activation by humanised monoclonal anti-human SAP antibodies in whole mouse serum supplemented with pure human SAP.

DETAILED DESCRIPTION OF THE INVENTION

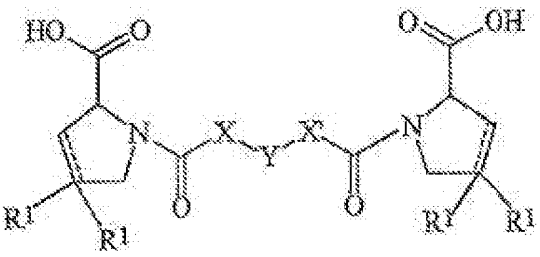
The present invention provides an antigen binding protein which binds to serum amyloid P component (SAP), for example human SAP, as its specific antigen (i.e. a SAP binding protein). In therapeutic applications of the invention, the antigen binding protein activates the body's potent mechanisms for clearance of abnormal debris from tissues. The antigen binding protein may be an antibody, for example a monoclonal antibody. An antigen binding protein of the invention is not a murine antibody. In an embodiment, an antigen binding protein of the invention is not a murine antigen binding protein. In particular, an antigen binding protein of the invention is a chimeric, humanised or human antigen binding protein.

"Serum amyloid P component" or "SAP" refers to a homopentameric plasma glycoprotein of the pentraxin family. Each molecule is composed of 5 identical protomers, each with a flattened β-jelly roll fold and single alpha helix, non-covalently associated in a disc-like ring with cyclic pentameric symmetry (Hutchinson et al., (2000) Mol. Med., 6: 482-493); Pepys et al., (2002) Nature, 417: 254-259). The term "SAP" as used herein also includes the individual subunit encoded by the human gene APCS (chromosome: 1; Location: 1q21-q23) or homologous genes in other organisms, for example the human SAP polypeptide subunit having the sequence as set forth in SEQ ID NO:43 as well as the native pentameric form of SAP, and any fragments and variants of SAP that retain the biological activity of binding to amyloid fibrils *in vivo*.

The SAP binding protein of the invention can bind to any one or any combination of the above described different forms of SAP. In a particular embodiment, the antigen binding protein of the invention binds human SAP. The SAP binding protein of the invention can bind to SAP when the SAP is bound to amyloid fibrils of any type and in any extracellular

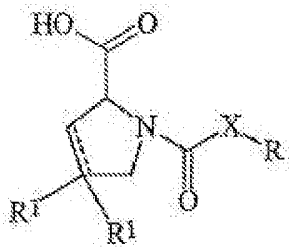
location within the body. The antigen binding protein of the invention may also bind to native unbound SAP.

An essential aspect of utilising SAP-binding proteins of the invention in therapeutic methods is that the concentration of SAP in the circulation must be reduced by at least 90% below its normal value before administration of the SAP-binding protein. Specifically, this can be achieved by compounds that decrease the amount of circulating SAP and, in particular, compounds that result in the depletion of circulating SAP, defined here as "SAP depleting compounds". Such compounds are ligands bound by SAP and are competitive inhibitors of the binding of SAP to amyloid fibrils, such as D-proline derivatives and glycerol cyclic pyruvate derivatives. D-proline derivatives are disclosed in EP 0915088, which is incorporated herein by reference in its entirety, and the term "D-proline derivatives" includes prodrugs, such as those disclosed in WO 03/051836, which is also incorporated herein by reference in its entirety. D-prolines of the following formula are contemplated:



I-A

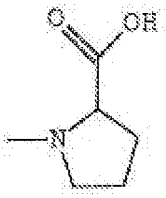
or



I-B

wherein

R is



and the group

R^1 is hydrogen or halogen;

and

X is $-(CH_2)_n-$; $-CH(R^2)(CH_2)_n-$; $-CH_2O(CH_2)_n-$; $-CH_2NH-$;

$-C(R^2)=CH-$; $-CH_2CH(OH)-$; or thiazol-2,5-diyl; -O-;

Y is –S-S-; $-(CH_2)n-$; -O-; -NH-; $-N(R^2)-$; -CH=CH-; -NHC(O)NH-; $-N(R^2)C(O)N(R^2)-$; $-N[CH_2C_6H_3(OCH_3)_2]-$; $-N(CH_2C_6H_5)-$; $-N(CH_2C_6H_5)C(O)N(CH_2C_6H_5)-$; -N(alkoxyalkyl)-; N(cycloalkyl-methyl)-; 2,6-pyridyl; 2,5-furanyl; 2,5-thienyl; 1,2-cyclohexyl; 1,3-cyclohexyl; 1,4-cyclohexyl; 1,2-naphthyl; 1,4-naphthyl; 1,5-naphthyl; 1,6-naphthyl; or 1,2-phenylene, 1,3-phenylene and 1,4-phenylene, wherein the phenylene groups are optionally substituted by 1-4 substituents, selected from halogen, lower alkyl, lower alkoxy, hydroxyl, carboxy, -COO-lower alkyl, nitrilo, 5-tetrazol, (2-carboxylic acid pyrrolidin-1-yl)-2-oxo-ethoxy, N-hydroxycarbamimiodyl, 5-oxo[1,2,4oxadiazolyl, 2-oxo [1,2,3,5] oxathiadiazolyl, 5-thioxo[1,2,4]oxadiazolyl and 5-tert-butylsulfanyl-[1,2,4]oxadiazolyl;

X' is $-(CH_2)n-$; $-(CH_2)_nCH(R_2)-$; $-(CH_2)_nOCH_2-$; $-NHCH_2-$; $-CH=C(R^2)-$; $CH(OH)CH_2$; or thiazol-2,5-diyl; -O-;

R^2 is lower alkyl, lower alkoxy or benzyl,

n is 0-3 and wherein

alkyl or lower alkyl is C_{1-6} alkyl; alkoxy or lower alkoxy is C_{1-6} alkoxy; cycloalkyl is C_{3-6} cyclocalkyl; halogen is F, Cl or Br; and the location where the dotted line appears in the formula is either a single or double bond;

or a pharmaceutically acceptable salt or mono- or diester thereof.

D-prolines of formula I-A above can be written as Ligand - linker - Ligand, wherein the X-Y-X' moiety of formal I-A forms the linker. The linker (X-Y-X') can be from 4 to 20 linear carbon atoms in length, including from 4-15 linear carbon atoms, 5-10 linear carbon atoms, and 6-8 linear carbon atoms in length. The linker can be a straight or branched chain, or can optionally form one or more ring structures, with the proviso that at least 4 linear or straight-chain carbon atoms are present in the linker. At least one of the linear or straight-

chain C atoms can be optionally substituted by at least one hetero atom selected from N, O, or S, advantageously O or S, advantageously O.

Thus, an "optionally substituted linker" can have one or more substitutions that lead to branching and/or one or more substitutions of carbon atom(s) of the linear or straight chain carbon atoms of the linker, e.g. the linker can be an ether or a substituted ether.

(R)-1-[6-[(R)-2-Carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid(CPHPC) is a specific D-proline contemplated by the invention. In a particular embodiment, CPHPC is to be administered to a human patient.

Gylcerol cyclic pyruvate derivatives are disclosed in WO 2004/099173, which is incorporated herein by reference in its entirety.

The term "antigen binding protein" as used herein refers to antibodies, antibody fragments and other protein constructs, such as domains, which are capable of binding to SAP.

The term "antibody" is used herein in the broadest sense to refer to molecules with an immunoglobulin-like domain and includes monoclonal, recombinant, polyclonal, chimeric, humanised, bispecific and heteroconjugate antibodies; a single variable domain, a domain antibody, antigen binding fragments, immunologically effective fragments, single chain Fv, diabodies, Tandabs™, etc. (for a summary of alternative "antibody" formats see Holliger and Hudson, Nature Biotechnology, 2005, Vol 23, No. 9, 1126-1136).

The phrase "single variable domain" refers to an antigen binding protein variable domain (for example, VH, VHH, VL) that specifically binds an antigen or epitope independently of a different variable region or domain.

A "domain antibody" or "dAb" may be considered the same as a "single variable domain" which is capable of binding to an antigen. A single variable domain may be a human antibody variable domain, but also includes single antibody variable domains from other species such as rodent (for example, as disclosed in WO 00/29004), nurse shark and Camelid

VHH dAbs. Camelid VHH are immunoglobulin single variable domain polypeptides that are derived from species including camel, llama, alpaca, dromedary, and guanaco, which produce heavy chain antibodies naturally devoid of light chains. Such VHH domains may be humanised according to standard techniques available in the art, and such domains are considered to be "domain antibodies". As used herein VH includes camelid VHH domains.

As used herein the term "domain" refers to a folded protein structure which has tertiary structure independent of the rest of the protein. Generally, domains are responsible for discrete functional properties of proteins, and in many cases may be added, removed or transferred to other proteins without loss of function of the remainder of the protein and/or of the domain. A "single variable domain" is a folded polypeptide domain comprising sequences characteristic of antibody variable domains. It therefore includes complete antibody variable domains and modified variable domains, for example, in which one or more loops have been replaced by sequences which are not characteristic of antibody variable domains, or antibody variable domains which have been truncated or comprise N- or C-terminal extensions, as well as folded fragments of variable domains which retain at least the binding activity and specificity of the full-length domain. A domain can bind an antigen or epitope independently of a different variable region or domain.

An antigen binding fragment may be provided by means of arrangement of one or more CDRs on non-antibody protein scaffolds such as a domain. The domain may be a domain antibody or may be a domain which is a derivative of a scaffold selected from the group consisting of CTLA-4, lipocalin, SpA, an Affibody, an avimer, GroEl, transferrin, GroES and fibronectin/adnectin, which has been subjected to protein engineering in order to obtain binding to an antigen, such as SAP, other than the natural ligand.

An antigen binding fragment or an immunologically effective fragment may comprise partial heavy or light chain variable sequences. Fragments are at least 5, 6, 7, 8, 9 or 10 amino acids in length. Alternatively the fragments are at least 15, at least 20, at least 50, at least 75, or at least 100 amino acids in length.

The term "specifically binds" as used throughout the present specification in relation to antigen binding proteins means that the antigen binding protein binds to SAP with no or insignificant binding to any other proteins, including closely related molecules such as C-reactive protein (CRP) which, in humans, shares 55% of strict residue for residue amino acid sequence homology and has essentially the same protein fold.

The equilibrium dissociation constant (KD) of the antigen binding protein-SAP interaction may be 1 mM or less, 100 nM or less, 10 nM or less, 2 nM or less or 1 nM or less. Alternatively the KD may be between 5 and 10 nM; or between 1 and 2 nM. The KD may be between 1 pM and 500 pM; or between 500 pM and 1 nM.

The binding affinity may be measured by BIAcore™, for example by antigen capture with SAP coupled onto a carboxymethydextran chip by primary amine coupling and antibody capture onto this surface. Alternatively, the binding affinity can be measured by BIAcore™ by binding of anti-SAP antibodies to human SAP captured by O-phosphoethanolamine immobilised on a CM5 chip. The BIAcore™ methods described in Example 8 may be used to measure binding affinity.

The dissociation rate constant (kd) may be $1x10^{-3}$ s^{-1} or less, $1x10^{-4}$ s^{-1} or less, or $1x10^{-5}$ s^{-1} or less. The kd may be between $1x10^{-5}$ s^{-1} and $1x10^{-4}$ s^{-1}; or between $1x10^{-4}$ s^{-1} and $1x10^{-3}$ s^{-1}. A small kd may result in a slow dissociation of the antigen binding protein-ligand complex and improved clearance of complexes of SAP bound to amyloid.

It will be apparent to those skilled in the art that the term "derived" is intended to define not only the source in the sense of it being the physical origin for the material but also to define material which is structurally identical to the material but which does not originate from the reference source. Thus "residues found in the donor antibody" need not necessarily have been purified from the donor antibody.

By "isolated" it is intended that the molecule, such as an antigen binding protein, is removed from the environment in which it may be found in nature. For example, the

molecule may be purified away from substances with which it would normally exist in nature. For example, the mass of the molecule in a sample may be 95% of the total mass.

A "chimeric antibody" refers to a type of engineered antibody which contains a naturally-occurring variable region (light chain and heavy chains) derived from a donor antibody in association with light and heavy chain constant regions derived from an acceptor antibody.

A "humanised antibody" refers to a type of engineered antibody having its CDRs derived from a non-human donor immunoglobulin, the remaining immunoglobulin-derived parts of the molecule being derived from one or more human immunoglobulin(s). In addition, framework support residues may be altered to preserve binding affinity (see, e.g., Queen et al. Proc. Natl Acad Sci USA, 86:10029-10032 (1989), Hodgson et al. Bio/Technology, 9:421 (1991)). A suitable human acceptor antibody may be one selected from a conventional database, e.g., the KABAT® database, Los Alamos database, and Swiss Protein database, by homology to the nucleotide and amino acid sequences of the donor antibody. A human antibody characterized by a homology to the framework regions of the donor antibody (on an amino acid basis) may be suitable to provide a heavy chain constant region and/or a heavy chain variable framework region for insertion of the donor CDRs. A suitable acceptor antibody capable of donating light chain constant or variable framework regions may be selected in a similar manner. It should be noted that the acceptor antibody heavy and light chains are not required to originate from the same acceptor antibody. The prior art describes several ways of producing such humanised antibodies – see for example EP-A-0239400 and EP-A-054951.

The term "donor antibody" refers to an antibody which contributes the amino acid sequences of its variable regions, CDRs, or other functional fragments or analogs thereof to a first immunoglobulin partner. The donor therefore provides the altered immunoglobulin coding region and resulting expressed altered antibody with the antigenic specificity and neutralising activity characteristic of the donor antibody.

The term "acceptor antibody" refers to an antibody which is heterologous to the donor antibody, which contributes all (or any portion) of the amino acid sequences encoding its

heavy and/or light chain framework regions and/or its heavy and/or light chain constant regions to the first immunoglobulin partner. A human antibody may be the acceptor antibody.

The term “human antibody” refers to an antibody derived from human immunoglobulin gene sequences. These fully human antibodies provide an alternative to re-engineered, or de-immunized, rodent monoclonal antibodies (e.g. humanised antibodies) as a source of low immunogenicity therapeutic antibodies and they are normally generated using either phage display or transgenic mouse platforms. In an embodiment, an antibody of the invention is a human antibody.

The terms “VH” and “VL” are used herein to refer to the heavy chain variable region and light chain variable region respectively of an antigen binding protein.

“CDRs” are defined as the complementarity determining region amino acid sequences of an antigen binding protein. These are the hypervariable regions of immunoglobulin heavy and light chains. There are three heavy chain and three light chain CDRs (or CDR regions) in the variable portion of an immunoglobulin. Thus, "CDRs" as used herein refers to all three heavy chain CDRs, all three light chain CDRs, all heavy and light chain CDRs, or at least two CDRs.

Throughout this specification, amino acid residues in variable domain sequences and full length antibody sequences are numbered according to the Kabat numbering convention. Similarly, the terms “CDR”, “CDRL1”, “CDRL2”, “CDRL3”, “CDRH1”, “CDRH2”, “CDRH3” used in the Examples follow the Kabat numbering convention. For further information, see Kabat et al., Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987).

However, although we use the Kabat numbering convention for amino acid residues in variable domain sequences and full length antibody sequences throughout this specification, it will be apparent to those skilled in the art that there are alternative numbering conventions for amino acid residues in variable domain sequences and full length antibody sequences. There are also alternative numbering conventions for CDR

sequences, for example those set out in Chothia et al. (1989) Nature 342: 877-883. The structure and protein folding of the antibody may mean that other residues are considered part of the CDR sequence and would be understood to be so by a skilled person.

Other numbering conventions for CDR sequences available to a skilled person include "AbM" (University of Bath) and "contact" (University College London) methods. The minimum overlapping region using at least two of the Kabat, Chothia, AbM and contact methods can be determined to provide the "minimum binding unit". The minimum binding unit may be a sub-portion of a CDR.

Table 1 below represents one definition using each numbering convention for each CDR or binding unit. The Kabat numbering scheme is used in Table 1 to number the variable domain amino acid sequence. It should be noted that some of the CDR definitions may vary depending on the individual publication used.

Table 1

	Kabat CDR	Chothia CDR	AbM CDR	Contact CDR	Minimum binding unit
H1	31-35/35A/35B	26-32/33/34	26-35/35A/35B	30-35/35A/35B	31-32
H2	50-65	52-56	50-58	47-58	52-56
H3	95-102	95-102	95-102	93-101	95-101
L1	24-34	24-34	24-34	30-36	30-34
L2	50-56	50-56	50-56	46-55	50-55
L3	89-97	89-97	89-97	89-96	89-96

As used herein, the term "antigen binding site" refers to a site on an antigen binding protein which is capable of specifically binding to an antigen. This may be a single domain (for example, an epitope-binding domain), or single-chain Fv (ScFv) domains or it may be paired VH/VL domains as can be found on a standard antibody.

The term "epitope" as used herein refers to that portion of the antigen that makes contact with a particular binding domain of the antigen binding protein. An epitope may be linear, comprising an essentially linear amino acid sequence from the antigen. Alternatively, an

epitope may be conformational or discontinuous. For example, a conformational epitope comprises amino acid residues which require an element of structural constraint. In the case of a conformational epitope, although the residues may be from different regions of the peptide chain, they may be in close proximity in the three dimensional structure of the antigen. In the case of multimeric antigens, such as SAP, a conformational epitope may include residues from different peptide chains that may be in close proximity in the three dimensional structure of the antigen. Such structurally neighbouring residues can be determined through computer modelling programs or via three-dimensional structures obtained through methods known in the art, such as X-ray crystallography.

A discontinuous epitope comprises amino acid residues that are separated by other sequences, i.e. not in a continuous sequence in the antigen's primary sequence. In the context of the antigen's tertiary and quaternary structure, the residues of a discontinuous epitope are near enough to each other to be bound by an antigen binding protein.

In an embodiment, an antigen binding protein of the invention binds to an epitope within residues 140-158 of human SAP.

For nucleotide and amino acid sequences, the term “identical" or “sequence identity” indicates the degree of identity between two nucleic acid or two amino acid sequences when optimally aligned and compared with appropriate insertions or deletions.

The percent identity between two sequences is a function of the number of identical positions shared by the sequences (i.e., % identity = number of identical positions/total number of positions multiplied by 100), taking into account the number of gaps, and the length of each gap, which need to be introduced for optimal alignment of the two sequences. The comparison of sequences and determination of percent identity between two sequences can be accomplished using a mathematical algorithm, as described below.

The percent identity between two nucleotide sequences can be determined using the GAP program in the GCG software package, using a NWSgapdna.CMP matrix and a gap weight of 40, 50, 60, 70, or 80 and a length weight of 1, 2, 3, 4, 5, or 6. The percent identity between

two nucleotide or amino acid sequences can also be determined using the algorithm of E. Meyers and W. Miller (Comput. Appl. Biosci., 4:11-17 (1988)) which has been incorporated into the ALIGN program (version 2.0), using a PAM120 weight residue table, a gap length penalty of 12 and a gap penalty of 4. In addition, the percent identity between two amino acid sequences can be determined using the Needleman and Wunsch (J. Mol. Biol. 48:444-453 (1970)) algorithm which has been incorporated into the GAP program in the GCG software package, using either a Blossum 62 matrix or a PAM250 matrix, and a gap weight of 16, 14, 12, 10, 8, 6, or 4 and a length weight of 1, 2, 3, 4, 5, or 6.

By way of example, a polynucleotide sequence may be identical to a reference polynucleotide sequence as described herein (see for example SEQ ID NO:8, 10, 18, 20, 45-48, 51-61, 63, 65-73), that is be 100% identical, or it may include up to a certain integer number of nucleotide alterations as compared to the reference sequence, such as at least 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical. Such alterations are selected from at least one nucleotide deletion, substitution, including transition and transversion, or insertion, and wherein said alterations may occur at the 5' or 3' terminal positions of the reference nucleotide sequence or anywhere between those terminal positions, interspersed either individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. The number of nucleotide alterations is determined by multiplying the total number of nucleotides in the reference polynucleotide sequence as described herein (see for example SEQ ID NO:8, 10, 18, 20, 45-48, 51-61, 63, 65-73), by the numerical percent of the respective percent identity (divided by 100) and subtracting that product from said total number of nucleotides in the reference polynucleotide sequence as described herein (see for example SEQ ID NO:8, 10, 18, 20, 45-48, 51-61, 63, 65-73), or:

$$n_n \leq x_n - (x_n \bullet y),$$

wherein n_n is the number of nucleotide alterations, x_n is the total number of nucleotides in the reference polynucleotide sequence as described herein (see for example SEQ ID NO:8, 10, 18, 20, 45-48, 51-61, 63, 65-73), and y is 0.50 for 50%, 0.60 for 60%, 0.70 for 70%, 0.75 for 75%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, 0.98 for 98%, 0.99 for 99% or 1.00 for 100%, • is the symbol for the multiplication operator, and wherein any non-

integer product of x_n and y is rounded down to the nearest integer prior to subtracting it from x_n.

Similarly, a polypeptide sequence may be identical to a polypeptide reference sequence as described herein (see for example SEQ ID NO:1-7, 9, 11-17, 19, 21-24, 27-31, 34-42, 62, 64, 74), that is be 100% identical, or it may include up to a certain integer number of amino acid alterations as compared to the reference sequence such that the % identity is less than 100%, such as at least 50, 60, 70, 75, 80, 85, 90, 95, 96, 97, 98, or 99% identical. Such alterations are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion, and wherein said alterations may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between those terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. The number of amino acid alterations for a given % identity is determined by multiplying the total number of amino acids in the polypeptide sequence encoded by the polypeptide reference sequence as described herein (see for example SEQ ID NO:1-7, 9, 11-17, 19, 21-24, 27-31, 34-42, 62, 64, 74) by the numerical percent of the respective percent identity (divided by 100) and then subtracting that product from said total number of amino acids in the polypeptide reference sequence as described herein (see for example SEQ ID NO:1-7, 9, 11-17, 19, 21-24, 27-31, 34-42, 62, 64, 74), or:

$$n_a \leq x_a - (x_a \bullet y),$$

wherein n_a is the number of amino acid alterations, x_a is the total number of amino acids in the reference polypeptide sequence as described herein (see for example SEQ ID NO:1-7, 9, 11-17, 19, 21-24, 27-31, 34-42, 62, 64, 74), and y is, 0.50 for 50%, 0.60 for 60%, 0.70 for 70%, 0.75 for 75%, 0.80 for 80%, 0.85 for 85%, 0.90 for 90%, 0.95 for 95%, 0.98 for 98%, 0.99 for 99%, or 1.00 for 100%, • is the symbol for the multiplication operator, and wherein any non-integer product of x_a and y is rounded down to the nearest integer prior to subtracting it from x_a.

The % identity may be determined across the length of the sequence.

The terms “peptide”, “polypeptide” and “protein” each refers to a molecule comprising two or more amino acid residues. A peptide may be monomeric or polymeric.

It is well recognised in the art that certain amino acid substitutions are regarded as being "conservative". Amino acids are divided into groups based on common side-chain properties and substitutions within groups that maintain all or substantially all of the binding affinity of the antigen binding protein are regarded as conservative substitutions, see Table 2 below:

Table 2

Side chain	**Members**
Hydrophobic	Met, Ala, Val, Leu, Ile
Neutral hydrophilic	Cys, Ser, Thr
Acidic	Aap, Glu
Basic	Asn, Gln, His, Lys, Arg
Residues that influence chain orientation	Gly, Pro
Aromatic	Trp, Tyr, Phe

The antigen binding protein may compete for binding to SAP with a reference antibody comprising a heavy chain variable region sequence of SEQ ID NO: 7, and a light chain variable region sequence of SEQ ID NO: 9. Alternatively, the antigen binding protein may compete for binding to SAP with a reference antibody comprising a heavy chain variable region sequence of SEQ ID NO: 17, and a light chain variable region sequence of SEQ ID NO: 19.

Competition between the antigen binding protein and the reference antibody may be determined by competition ELISA, FMAT or BIAcore. A competing antigen binding protein may bind to the same epitope, an overlapping epitope, or an epitope in close proximity of the epitope to which the reference antibody binds.

The present invention also provides an antigen binding protein which specifically binds to SAP and comprises CDRH3 of SEQ ID NO:3 or a variant CDR thereof. The antigen binding protein may further comprise one or more CDRs, or all CDRs, in any combination, selected

from: CDRH1 (SEQ ID NO:1), CDRH2 (SEQ ID NO:2), CDRL1 (SEQ ID NO:4), CDRL2 (SEQ ID NO:5), and CDRL3 (SEQ ID NO:6); or a variant thereof.

For example, the antigen binding protein may comprise CDRH3 (SEQ ID NO:3) and CDRH1 (SEQ ID NO:1), or variants thereof. The antigen binding protein may comprise CDRH3 (SEQ ID NO:3) and CDRH2 (SEQ ID NO:2), or variants thereof. The antigen binding protein may comprise CDRH1 (SEQ ID NO:1) and CDRH2 (SEQ ID NO:2), and CDRH3 (SEQ ID NO:3), or variants thereof.

The antigen binding protein may comprise CDRL1 (SEQ ID NO:4) and CDRL2 (SEQ ID NO:5), or variants thereof. The antigen binding protein may comprise CDRL2 (SEQ ID NO:5) and CDRL3 (SEQ ID NO:6), or variants thereof. The antigen binding protein may comprise CDRL1 (SEQ ID NO:4), CDRL2 (SEQ ID NO:5) and CDRL3 (SEQ ID NO:6), or variants thereof.

The antigen binding protein may comprise CDRH3 (SEQ ID NO:3) and CDRL3 (SEQ ID NO:6), or variants thereof. The antigen binding protein may comprise CDRH3 (SEQ ID NO:3), CDRH2 (SEQ ID NO:2) and CDRL3 (SEQ ID NO:6), or variants thereof. The antigen binding protein may comprise CDRH3 (SEQ ID NO:3), CDRH2 (SEQ ID NO:2), CDRL2 (SEQ ID NO:5) and CDRL3 (SEQ ID NO:6), or variants thereof.

The antigen binding protein may comprise CDRH1 (SEQ ID NO:1), CDRH2 (SEQ ID NO:2), CDRH3 (SEQ ID NO:3), CDRL1 (SEQ ID NO:4), CDRL2 (SEQ ID NO:5) and CDRL3 (SEQ ID NO:6), or variants thereof.

The present invention also provides an antigen binding protein which specifically binds to SAP and comprises CDRH3 of SEQ ID NO:13 or a variant CDR thereof. The antigen binding protein may further comprise one or more CDRs, or all CDRs, in any combination, selected from: CDRH1 (SEQ ID NO:11), CDRH2 (SEQ ID NO:12), CDRL1 (SEQ ID NO:14), CDRL2 (SEQ ID NO:15), and CDRL3 (SEQ ID NO:16); or a variant thereof.

The present invention also provides an antigen binding protein which specifically binds to SAP, wherein the antigen binding protein is a chimeric or a humanised antibody comprising

the corresponding CDRH3 of the variable domain sequence of SEQ ID NO:7, or a variant CDRH3.

The chimeric or humanised antigen binding protein may further comprise one or more, or all of the corresponding CDRs selected from the variable domain sequence of SEQ ID NO:7 or SEQ ID NO:9, or a variant CDR thereof.

For example, the antigen binding protein may comprise corresponding CDRH3 and corresponding CDRH1, or variants thereof. The antigen binding protein may comprise corresponding CDRH3 and corresponding CDRH2, or variants thereof. The antigen binding protein may comprise corresponding CDRH1, corresponding CDRH2, and corresponding CDRH3; or variants thereof.

The antigen binding protein may comprise corresponding CDRL1 and corresponding CDRL2, or variants thereof. The antigen binding protein may comprise corresponding CDRL2 and corresponding CDRL3, or variants thereof. The antigen binding protein may comprise corresponding CDRL1, corresponding CDRL2 and corresponding CDRL3, or variants thereof.

The antigen binding protein may comprise corresponding CDRH3 and corresponding CDRL3, or variants thereof. The antigen binding protein may comprise corresponding CDRH3, corresponding CDRH2 and corresponding CDRL3, or variants thereof. The antigen binding protein may comprise corresponding CDRH3, corresponding CDRH2, corresponding CDRL2 and corresponding CDRL3, or variants thereof.

The antigen binding protein may comprise corresponding CDRH1, corresponding CDRH2, corresponding CDRH3, corresponding CDRL1, corresponding CDRL2 and corresponding CDRL3, or variants thereof.

The corresponding CDRs can be defined by reference to Kabat (1987), Chothia (1989), AbM or contact methods, or a combination of these methods. One definition of each of the methods can be found at Table 1 and can be applied to the reference heavy chain variable

domain SEQ ID NO:7 and the reference light chain variable domain SEQ ID NO:9 to determine the corresponding CDR.

The present invention also provides an antigen binding protein which specifically binds to SAP, wherein the antigen binding protein is a chimeric or a humanised antibody comprising the corresponding CDRH3 of the variable domain sequence of SEQ ID NO:17, or a variant CDRH3.

The chimeric or humanised antigen binding protein may further comprise one or more, or all of the corresponding CDRs selected from the variable domain sequence of SEQ ID NO:17 or SEQ ID NO:19, or a variant CDR thereof.

The present invention also provides an antigen binding protein which specifically binds to SAP, and comprises a binding unit H3 comprising Kabat residues 95-101 of SEQ ID NO:7, or a variant H3. The antigen binding protein may further comprise one or more or all binding units selected from: H1 comprising Kabat residues 31-32 of SEQ ID NO:7, H2 comprising Kabat residues 52-56 of SEQ ID NO:7, L1 comprising Kabat residues 30-34 of SEQ ID NO:9, L2 comprising Kabat residues 50-55 of SEQ ID NO:9 and L3 comprising Kabat residues 89-96 of SEQ ID NO:9; or a variant binding unit.

For example, the antigen binding protein may comprise a binding unit H3 and a binding unit H1, or variants thereof. The antigen binding protein may comprise a binding unit H3 and a binding unit H2, or variants thereof. The antigen binding protein may comprise a binding unit H1, a binding unit H2, and a binding unit H3; or variants thereof.

The antigen binding protein may comprise a binding unit L1 and a binding unit L2, or variants thereof. The antigen binding protein may comprise a binding unit L2 and a binding unit L3, or variants thereof. The antigen binding protein may comprise a binding unit L1, a binding unit L2, and a binding unit L3; or variants thereof.

The antigen binding protein may comprise a binding unit H3 and a binding unit L3, or variants thereof. The antigen binding protein may comprise a binding unit H3, a binding unit

H2, and a binding unit L3; or variants thereof. The antigen binding protein may comprise a binding unit H3, a binding unit H2, a binding unit L2, and a binding unit L3; or variants thereof.

The antigen binding protein may comprise a binding unit H1, a binding unit H2, a binding unit H3, a binding unit L1, a binding unit L2, and a binding unit L3; or variants thereof.

The present invention also provides an antigen binding protein which specifically binds to SAP, and comprises a binding unit H3 comprising Kabat residues 95-101 of SEQ ID NO:17, or a variant H3. The antigen binding protein may further comprise one or more or all binding units selected from: H1 comprising Kabat residues 31-32 of SEQ ID NO:17, H2 comprising Kabat residues 52-56 of SEQ ID NO:17, L1 comprising Kabat residues 30-34 of SEQ ID NO:19, L2 comprising Kabat residues 50-55 of SEQ ID NO:19 and L3 comprising Kabat residues 89-96 of SEQ ID NO:19; or a variant binding unit.

A CDR variant or variant binding unit includes an amino acid sequence modified by at least one amino acid, wherein said modification can be chemical or a partial alteration of the amino acid sequence (for example by no more than 10 amino acids), which modification permits the variant to retain the biological characteristics of the unmodified sequence. For example, the variant is a functional variant which specifically binds to SAP and activates clearance of complexes of SAP bound to amyloid from tissues. A partial alteration of the CDR amino acid sequence may be by deletion or substitution of one to several amino acids, or by addition or insertion of one to several amino acids, or by a combination thereof (for example by no more than 10 amino acids). The CDR variant or binding unit variant may contain 1, 2, 3, 4, 5 or 6 amino acid substitutions, additions or deletions, in any combination, in the amino acid sequence. The CDR variant or binding unit variant may contain 1, 2 or 3 amino acid substitutions, insertions or deletions, in any combination, in the amino acid sequence. The substitutions in amino acid residues may be conservative substitutions, for example, substituting one hydrophobic amino acid for an alternative hydrophobic amino acid. For example leucine may be substituted with valine, or isoleucine.

One or more of the CDRs, corresponding CDRs, variant CDRs or binding units described herein may be present in the context of a human framework, for example as a humanised or chimeric variable domain. Fully human antibodies comprising one or more of the CDRs, corresponding CDRs, variant CDRs or binding units described herein are also contemplated and are within the scope of the invention.

The CDRs L1, L2, L3, H1 and H2 tend to structurally exhibit one of a finite number of main chain conformations. The particular canonical structure class of a CDR is defined by both the length of the CDR and by the loop packing, determined by residues located at key positions in both the CDRs and the framework regions (structurally determining residues or SDRs). Martin and Thornton (1996; J Mol Biol 263:800-815) have generated an automatic method to define the "key residue" canonical templates. Cluster analysis is used to define the canonical classes for sets of CDRs, and canonical templates are then identified by analysing buried hydrophobics, hydrogen-bonding residues, and conserved glycines and prolines. The CDRs of antibody sequences can be assigned to canonical classes by comparing the sequences to the key residue templates and scoring each template using identity or similarity matrices.

Examples of CDR canonicals within the scope of the invention are given below. The amino acid numbering used is Kabat.

Examples of canonicals for CDRH1 as set out in SEQ ID NO:1, a variant thereof, the CDRH1 of SEQ ID NO:7 or a corresponding CDR are: Tyr 32 is substituted for Ile, His, Phe, Thr, Asn, Cys, Glu or Asp; Asn 33 is substituted for Tyr, Ala, Trp, Gly, Thr, Leu or Val; Met 34 is substituted for Ile, Val or Trp; and/or His 35 is substituted for Glu, Asn, Gln, Ser, Tyr or Thr.

Examples of canonicals for CDRH2 as set out in SEQ ID NO:2, a variant thereof, the CDRH2 of SEQ ID NO:7 or a corresponding CDR are: Tyr 50 is substituted for Arg, Glu, Trp, Gly, Gln, Val, Leu, Asn, Lys or Ala; Ile51 is substituted for Leu, Val, Thr, Ser or Asn; Tyr 52 is substituted for Asp, Leu, Asn or Ser; Gly 53 is substituted for Ala, Tyr, Ser, Lys, Thr or Asn; Asp 54 is substituted for Asn, Ser, Thr, Lys or Gly; Asn 56 is substituted for Tyr, Arg, Glu, Asp, Gly, Val, Ser or Ala; and/or Asn 58 is substituted for Lys, Thr, Ser, Asp, Arg, Gly, Phe or Tyr.

Examples of canonicals for CDRH3 as set out in SEQ ID NO:3, a variant thereof, the CDRH3 of SEQ ID NO:7 or a corresponding CDR are: Ser 102 is substituted for Tyr, His, Val, Ile, Asp or Gly.

Examples of canonicals for CDRL1 as set out in SEQ ID NO:4, a variant thereof, the CDRL1 of SEQ ID NO:9 or a corresponding CDR are: Asn 28 is substituted for Ser, Asp, Thr or Glu; Ile 29 is substituted for Val; Tyr 30 is substituted for Asp, Leu, Val, Ile, Ser, Asn, Phe, His, Gly or Thr; Ser 31 is substituted for Asn, Thr, Lys or Gly; Tyr 32 is substituted for Phe, Asn, Ala, His, Ser or Arg; Leu 33 is substituted for Met, Val, Ile or Phe; and/or Ala 34 is substituted for Gly, Asn, Ser, His, Val or Phe.

Examples of canonicals for CDRL2 as set out in SEQ ID NO:5, a variant thereof, the CDRL1 of SEQ ID NO:9 or a corresponding CDR are: Ala 51 is substituted for Thr, Gly or Val.

Examples of canonicals for CDRL3 as set out in SEQ ID NO:6, a variant thereof, the CDRL1 of SEQ ID NO:9 or a corresponding CDR are: Gln 89 is substituted for Ser, Gly, Phe or Leu; His 90 is substituted for Gln or Asn; His 91 is substituted for Asn, Phe, Gly, Ser, Arg, Asp, Thr, Tyr or Val; Tyr 92 is substituted for Asn, Trp, Thr, Ser, Arg, Gln, His, Ala or Asp; Gly 93 is substituted for Glu, Asn, His, Thr, Ser, Arg or Ala; Ala 94 is substituted for Asp, Tyr, Thr, Val, Leu, His, Asn, Ile, Trp, Pro or Ser; and/or Leu 96 is substituted for Pro, Tyr, Arg, Ile, Trp or Phe.

Examples of canonicals for CDRH1 as set out in SEQ ID NO:11, a variant thereof, the CDRH1 of SEQ ID NO:17 or a corresponding CDR are: Tyr 32 is substituted for Ile, His, Phe, Thr, Asn, Cys, Glu or Asp; Trp 33 is substituted for Tyr, Ala, Gly, Thr, Leu or Val; Met 34 is substituted for Ile, Val or Trp; and/or His 35 is substituted for Glu, Asn, Gln, Ser, Tyr or Thr.

Examples of canonicals for CDRH2 as set out in SEQ ID NO:12, a variant thereof, the CDRH1 of SEQ ID NO:17 or a corresponding CDR are: Met 50 is substituted for Arg, Glu, Trp, Tyr, Gly, Gln, Val, Leu, Asn, Lys or Ala; Ile51 is substituted for Leu, Val, Thr, Ser or Asn; His 52 is substituted for Asp, Leu, Asn, Ser or Tyr; Asn 53 is substituted for Ala, Gly, Tyr, Ser, Lys or Thr; Ser 54 is substituted for Asn, Thr, Lys, Asp or Gly; Asn 56 is substituted for Tyr, Arg, Glu, Asp, Gly, Val, Ser or Ala; and/or Asn 58 is substituted for Lys, Thr, Ser, Asp, Arg, Gly, Phe or Tyr.

Examples of canonicals for CDRH3 as set out in SEQ ID NO:13, a variant thereof, the CDRH1 of SEQ ID NO:17 or a corresponding CDR are: Val 102 is substituted for Tyr, His, Ile, Ser, Asp or Gly.

Examples of canonicals for CDRL1 as set out in SEQ ID NO:14, a variant thereof, the CDRL1 of SEQ ID NO:19 or a corresponding CDR are: Asn 28 is substituted for Ser, Asp, Thr or Glu; Val 29 is substituted for Ile; Asn 30 is substituted for Asp, Leu, Tyr, Val, Ile, Ser, Phe, His, Gly or Thr; Ser 31 is substituted for Asn, Thr, Lys or Gly; Asn 32 is substituted for Phe, Tyr, Ala, His, Ser or Arg; Val 33 is substituted for Met, Leu, Ile or Phe; Ala 34 is substituted for Gly, Asn, Ser, His, Val or Phe.

Examples of canonicals for CDRL2 as set out in SEQ ID NO:15, a variant thereof, the CDRL1 of SEQ ID NO:19 or a corresponding CDR are: Ala 51 is substituted for Thr, Gly or Val.

Examples of canonicals for CDRL3 as set out in SEQ ID NO:16, a variant thereof, the CDRL1 of SEQ ID NO:19 or a corresponding CDR are: Gln 89 is substituted for Ser, Gly, Phe or Leu; Gln 90 is substituted for Asn or His; Cys 91 is substituted for Asn, Phe, Gly, Ser, Arg, Asp, His, Thr, Tyr or Val; Asn 92 is substituted for Tyr, Trp, Thr, Ser, Arg, Gln, His, Ala or Asp; Asn 93 is substituted for Glu, Gly, His, Thr, Ser, Arg or Ala; Tyr 94 is substituted for Asp, Thr, Val, Leu, His, Asn, Ile, Trp, Pro or Ser; and/or Phe 96 is substituted for Pro, Leu, Tyr, Arg, Ile or Trp.

There may be multiple variant CDR canonical positions per CDR, per corresponding CDR, per binding unit, per heavy or light chain variable region, per heavy or light chain, and per antigen binding protein, and therefore any combination of substitution may be present in the antigen binding protein of the invention, provided that the canonical structure of the CDR is maintained such that the antigen binding protein is capable of specifically binding SAP.

As discussed above, the particular canonical structure class of a CDR is defined by both the length of the CDR and by the loop packing, determined by residues located at key positions in both the CDRs and the framework regions.

Thus in addition to the CDRs listed in SEQ ID NO: 1-6 or 11-16, CDRs of SEQ ID NO:7, 9, 17 or 19, corresponding CDRs, binding units, or variants thereof, the canonical framework

residues of an antigen binding protein of the invention may include (using Kabat numbering):

Heavy chain: Val, Ile or Gly at position 2; Leu or Val at position 4; Leu, Ile, Met or Val at position 20; Cys at position 22; Thr, Ala, Val, Gly or Ser at position 24; Gly at position 26; Ile, Phe, Leu or Ser at position 29; Trp at position 36; Trp or Tyr at position 47; Ile, Met, Val or Leu at position 48; Ile, Leu, Phe, Met or Val at position 69; Val, Ala or Leu at position 71; Ala, Leu, Val, Tyr or Phe at position 78; Leu or Met at position 80; Tyr or Phe at position 90; Cys at position 92; and/or Arg, Lys, Gly, Ser, His or Asn at position 94.

Light chain: Ile, Leu or Val at position 2; Val, Gln, Leu or Glu at position 3; Met or Leu at position 4; Cys at position 23; Trp at position 35; Tyr, Leu or Phe at position 36; Leu, Arg or Val at position 46; Tyr, His, Phe or Lys at position 49; Tyr or Phe at position 71; Cys at position 88; and/or Phe at position 98.

In a particular embodiment, the heavy chain framework comprises the following residues: Val at position 2, Leu at position 4, Val at position 20, Cys at position 22, Ala at position 24, Gly at position 26, Phe at position 29, Trp at position 36, Trp at position 47, Met at position 48, Ile at position 69, Ala at position 71, Ala at position 78, Met at position 80, Tyr at position 90, Cys at position 92, and Arg at position 94; and the light chain framework comprises the following residues: Ile at position 2, Gln at position 3, Met at position 4, Cys at position 23, Trp at position 35, Tyr at position 36, Leu at position 46, His at position 49, Phe at position 71, Cys at position 88, and Phe at position 98.

Any one, any combination, or all of the framework positions described above may be present in the antigen binding protein of the invention. There may be multiple variant framework canonical positions per heavy or light chain variable region, per heavy or light chain, and per antigen binding protein, and therefore any combination may be present in the antigen binding protein of the invention, provided that the canonical structure of the framework is maintained.

The humanised heavy chain variable domain may comprise the CDRs listed in SEQ ID NO:1-3; variant CDRs; corresponding CDRs in SEQ ID NO:7; binding units; or variants thereof, within an acceptor antibody framework having 75% or greater, 80% or greater, 85% or

greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater or 100% identity in the framework regions to the human acceptor variable domain sequence in SEQ ID NO:25. The humanised light chain variable domain may comprise the CDRs listed in SEQ ID NO:4-6; variant CDRs; corresponding CDRs in SEQ ID NO:9; binding units; or variants thereof, within an acceptor antibody framework having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater or 100% identity in the framework regions to the human acceptor variable domain sequence in SEQ ID NO:32.

The humanised heavy chain variable domain may comprise the CDRs listed in SEQ ID NO:11-13; variant CDRs; corresponding CDRs in SEQ ID NO:17; binding units; or variants thereof, within an acceptor antibody framework having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater or 100% identity in the framework regions to the human acceptor variable domain sequence in SEQ ID NO:25. The humanised light chain variable domain may comprise the CDRs listed in SEQ ID NO:14-16; variant CDRs; corresponding CDRs in SEQ ID NO:19; binding units; or variants thereof, within an acceptor antibody framework having 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 98% or greater, 99% or greater or 100% identity in the framework regions to the human acceptor variable domain sequence in SEQ ID NO:32.

The invention also provides an antigen binding protein which specifically binds to SAP and comprises a heavy chain variable region selected from any one of SEQ ID NO:27-31. The antigen binding protein may comprise a light chain variable region selected from any one of SEQ ID NO:34-36 Any of the heavy chain variable regions may be combined with any of the light chain variable regions.

The antigen binding protein may comprise any one of the following heavy chain and light chain variable region combinations: H0L0 (SEQ ID NO:27 and SEQ ID NO:34), H0L1 (SEQ ID NO:27 and SEQ ID NO:35), H0L2 (SEQ ID NO:27 and SEQ ID NO:36), H1L0 (SEQ ID NO:28 and SEQ ID NO:34), H1L1 (SEQ ID NO:28 and SEQ ID NO:35), H1L2 (SEQ ID NO:28 and SEQ ID NO:36), H2L0 (SEQ ID NO:29 and SEQ ID NO:34), H2L1 (SEQ ID NO:29 and SEQ ID NO:35), H2L2 (SEQ ID NO:29 and SEQ ID NO:36), H3L0 (SEQ ID NO:30 and SEQ ID NO:34), H3L1 (SEQ ID NO:30 and SEQ ID NO:35), H3L2 (SEQ ID NO:30 and SEQ ID NO:36), H4L0 (SEQ ID NO:31

and SEQ ID NO:34), H4L1 (SEQ ID NO:31 and SEQ ID NO:35), or H4L2 (SEQ ID NO:31 and SEQ ID NO:36).

The invention also provides an antigen binding protein which specifically binds to SAP and comprises a heavy chain variable region selected from any one of SEQ ID NO:37-40. The antigen binding protein may comprise a light chain variable region of SEQ ID NO:41, SEQ ID NO:42 or SEQ ID NO:74. Any of the heavy chain variable regions may be combined with any of the light chain variable regions.

The antigen binding protein may comprise any one of the following heavy chain and light chain variable region combinations: H0L0 (SEQ ID NO:37 and SEQ ID NO:41), H0L1 (SEQ ID NO:37 and SEQ ID NO:42), H1L0 (SEQ ID NO:38 and SEQ ID NO:41), H1L1 (SEQ ID NO:38 and SEQ ID NO:42), H2L0 (SEQ ID NO:39 and SEQ ID NO:41), H2L1 (SEQ ID NO:39 and SEQ ID NO:42), H3L0 (SEQ ID NO:40 and SEQ ID NO:41), or H3L1 (SEQ ID NO:40 and SEQ ID NO:42).

L0 (SEQ ID NO:41) may be substituted with L0 91 A (SEQ ID NO:74).

The antibody heavy chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater or 100% identity to SEQ ID NO:28. The antibody light chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater, or 100% identity to SEQ ID NO:35.

The antibody heavy chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater or 100% identity to SEQ ID NO:40. The antibody light chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater, or 100% identity to SEQ ID NO:41. The antibody light chain variable region may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater, or 100% identity to SEQ ID NO:74.

The antibody heavy chain variable region may be a variant of any one of SEQ ID NO:27-31 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions. The antibody light chain variable region may be a variant of any one of SEQ ID

NO:34-36 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions.

The antibody heavy chain variable region may be a variant of any one of SEQ ID NO:37-40 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions. The antibody light chain variable region may be a variant of SEQ ID NO:41, 42 or 74 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions.

For example, the canonical CDRs and canonical framework residue substitutions described above may also be present in the variant heavy or light chain variable regions as variant sequences that are at least 75% identical or which contain up to 30 amino acid substitutions.

Any of the heavy chain variable regions may be combined with a suitable human constant region. Any of the light chain variable regions may be combined with a suitable constant region.

The antigen binding protein of the invention may comprise a heavy chain of SEQ ID NO:62 and/or a light chain variable region of SEQ ID NO:64.

The antibody heavy chain may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater or 100% identity to SEQ ID NO:62. The antibody light chain may have 75% or greater, 80% or greater, 85% or greater, 90% or greater, 95% or greater, 96% or greater, 97% or greater, 98% or greater, 99% or greater, or 100% identity to SEQ ID NO:64.

The antibody heavy chain may be a variant of any one of SEQ ID NO:62 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions. The antibody light chain may be a variant of any one of SEQ ID NO:64 which contains 30, 25, 20, 15, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, insertions or deletions.

The disc-like SAP molecule has two faces. The single alpha helix present on each of the 5 protomers is located on the A face. The calcium dependent ligand binding pocket of each protomer is located on the B face and this face is therefore occluded when SAP is bound to amyloid fibrils. For antigen binding proteins of the present invention to have therapeutic utility, the epitope recognised by the antigen binding protein described herein is desirably

accessible in SAP when SAP is bound to amyloid deposits and is therefore located on the A face or the edges of the SAP molecule. The antigen binding protein can then recognise and bind to amyloid bound SAP, leading to complement activation that triggers the body's efficient macrophage dependent clearance mechanism. Accordingly, in an embodiment of the invention the antigen binding protein binds human SAP which is bound to amyloid fibrils *in vivo*. In another embodiment of the invention, the antigen binding protein binds to the A face of human SAP.

The antigen binding protein may be derived from rat, mouse, rabbit, camel (or related camelid species), or primate (e.g. cynomolgus, Old World monkey, Great Ape or human). In a particular embodiment the antigen binding protein is derived from mouse. In another embodiment the antigen binding protein is derived from human. The antigen binding protein may be a humanised or chimeric antibody. The antigen binding protein may be a human antibody. The antigen binding protein is not a murine antibody.

The antigen binding protein may comprise a constant region, which may be of any isotype or subclass. The constant region may be of the IgG isotype, for example IgG1, IgG2, IgG3, IgG4 or variants thereof. The antigen binding protein constant region may be IgG1.

In a particular embodiment of the invention, the antigen binding protein comprises a constant region that is functional in activating complement e.g. human IgG1, IgG2 or IgG3.

In another embodiment of the invention, the antigen binding protein comprises a constant region that is functional in binding macrophages e.g. human IgG1 or IgG3.

In a further embodiment of the invention, the antigen binding protein comprises a constant region that is functional in both activating complement and binding macrophages e.g. human IgG1 or IgG3.

The antigen binding protein may comprise one or more modifications selected from a mutated constant domain such that the antibody has altered effector functions/ADCC and/or complement activation. Examples of suitable modifications are described in Shields et al. J. Biol. Chem (2001) 276: 6591-6604, Lazar et al. PNAS (2006) 103: 4005-4010 and US6737056, WO2004063351 and WO2004029207.

The antigen binding protein may comprise a constant domain with an altered glycosylation profile such that the antigen binding protein has altered effector functions/ADCC and/or

complement activation. Examples of suitable methodologies to produce an antigen binding protein with an altered glycosylation profile are described in WO2003/011878, WO2006/014679 and EP1229125.

In an embodiment of the invention, antigen binding proteins are selected which do not have residues within regions that are responsible for antigen binding, e.g. the CDRs, that are susceptible to deamidation. In a further embodiment of the invention, antigen binding proteins are selected which do not have residues within regions responsible for complement activation that are susceptible to deamidation.

The present invention also provides a nucleic acid molecule which encodes an antigen binding protein as described herein. The nucleic acid molecule may comprise sequences encoding both the heavy chain variable or full length sequence; and the light chain variable or full length sequence. Alternatively, the nucleic acid molecule which encodes an antigen binding protein described herein may comprise sequences encoding the heavy chain variable or full length sequence; or light chain variable or full length sequence.

The nucleic acid molecule which encodes the heavy chain variable region may comprise any one of SEQ ID NO:51 or 53-57. The nucleic acid molecule which encodes the light chain variable region may comprise any one of SEQ ID NO:52 or 58-60.

The nucleic acid molecule which encodes the heavy chain may comprise SEQ ID NO:61. The nucleic acid molecule which encodes the light chain may comprise SEQ ID NO:63.

The nucleic acid molecule which encodes the heavy chain variable region may comprise any one of SEQ ID NO:65 or 67-70. The nucleic acid molecule which encodes the light chain variable region may comprise any one of SEQ ID NO:66 or 71-73.

The nucleic acid molecule may also contain one or more nucleotide substitutions which do not alter the amino acid sequence of the encoded heavy and/or light chain.

The present invention also provides an expression vector comprising a nucleic acid molecule as described herein. Also provided is a recombinant host cell, comprising an expression vector as described herein.

The antigen binding protein described herein may be produced in a suitable host cell. A method for the production of the antigen binding protein as described herein may comprise

the step of culturing a host cell as described herein and recovering the antigen binding protein. A recombinant transformed, transfected, or transduced host cell may comprise at least one expression cassette, whereby said expression cassette comprises a polynucleotide encoding a heavy chain of the antigen binding protein described herein and further comprises a polynucleotide encoding a light chain of the antigen binding protein described herein. Alternatively, a recombinant transformed, transfected or transduced host cell may comprise at least one expression cassette, whereby a first expression cassette comprises a polynucleotide encoding a heavy chain of the antigen binding protein described herein and further comprise a second cassette comprising a polynucleotide encoding a light chain of the antigen binding protein described herein. A stably transformed host cell may comprise a vector comprising one or more expression cassettes encoding a heavy chain and/or a light chain of the antigen binding protein described herein. For example such host cells may comprise a first vector encoding the light chain and a second vector encoding the heavy chain.

The host cell may be eukaryotic, for example mammalian. Examples of such cell lines include CHO or NS0. The host cell may be cultured in a culture media, for example serum-free culture media. The antigen binding protein may be secreted by the host cell into the culture media. The antigen binding protein can be purified to at least 95% or greater (e.g. 98% or greater) with respect to said culture media containing the antigen binding protein.

A pharmaceutical composition comprising the antigen binding protein and a pharmaceutically acceptable carrier may be provided. A kit-of-parts comprising the pharmaceutical composition together with instructions for use may be provided. For convenience, the kit may comprise the reagents in predetermined amounts with instructions for use.

Antibody Structures

Intact Antibodies

The light chains of antibodies from most vertebrate species can be assigned to one of two types called Kappa and Lambda based on the amino acid sequence of the constant region. Depending on the amino acid sequence of the constant region of their heavy chains, human

antibodies can be assigned to five different classes, IgA, IgD, IgE, IgG and IgM. IgG and IgA can be further subdivided into subclasses, IgG1, IgG2, IgG3 and IgG4; and IgA1 and IgA2. Species variants exist with mouse and rat having at least IgG2a, IgG2b.

The more conserved portions of the variable region are called Framework regions (FR). The variable domains of intact heavy and light chains each comprise four FR connected by three CDRs. The CDRs in each chain are held together in close proximity by the FR regions and with the CDRs from the other chain contribute to the formation of the antigen binding site of antibodies.

The constant regions are not directly involved in the binding of the antibody to the antigen but exhibit various effector functions such as participation in antibody dependent cell-mediated cytotoxicity (ADCC), phagocytosis via binding to Fcγ receptor, half-life/clearance rate via neonatal Fc receptor (FcRn) and complement activation via the C1q component, leading to the chemotactic, opsonic and, potentially in the case of a viable cellular antigen target, cytolytic actions of complement. Human antibodies of the IgG1 class are the most potent in activating the complement system and are therefore the desirable isotype for the therapeutic application of the antibodies of the present invention.

The human IgG2 constant region has been reported to essentially lack the ability to activate complement by the classical pathway or to mediate antibody-dependent cellular cytotoxicity. The IgG4 constant region has been reported to lack the ability to activate complement by the classical pathway and mediates antibody-dependent cellular cytotoxicity only weakly. Antibodies essentially lacking these effector functions may be termed 'non-lytic' antibodies.

Human antibodies

Human antibodies may be produced by a number of methods known to those of skill in the art. Human antibodies can be made by the hybridoma method using human myeloma or mouse-human heteromyeloma cells lines see Kozbor (1984) J. Immunol 133, 3001, and Brodeur, Monoclonal Antibody Production Techniques and Applications, 51-63 (Marcel Dekker Inc, 1987). Alternative methods include the use of phage libraries or transgenic mice both of which utilize human variable region repertories (see Winter (1994) Annu. Rev. Immunol 12: 433-455; Green (1999) J. Immunol. Methods 231: 11-23).

Several strains of transgenic mice are now available wherein their mouse immunoglobulin loci has been replaced with human immunoglobulin gene segments (see Tomizuka (2000) PNAS 97: 722-727; Fishwild (1996) Nature Biotechnol. 14: 845-851; Mendez (1997) Nature Genetics, 15: 146-156). Upon antigen challenge such mice are capable of producing a repertoire of human antibodies from which antibodies of interest can be selected.

Phage display technology can be used to produce human antigen binding proteins (and fragments thereof), see McCafferty (1990) Nature 348: 552-553 and Griffiths et al. (1994) EMBO 13: 3245-3260.

The technique of affinity maturation (Marks Bio/technol (1992) 10: 779-783) may be used to improve binding affinity wherein the affinity of the primary human antibody is improved by sequentially replacing the heavy (H) and light (L) chain variable regions with naturally occurring variants and selecting on the basis of improved binding affinities. Variants of this technique such as "epitope imprinting" are now also available, see for example WO 93/06213; Waterhouse (1993) Nucl. Acids Res. 21: 2265-2266.

Chimeric and Humanised Antibodies

Chimeric antibodies are typically produced using recombinant DNA methods. DNA encoding the antibodies (e.g. cDNA) is isolated and sequenced using conventional procedures (e.g. by using oligonucleotide probes that are capable of binding specifically to genes encoding the H and L chains of the antibody. Hybridoma cells serve as a typical source of such DNA. Once isolated, the DNA is placed into expression vectors which are then transfected into host cells such as E. coli, COS cells, CHO cells or myeloma cells that do not otherwise produce immunoglobulin protein to obtain synthesis of the antibody. The DNA may be modified by substituting the coding sequence for human L and H chains for the corresponding non-human (e.g. murine) H and L constant regions, see for example Morrison (1984) PNAS 81: 6851.

A large decrease in immunogenicity can be achieved by grafting only the CDRs of non-human (e.g. murine) antibodies ("donor" antibodies) onto human framework ("acceptor framework") and constant regions to generate humanised antibodies (see Jones et al. (1986) Nature 321: 522-525; and Verhoeyen et al. (1988) Science 239: 1534-1536). However, CDR grafting per se may not result in the complete retention of antigen-binding

properties and it is frequently found that some framework residues (sometimes referred to as “back mutations”) of the donor antibody need to be preserved in the humanised molecule if significant antigen-binding affinity is to be recovered (see Queen et al. (1989) PNAS 86: 10,029-10,033: Co et al. (1991) Nature 351: 501-502). In this case, human variable regions showing the greatest sequence homology to the non-human donor antibody are chosen from a database in order to provide the human framework (FR). The selection of human FRs can be made either from human consensus or individual human antibodies. Where necessary, key residues from the donor antibody can be substituted into the human acceptor framework to preserve CDR conformations. Computer modelling of the antibody maybe used to help identify such structurally important residues, see WO 99/48523.

Alternatively, humanisation maybe achieved by a process of "veneering". A statistical analysis of unique human and murine immunoglobulin heavy and light chain variable regions revealed that the precise patterns of exposed residues are different in human and murine antibodies, and most individual surface positions have a strong preference for a small number of different residues (see Padlan et al. (1991) Mol. Immunol. 28: 489-498; and Pedersen et al. (1994) J. Mol. Biol. 235: 959-973). Therefore it is possible to reduce the immunogenicity of a non-human Fv by replacing exposed residues in its framework regions that differ from those usually found in human antibodies. Because protein antigenicity may be correlated with surface accessibility, replacement of the surface residues may be sufficient to render the mouse variable region "invisible" to the human immune system (see also Mark et al. (1994) in Handbook of Experimental Pharmacology Vol. 113: The pharmacology of Monoclonal Antibodies, Springer-Verlag, 105-134). This procedure of humanisation is referred to as "veneering" because only the surface of the antibody is altered, the supporting residues remain undisturbed. Further alternative approaches include that set out in WO04/006955 and the procedure of Humaneering™ (Kalobios) which makes use of bacterial expression systems and produces antibodies that are close to human germline in sequence (Alfenito-M Advancing Protein Therapeutics January 2007, San Diego, California).

Bispecific antigen binding proteins

A bispecific antigen binding protein is an antigen binding protein having binding specificities for at least two different epitopes. Methods of making such antigen binding proteins are

known in the art. Traditionally, the recombinant production of bispecific antigen binding proteins is based on the co-expression of two immunoglobulin H chain-L chain pairs, where the two H chains have different binding specificities, see Millstein et al. (1983) Nature 305: 537-539; WO 93/08829; and Traunecker et al. (1991) EMBO 10: 3655-3659. Because of the random assortment of H and L chains, a potential mixture of ten different antibody structures are produced of which only one has the desired binding specificity. An alternative approach involves fusing the variable domains with the desired binding specificities to heavy chain constant region comprising at least part of the hinge region, CH2 and CH3 regions. The CH1 region containing the site necessary for light chain binding may be present in at least one of the fusions. DNA encoding these fusions, and if desired the L chain are inserted into separate expression vectors and are then co-transfected into a suitable host organism. It is possible though to insert the coding sequences for two or all three chains into one expression vector. In one approach, the bispecific antibody is composed of a H chain with a first binding specificity in one arm and a H-L chain pair, providing a second binding specificity in the other arm, see WO 94/04690. Also see Suresh et al. (1986) Methods in Enzymology 121: 210.

Antigen Binding Fragments

Fragments lacking the constant region lack the ability to activate complement by the classical pathway or to mediate antibody-dependent cellular cytotoxicity. Traditionally such fragments are produced by the proteolytic digestion of intact antibodies by e.g. papain digestion (see for example, WO 94/29348) but may be produced directly from recombinantly transformed host cells. For the production of ScFv, see Bird et al. (1988) Science 242: 423-426. In addition, antigen binding fragments may be produced using a variety of engineering techniques as described below.

Fv fragments appear to have lower interaction energy of their two chains than Fab fragments. To stabilise the association of the VH and VL domains, they have been linked with peptides (Bird et al. (1988) Science 242: 423-426; Huston et al. (1988) PNAS 85(16): 5879-5883), disulphide bridges (Glockshuber et al. (1990) Biochemistry 29: 1362-1367) and "knob in hole" mutations (Zhu et al. (1997) Protein Sci., 6: 781-788). ScFv fragments can be produced by methods well known to those skilled in the art, see Whitlow et al. (1991) Methods Companion Methods Enzymol, 2: 97-105 and Huston et al. (1993) Int. Rev.

Immunol 10: 195-217. ScFv may be produced in bacterial cells such as E. coli or in eukaryotic cells. One disadvantage of ScFv is the monovalency of the product, which precludes an increased avidity due to polyvalent binding, and their short half-life. Attempts to overcome these problems include bivalent (ScFv')2 produced from ScFv containing an additional C-terminal cysteine by chemical coupling (Adams et al. (1993) Can. Res 53: 4026-4034; and McCartney et al. (1995) Protein Eng. 8: 301-314) or by spontaneous site-specific dimerisation of ScFv containing an unpaired C-terminal cysteine residue (see Kipriyanov et al. (1995) Cell. Biophys 26: 187-204). Alternatively, ScFv can be forced to form multimers by shortening the peptide linker to 3 to 12 residues to form "diabodies", see Holliger et al. (1993) PNAS 90: 6444-6448. Reducing the linker still further can result in ScFv trimers ("triabodies", see Kortt et al. (1997) Protein Eng 10: 423-433) and tetramers ("tetrabodies", see Le Gall et al. (1999) FEBS Lett, 453: 164-168). Construction of bivalent ScFv molecules can also be achieved by genetic fusion with protein dimerising motifs to form "miniantibodies" (see Pack et al. (1992) Biochemistry 31: 1579-1584) and "minibodies" (see Hu et al. (1996) Cancer Res. 56: 3055-3061). ScFv-Sc-Fv tandems ((ScFV)2) may also be produced by linking two ScFv units by a third peptide linker, see Kurucz et al. (1995) J. Immol. 154: 4576-4582. Bispecific diabodies can be produced through the non-covalent association of two single chain fusion products consisting of VH domain from one antibody connected by a short linker to the VL domain of another antibody, see Kipriyanov et al. (1998) Int. J. Can 77: 763-772. The stability of such bispecific diabodies can be enhanced by the introduction of disulphide bridges or "knob in hole" mutations as described supra or by the formation of single chain diabodies (ScDb) wherein two hybrid ScFv fragments are connected through a peptide linker see Kontermann et al. (1999) J. Immunol. Methods 226:179-188. Tetravalent bispecific molecules are available by e.g. fusing a ScFv fragment to the CH3 domain of an IgG molecule or to a Fab fragment through the hinge region, see Coloma et al. (1997) Nature Biotechnol. 15: 159-163. Alternatively, tetravalent bispecific molecules have been created by the fusion of bispecific single chain diabodies (see Alt et al. (1999) FEBS Lett 454: 90-94. Smaller tetravalent bispecific molecules can also be formed by the dimerization of either ScFv-ScFv tandems with a linker containing a helix-loop-helix motif (DiBi miniantibodies, see Muller et al. (1998) FEBS Lett 432: 45-49) or a single chain molecule comprising four antibody variable domains (VH and VL) in an orientation preventing intramolecular pairing (tandem diabody, see Kipriyanov et al. (1999) J. Mol. Biol.

293: 41-56). Bispecific F(ab')2 fragments can be created by chemical coupling of Fab' fragments or by heterodimerization through leucine zippers (see Shalaby et al. (1992) J. Exp. Med. 175: 217-225; and Kostelny et al. (1992), J. Immunol. 148: 1547-1553). Also available are isolated VH and VL domains (Domantis plc), see US 6,248,516; US 6,291,158; and US 6,172,197.

Heteroconjugate antibodies

Heteroconjugate antibodies are composed of two covalently joined antibodies formed using any convenient cross-linking methods. See, for example, US 4,676,980.

Other Modifications

The antigen binding proteins of the present invention may comprise other modifications to enhance or change their effector functions. The interaction between the Fc region of an antibody and various Fc receptors (FcγR) is believed to mediate the effector functions of the antibody which include antibody-dependent cellular cytotoxicity (ADCC), fixation of complement, phagocytosis and half-life/clearance of the antibody. Various modifications to the Fc region of antibodies may be carried out depending on the desired property. For example, specific mutations in the Fc region to render an otherwise lytic antibody, non-lytic are detailed in EP 0629240 and EP 0307434 or one may incorporate a salvage receptor binding epitope into the antibody to increase serum half life see US 5,739,277. Human Fcγ receptors include FcγR (I), FcγRIIa, FcγRIIb, FcγRIIIa and neonatal FcRn. Shields et al. (2001) J. Biol. Chem 276: 6591-6604 demonstrated that a common set of IgG1 residues is involved in binding all FcγRs, while FcγRII and FcγRIII utilize distinct sites outside of this common set. One group of IgG1 residues reduced binding to all FcγRs when altered to alanine: Pro-238, Asp-265, Asp-270, Asn-297 and Pro-239. All are in the IgG CH2 domain and clustered near the hinge joining CH1 and CH2. While FcγRI utilizes only the common set of IgG1 residues for binding, FcγRII and FcγRIII interact with distinct residues in addition to the common set. Alteration of some residues reduced binding only to FcγRII (e.g. Arg-292) or FcγRIII (e.g. Glu-293). Some variants showed improved binding to FcγRII or FcγRIII but did not affect binding to the other receptor (e.g. Ser-267Ala improved binding to FcγRII but binding to FcγRIII was unaffected). Other variants exhibited improved binding to FcγRII or FcγRIII with reduction in binding to the other receptor (e.g. Ser-298Ala improved binding to FcγRIII and reduced binding to FcγRII). For FcγRIIIa, the best binding IgG1 variants had combined alanine

substitutions at Ser-298, Glu-333 and Lys-334. The neonatal FcRn receptor is believed to be involved in both antibody clearance and the transcytosis across tissues (see Junghans (1997) Immunol. Res 16: 29-57; and Ghetie et al. (2000) Annu. Rev. Immunol. 18: 739-766). Human IgG1 residues determined to interact directly with human FcRn includes Ile253, Ser254, Lys288, Thr307, Gln311, Asn434 and His435. Substitutions at any of the positions described in this section may enable increased serum half-life and/or altered effector properties of the antibodies.

Other modifications include glycosylation variants of the antibodies. Glycosylation of antibodies at conserved positions in their constant regions is known to have a profound effect on antibody function, particularly effector functioning such as those described above, see for example, Boyd et al. (1996) Mol. Immunol. 32: 1311-1318. Glycosylation variants of the antibodies or antigen binding fragments thereof wherein one or more carbohydrate moiety is added, substituted, deleted or modified are contemplated. Introduction of an asparagine-X-serine or asparagine-X-threonine motif creates a potential site for enzymatic attachment of carbohydrate moieties and may therefore be used to manipulate the glycosylation of an antibody. In Raju et al. (2001) Biochemistry 40: 8868-8876 the terminal sialyation of a TNFR-IgG immunoadhesin was increased through a process of regalactosylation and/or resialylation using beta-1, 4-galactosyltransferace and/or alpha, 2,3 sialyltransferase. Increasing the terminal sialylation is believed to increase the half-life of the immunoglobulin. Antibodies, in common with most glycoproteins, are typically produced as a mixture of glycoforms. This mixture is particularly apparent when antibodies are produced in eukaryotic, particularly mammalian cells. A variety of methods have been developed to manufacture defined glycoforms, see Zhang et al. (2004) Science 303: 371: Sears et al. (2001) Science 291: 2344; Wacker et al. (2002) Science 298: 1790; Davis et al. (2002) Chem. Rev. 102: 579; Hang et al. (2001) Acc. Chem. Res 34: 727. The antibodies (for example of the IgG isotype, e.g. IgG1) as herein described may comprise a defined number (e.g. 7 or less, for example 5 or less, such as two or a single) of glycoform(s).

The antibodies may be coupled to a non-proteinaeous polymer such as polyethylene glycol (PEG), polypropylene glycol or polyoxyalkylene. Conjugation of proteins to PEG is an established technique for increasing half-life of proteins, as well as reducing antigenicity and immunogenicity of proteins. The use of PEGylation with different molecular weights and

styles (linear or branched) has been investigated with intact antibodies as well as Fab' fragments, see Koumenis et al. (2000) Int. J. Pharmaceut. 198: 83-95.

Production Methods

Antigen binding proteins may be produced in transgenic organisms such as goats (see Pollock et al. (1999) J. Immunol. Methods 231: 147-157), chickens (see Morrow (2000) Genet. Eng. News 20: 1-55, mice (see Pollock et al.) or plants (see Doran (2000) Curr. Opinion Biotechnol. 11: 199-204; Ma (1998) Nat. Med. 4: 601-606; Baez et al. (2000) BioPharm 13: 50-54; Stoger et al. (2000) Plant Mol. Biol. 42: 583-590).

Antigen binding proteins may also be produced by chemical synthesis. However, antigen binding proteins are typically produced using recombinant cell culturing technology well known to those skilled in the art. A polynucleotide encoding the antigen binding protein is isolated and inserted into a replicable vector such as a plasmid for further cloning (amplification) or expression. One expression system is a glutamate synthetase system (such as sold by Lonza Biologics), particularly where the host cell is CHO or NS0. Polynucleotide encoding the antigen binding protein is readily isolated and sequenced using conventional procedures (e.g. oligonucleotide probes). Vectors that may be used include plasmid, virus, phage, transposons, minichromosomes of which plasmids are typically used. Generally such vectors further include a signal sequence, origin of replication, one or more marker genes, an enhancer element, a promoter and transcription termination sequences operably linked to the antigen binding protein polynucleotide so as to facilitate expression. Polynucleotide encoding the light and heavy chains may be inserted into separate vectors and introduced (for example by transformation, transfection, electroporation or transduction) into the same host cell concurrently or sequentially or, if desired, both the heavy chain and light chain can be inserted into the same vector prior to said introduction.

Codon optimisation may be used with the intent that the total level of protein produced by the host cell is greater when transfected with the codon-optimised gene in comparison with the level when transfected with the sequence. Several methods have been published (Nakamura et al. (1996) Nucleic Acids Research 24: 214-215; W098/34640; W097/11086). Due to the redundancy of the genetic code, alternative polynucleotides to those disclosed herein (particularly those codon optimised for expression in a given host cell) may also

encode the antigen binding proteins described herein. The codon usage of the antigen binding protein of this invention therefore can be modified to accommodate codon bias of the host cell such to augment transcript and/or product yield (e.g. Hoekema et al Mol Cell Biol 1987 7(8): 2914-24). The choice of codons may be based upon suitable compatibility with the host cell used for expression.

Signal sequences

Antigen binding proteins may be produced as a fusion protein with a heterologous signal sequence having a specific cleavage site at the N-terminus of the mature protein. The signal sequence should be recognised and processed by the host cell. For prokaryotic host cells, the signal sequence may be for example an alkaline phosphatase, penicillinase, or heat stable enterotoxin II leaders. For yeast secretion the signal sequences may be for example a yeast invertase leader, α factor leader or acid phosphatase leaders see e.g. WO90/13646. In mammalian cell systems, viral secretory leaders such as herpes simplex gD signal and a native immunoglobulin signal sequence may be suitable. Typically the signal sequence is ligated in reading frame to DNA encoding the antigen binding protein. A murine signal sequence such as that shown in SEQ ID NO: 79 may be used.

Origin of replication

Origin of replications are well known in the art with pBR322 suitable for most gram-negative bacteria, 2μ plasmid for most yeast and various viral origins such as SV40, polyoma, adenovirus, VSV or BPV for most mammalian cells. Generally the origin of replication component is not needed for mammalian expression vectors but the SV40 may be used since it contains the early promoter.

Selection marker

Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins e.g. ampicillin, neomycin, methotrexate or tetracycline or (b) complement auxiotrophic deficiencies or supply nutrients not available in the complex media or (c) combinations of both. The selection scheme may involve arresting growth of the host cell. Cells, which have been successfully transformed with the genes encoding the antigen binding protein, survive due to e.g. drug resistance conferred by the co-delivered selection marker. One example is the DHFR selection marker wherein transformants are cultured in

the presence of methotrexate. Cells can be cultured in the presence of increasing amounts of methotrexate to amplify the copy number of the exogenous gene of interest. CHO cells are a particularly useful cell line for the DHFR selection. A further example is the glutamate synthetase expression system (Lonza Biologics). An example of a selection gene for use in yeast is the trp1 gene, see Stinchcomb et al. (1979) Nature 282: 38.

Promoters

Suitable promoters for expressing antigen binding proteins are operably linked to DNA/polynucleotide encoding the antigen binding protein. Promoters for prokaryotic hosts include phoA promoter, beta-lactamase and lactose promoter systems, alkaline phosphatase, tryptophan and hybrid promoters such as Tac. Promoters suitable for expression in yeast cells include 3-phosphoglycerate kinase or other glycolytic enzymes e.g. enolase, glyceralderhyde 3 phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose 6 phosphate isomerase, 3-phosphoglycerate mutase and glucokinase. Inducible yeast promoters include alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, metallothionein and enzymes responsible for nitrogen metabolism or maltose/galactose utilization.

Promoters for expression in mammalian cell systems include viral promoters such as polyoma, fowlpox and adenoviruses (e.g. adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus (in particular the immediate early gene promoter), retrovirus, hepatitis B virus, actin, rous sarcoma virus (RSV) promoter and the early or late Simian virus 40. Of course the choice of promoter is based upon suitable compatibility with the host cell used for expression. A first plasmid may comprise a RSV and/or SV40 and/or CMV promoter, DNA encoding light chain variable region (VL), κC region together with neomycin and ampicillin resistance selection markers and a second plasmid comprising a RSV or SV40 promoter, DNA encoding the heavy chain variable region (VH), DNA encoding the γ1 constant region, DHFR and ampicillin resistance markers.

Enhancer element

Where appropriate, e.g. for expression in higher eukaryotes, an enhancer element operably linked to the promoter element in a vector may be used. Mammalian enhancer sequences include enhancer elements from globin, elastase, albumin, fetoprotein and insulin.

Alternatively, one may use an enhancer element from a eukaroytic cell virus such as SV40 enhancer (at bp100-270), cytomegalovirus early promoter enhancer, polyma enhancer, baculoviral enhancer or murine IgG2a locus (see WO04/009823). The enhancer may be located on the vector at a site upstream to the promoter. Alternatively, the enhancer may be located elsewhere, for example within the untranslated region or downstream of the polyadenylation signal. The choice and positioning of enhancer may be based upon suitable compatibility with the host cell used for expression.

Polyadenylation/termination

In eukaryotic systems, polyadenylation signals are operably linked to DNA/polynucleotide encoding the antigen binding protein. Such signals are typically placed 3' of the open reading frame. In mammalian systems, non-limiting examples include signals derived from growth hormones, elongation factor-1 alpha and viral (e.g. SV40) genes or retroviral long terminal repeats. In yeast systems non-limiting examples of polydenylation/termination signals include those derived from the phosphoglycerate kinase (PGK) and the alcohol dehydrogenase 1 (ADH) genes. In prokaryotic systems, polyadenylation signals are typically not required and it is instead usual to employ shorter and more defined terminator sequences. The choice of polyadenylation/termination sequences may be based upon suitable compatibility with the host cell used for expression.

Other methods/elements for enhanced yields

In addition to the above, other features that can be employed to enhance yields include chromatin remodelling elements, introns and host-cell specific codon modification.

Host cells

Suitable host cells for cloning or expressing vectors encoding antigen binding proteins are prokaroytic, yeast or higher eukaryotic cells. Suitable prokaryotic cells include eubacteria e.g. enterobacteriaceae such as Escherichia e.g. E. coli (for example ATCC 31,446; 31,537; 27,325), Enterobacter, Erwinia, Klebsiella Proteus, Salmonella e.g. Salmonella typhimurium, Serratia e.g. Serratia marcescans and Shigella as well as Bacilli such as B. subtilis and B. licheniformis (see DD 266 710), Pseudomonas such as P. aeruginosa and Streptomyces. Of the yeast host cells, Saccharomyces cerevisiae, Schizosaccharomyces pombe, Kluyveromyces (e.g. ATCC 16,045; 12,424; 24178; 56,500), yarrowia (EP402, 226), Pichia pastoris (EP 183

070, see also Peng et al. (2004) J. Biotechnol. 108: 185-192), Candida, Trichoderma reesia (EP 244 234), Penicillin, Tolypocladium and Aspergillus hosts such as A. nidulans and A. niger are also contemplated.

Higher eukaryotic host cells include mammalian cells such as COS-1 (ATCC No.CRL 1650) COS-7 (ATCC CRL 1651), human embryonic kidney line 293, baby hamster kidney cells (BHK) (ATCC CRL.1632), BHK570 (ATCC NO: CRL 10314), 293 (ATCC NO.CRL 1573), Chinese hamster ovary cells CHO (e.g. CHO-K1, ATCC NO: CCL 61, DHFR-CHO cell line such as DG44 (see Urlaub et al. (1986) Somatic Cell Mol. Genet.12: 555-556), particularly those CHO cell lines adapted for suspension culture, mouse sertoli cells, monkey kidney cells, African green monkey kidney cells (ATCC CRL-1587), HELA cells, canine kidney cells (ATCC CCL 34), human lung cells (ATCC CCL 75), Hep G2 and myeloma or lymphoma cells e.g. NS0 (see US 5,807,715), Sp2/0, Y0.

Such host cells may also be further engineered or adapted to modify quality, function and/or yield of the antigen binding protein. Non-limiting examples include expression of specific modifying (e.g. glycosylation) enzymes and protein folding chaperones.

Cell Culturing Methods

Host cells transformed with vectors encoding antigen binding proteins may be cultured by any method known to those skilled in the art. Host cells may be cultured in spinner flasks, roller bottles or hollow fibre systems but for large scale production that stirred tank reactors are used particularly for suspension cultures. The stirred tankers may be adapted for aeration using e.g. spargers, baffles or low shear impellers. For bubble columns and airlift reactors direct aeration with air or oxygen bubbles maybe used. Where the host cells are cultured in a serum free culture media, the media is supplemented with a cell protective agent such as pluronic F-68 to help prevent cell damage as a result of the aeration process. Depending on the host cell characteristics, either microcarriers maybe used as growth substrates for anchorage dependent cell lines or the cells may be adapted to suspension culture (which is typical). The culturing of host cells, particularly invertebrate host cells may utilise a variety of operational modes such as fed-batch, repeated batch processing (see Drapeau et al. (1994) Cytotechnology 15: 103-109), extended batch process or perfusion culture. Although recombinantly transformed mammalian host cells may be cultured in serum-containing media such as fetal calf serum (FCS), such host cells may be cultured in

synthetic serum–free media such as disclosed in Keen et al. (1995) Cytotechnology 17: 153-163, or commercially available media such as ProCHO-CDM or UltraCHO™ (Cambrex NJ, USA), supplemented where necessary with an energy source such as glucose and synthetic growth factors such as recombinant insulin. The serum-free culturing of host cells may require that those cells are adapted to grow in serum free conditions. One adaptation approach is to culture such host cells in serum containing media and repeatedly exchange 80% of the culture medium for the serum-free media so that the host cells learn to adapt in serum free conditions (see e.g. Scharfenberg et al. (1995) in Animal Cell Technology: Developments towards the 21st century (Beuvery et al. eds, 619-623, Kluwer Academic publishers).

Antigen binding proteins secreted into the media may be recovered and purified using a variety of techniques to provide a degree of purification suitable for the intended use. For example the use of antigen binding proteins for the treatment of human patients typically mandates at least 95% purity, more typically 98% or 99% or greater purity (compared to the crude culture medium). Cell debris from the culture media is typically removed using centrifugation followed by a clarification step of the supernatant using e.g. microfiltration, ultrafiltration and/or depth filtration. A variety of other techniques such as dialysis and gel electrophoresis and chromatographic techniques such as hydroxyapatite (HA), affinity chromatography (optionally involving an affinity tagging system such as polyhistidine) and/or hydrophobic interaction chromatography (HIC, see US 5, 429,746) are available. The antibodies, following various clarification steps, can be captured using Protein A or G affinity chromatography. Further chromatography steps can follow such as ion exchange and/or HA chromatography, anion or cation exchange, size exclusion chromatography and ammonium sulphate precipitation. Various virus removal steps may also be employed (e.g. nanofiltration using e.g. a DV-20 filter). Following these various steps, a purified (for example a monoclonal) preparation comprising at least 75mg/ml or greater, or 100mg/ml or greater, of the antigen binding protein is provided. Such preparations are substantially free of aggregated forms of antigen binding proteins.

Bacterial systems may be used for the expression of antigen binding fragments. Such fragments can be localised intracellularly, within the periplasm or secreted extracellularly. Insoluble proteins can be extracted and refolded to form active proteins according to

methods known to those skilled in the art, see Sanchez et al. (1999) J. Biotechnol. 72: 13-20; and Cupit et al. (1999) Lett Appl Microbiol 29: 273-277.

Deamidation is a chemical reaction in which an amide functional group is removed. In biochemistry, the reaction is important in the degradation of proteins because it damages the amide-containing side chains of the amino acids asparagine and glutamine. Asparagine is converted to a mixture of isoaspartate and aspartate. Deamidation of glutamine residues occurs at a much lower rate. Deamidation reactions are believed to be one of the factors that can limit the useful lifetime of a protein, they are also one of the most common post-translational modifications occurring during the manufacture of therapeutic proteins. For example, a reduction or loss of in vitro or in vivo biological activity has been reported for recombinant human DNAse and recombinant soluble CD4, whereas other recombinant proteins appear to be unaffected.

Pharmaceutical Compositions

Purified preparations of an antigen binding protein as described herein may be incorporated into pharmaceutical compositions for use in the treatment of the human diseases, disorders and conditions described herein. The terms diseases, disorders and conditions are used interchangeably. The pharmaceutical composition can be used in the treatment of any diseases where amyloid deposits are present in the tissues and contribute to structural and functional damage leading to clinical illness. SAP is always present in all amyloid deposits *in vivo* and the pharmaceutical composition comprising a therapeutically effective amount of the antigen binding protein described herein can be used in the treatment of diseases responsive to clearance of amyloid deposits from the tissues.

The pharmaceutical preparation may comprise an antigen binding protein in combination with a pharmaceutically acceptable carrier. The antigen binding protein may be administered alone, or as part of a pharmaceutical composition.

Typically such compositions comprise a pharmaceutically acceptable carrier as known and called for by acceptable pharmaceutical practice, see e.g. Remingtons Pharmaceutical Sciences, 16th edition (1980) Mack Publishing Co. Examples of such carriers include

sterilised carriers such as saline, Ringers solution or dextrose solution, optionally buffered with suitable buffers to a pH within a range of 5 to 8.

Pharmaceutical compositions may be administered by injection or continuous infusion (e.g. intravenous, intraperitoneal, intradermal, subcutaneous, intramuscular or intraportal). Such compositions are suitably free of visible particulate matter. Pharmaceutical compositions may also be administered orally, specifically those containing CPHPC.

Pharmaceutical compositions may comprise between 1mg to 10g of antigen binding protein, for example between 5 mg and 1 g of antigen binding protein. Alternatively, the composition may comprise between 5 mg and 500 mg, for example between 5 mg and 50 mg.

Methods for the preparation of such pharmaceutical compositions are well known to those skilled in the art. Pharmaceutical compositions may comprise between 1 mg to 10 g of antigen binding protein in unit dosage form, optionally together with instructions for use. Pharmaceutical compositions may be lyophilised (freeze dried) for reconstitution prior to administration according to methods well known or apparent to those skilled in the art. Where antibodies have an IgG1 isotype, a chelator of copper, such as citrate (e.g. sodium citrate) or EDTA or histidine, may be added to the pharmaceutical composition to reduce the degree of copper-mediated degradation of antibodies of this isotype, see EP0612251. Pharmaceutical compositions may also comprise a solubiliser such as arginine base, a detergent/anti-aggregation agent such as polysorbate 80, and an inert gas such as nitrogen to replace vial headspace oxygen.

Effective doses and treatment regimes for administering the antigen binding protein are generally determined empirically and may be dependent on factors such as the age, weight and health status of the patient and disease or disorder to be treated. Such factors are within the purview of the attending physician. Guidance in selecting appropriate doses may be found in e.g. Smith et al (1977) Antibodies in human diagnosis and therapy, Raven Press, New York.

The dosage of antigen binding protein administered to a subject is generally between 1 µg/kg to 150 mg/kg, between 0.1 mg/kg and 100 mg/kg, between 0.5 mg/kg and 50 mg/kg, between 1 and 25 mg/kg or between 1 and 10 mg/kg of the subject's body weight. For

example, the dose may be 10 mg/kg, 30 mg/kg, or 60 mg/kg. The antigen binding protein may be administered parenterally, for example subcutaneously, intravenously or intramuscularly.

The SAP-depleting compound may be administered at a dose of between 0.1 mg/kg and 2 mg/kg, depending on its activity. The SAP-depleting compound may be administered as a fixed dose, independent of a dose per subject weight ratio. The SAP-depleting compound may be administered in one or more separate, simultaneous or sequential parenteral doses of 100 mg or less, of 50 mg or less, 25 mg or less, or 10 mg or less.

If desired, the effective daily dose of a therapeutic composition may be administered as two, three, four, five, six or more sub-doses administered separately at appropriate intervals throughout the day, optionally, in unit dosage forms.

The antigen binding protein may be administered in a single large dose or in smaller repeated doses.

The administration of a dose may be by slow continuous infusion over a period of from 2 to 24 hours, such as from 2 to 12 hours, or from 2 to 6 hours. This may result in reduced toxic side effects.

The administration of a dose may be repeated one or more times as necessary, for example, three times daily, once every day, once every 2 days, once a week, once a fortnight, once a month, once every 3 months, once every 6 months, or once every 12 months. The antigen binding proteins may be administered by maintenance therapy, for example once a week for a period of 6 months or more. The antigen binding proteins may be administered by intermittent therapy, for example for a period of 3 to 6 months and then no dose for 3 to 6 months, followed by administration of antigen binding proteins again for 3 to 6 months, and so on in a cycle.

For example, the dose may be administered subcutaneously, once every 14 or 28 days in the form of multiple sub-doses on each day of administration.

The antigen binding protein may be administered to the subject in such a way as to target therapy to a particular site. For example, the antigen binding protein may be injected locally into a circumscribed local amyloid mass in the tissues, or infused into the blood supply to an amyloidotic organ.

The antigen binding protein must be used in combination with one or more other therapeutically active agents, specifically SAP depleting compounds, for the treatment of the diseases described herein. Effective depletion of SAP from the circulation must be achieved before administration of the SAP binding protein in order for the latter to be given both safely and effectively.

The SAP depleting compound is administered first so that almost all of the circulating SAP is cleared. Since this leaves substantial amounts of SAP associated with the amyloid deposits in the tissues the sequential administration of an anti-SAP antigen binding protein enables the localisation and specific binding to the amyloid deposits to promote their rapid and extensive regression. Suitably, the anti-SAP antigen binding protein may be administered 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20 or 25 or more days after starting the treatment(s) with the SAP depleting compound.

The sequential administration may involve two or more sequential treatments with SAP depleting compound followed by two or more sequential treatments with the anti-SAP antigen binding protein.

The sequential administration may involve one treatment with SAP depleting compound followed by one sequential treatment with the anti-SAP antigen binding protein, which is then repeated one or more times.

The sequential/subsequent dose may be an amount that is more than the initial/previous dose or less than the initial/previous dose.

The administration of an initial dose of SAP-depleting compound protein may be followed by the administration of one or more sequential (e.g. subsequent) doses of SAP depleting compound and/or the anti-SAP antigen binding protein, and wherein said one or more sequential doses may be in an amount that is approximately the same or less than the initial dose.

After initial depletion of circulating SAP, the administration of further doses of SAP depleting compound and the first dose of anti-SAP antigen binding protein may be followed by the administration of one or more sequential (e.g. subsequent) doses, and wherein at least one of the subsequent doses is in an amount that is more than the initial dose.

Accordingly, the administration may use a pre-determined or routine schedule for administration, thereby resulting in a predetermined designated period of time between dose administrations. The schedule may encompass periods of time which are identical or which differ in length, as long as the schedule is predetermined. Any particular combination would be covered by the schedule as long as it is determined ahead of time that the appropriate schedule involves administration on a certain day.

The pharmaceutical composition may comprise a kit of parts of the antigen binding protein together with other medicaments, optionally with instructions for use. For convenience, the kit may comprise the reagents in predetermined amounts with instructions for use.

The terms “individual”, “subject” and “patient” are used herein interchangeably. The subject may be a primate (e.g. a marmoset or monkey). The subject is typically a human.

Treatment can be therapeutic, prophylactic or preventative. The subject will be one who is in need thereof. Those in need of treatment may include individuals already suffering from a particular medical disease in addition to those who may develop the disease in the future.

Thus, the SAP depleting compound followed by the SAP antigen binding protein described herein can be used for prophylactic or preventative treatment. In this case, the sequential treatments described herein are administered to an individual in order to prevent or delay the onset of one or more aspects or symptoms of the disease. The subject can be asymptomatic or may have a genetic predisposition to the disease, as amyloid deposits are known to be present in the tissues and to accumulate for periods of time before they cause sufficient damage to produce clinical symptoms. Such sub-clinical amyloid deposition can be detected by histological examination of tissue biopsies or by non-invasive imaging procedures, including radiolabelled SAP scintigraphy, echocardiography and cardiac magnetic resonance imaging. After first depleting circulating SAP, a prophylactically effective amount of the antigen binding protein is administered to such an individual. A prophylactically effective amount is an amount which prevents or delays the onset of one or more aspects or symptoms of a disease described herein.

The antigen binding protein described herein may also be used in methods of therapy. The term "therapy" encompasses alleviation, reduction, or prevention of at least one aspect or symptom of a disease. For example, the antigen binding protein described herein may be

used to ameliorate or reduce one or more aspects or symptoms of a disease described herein.

The antigen binding protein described herein is used in an effective amount for therapeutic, prophylactic or preventative treatment. A therapeutically effective amount of the antigen binding protein described herein is an amount effective to ameliorate or reduce one or more aspects or symptoms of the disease. The antigen binding protein described herein may also be used to treat, prevent, or cure the disease described herein.

The antigen binding protein described herein can have a generally beneficial effect on the subject's health, for example it can increase the subject's expected longevity.

The antigen binding protein described herein need not affect a complete cure, or eradicate every symptom or manifestation of the disease to constitute a viable therapeutic treatment. As is recognised in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a disease in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur (for example by delaying the onset of the disease) or worsen in a subject, is sufficient.

Antigen binding proteins described herein may be used in treating or preventing a disease associated with amyloid deposition i.e. amyloidosis.

“Amyloidosis” is any disease characterized by the extracellular accumulation of amyloid in various organs and tissues of the body.

The term "amyloid” refers to extracellular deposits in the tissues of insoluble protein fibres composed of fibrils with characteristic ultrastructural morphology, a cross-β sheet core structure and the pathognomonic histochemical tinctorial property of binding Congo red dye from alkaline alcoholic solution and then giving red-green dichroism when viewed microscopically in strong cross polarised light. About 25 different unrelated proteins are known to form amyloid fibrils which deposit in human tissues and share all these typical

properties. Amyloid deposits in the brain substance, cerebral amyloid, differ somewhat from amyloid deposits elsewhere in the body in that they are always focal and microscopic in size, and are commonly referred to as amyloid plaques.

Amyloidosis, that is disease directly caused by deposition of amyloid in the tissues, comprises both local amyloidosis, in which the deposits are confined to one anatomical region and/or one tissue or organ system, and systemic amyloidosis in which the deposits can occur in any organ or tissue in the body, including blood vessels and connective tissues. The cause of amyloidosis can be either acquired or hereditary. Acquired amyloidosis arises as a complication of a preceding medical condition, which can itself be either acquired or hereditary. Thus reactive systemic amyloidosis, known as amyloid A protein (AA) type is a complication of chronic active inflammatory diseases such as rheumatoid arthritis, juvenile rheumatoid arthritis, Crohn's disease, chronic infections and chronic sepsis, and of hereditary periodic fever syndromes such as familial Mediterranean fever, Muckle-Wells syndrome and CINCA syndrome. Dialysis related amyloidosis is caused by accumulation of β2-microglobulin as a result of end stage renal failure. Monoclonal immunoglobulin light chain (AL) amyloidosis is a complication of multiple myeloma or otherwise benign monoclonal gammopathy (monoclonal gammopathy of uncertain significance, MGUS). Acquired amyloidosis of transthyretin type can occur without any preceding illness and is merely a complication of old age. Hereditary amyloidosis is caused by mutations in the genes for various proteins which encode expression of variant proteins having an increased propensity to form amyloid fibrils, and includes disease caused by transthyretin, apolipoprotein AI, gelsolin, lysozyme, cystatin C and amyloid β-protein. Comprehensive descriptions of all the different forms of amyloidosis and the proteins involved are available in textbooks and the scientific literature (Pepys, M.B. (2006) Annu. Rev. Med., 57: 223-241; Pepys and Hawkins (2003) Amyloidosis. Oxford Textbook of Medicine, 4th Ed., Vol. 2, Oxford University Press, Oxford, pp. 162-173; Pepys and Hawkins (2001) Amyloidosis. Samter's Immunologic Diseases, Sixth Ed., Vol. 1, Lippincott Williams & Williams, Philadelphia, pp. 401-412).

Local amyloid deposition, confined to one organ or tissue, can be clinically silent or can cause serious tissue damage and disease. For example, cerebral amyloid angiopathy in which the vascular amyloid deposits are composed of Aβ protein, is usually a sporadic

acquired condition arising for reasons which are not understood in the absence of any other pathology, and is a major cause of cerebral haemorrhage and stroke. There are several very important and common diseases, particularly Alzheimer's disease (AD) and type 2 diabetes, in which amyloid deposits are always present but in which the precise mechanisms causing these respective diseases are not yet known. Nevertheless the local deposition of amyloid in the brain and cerebral blood vessels in Alzheimer's disease, and in the pancreatic islets in diabetes is very likely to exacerbate pathology and disease. Accordingly, the present invention includes treatment of both Alzheimer's disease and type 2 diabetes, indeed of any condition associated with the presence of amyloid deposits in the tissues, with antigen binding proteins as disclosed herein.

Many forms of transmissible spongiform encephalopathy (prion diseases) are associated with amyloid deposits in the brain, and the present invention therefore relates to all these conditions, including variant Creutzfeldt-Jakob disease in humans, Creutzfeldt-Jakob disease itself, kuru and the various other forms of human prion disease, and also bovine spongiform encephalopathy, chronic wasting disease of mule-deer and elk, and transmissible encephalopathy of mink.

Diagnostic methods of use

The antigen binding proteins described herein may be used to detect SAP in a biological sample in vitro or in vivo for diagnostic purposes. For example, the anti-SAP antigen binding proteins can be used to detect SAP in serum or in associated with amyloid e.g. amyloid plaques. The amyloid may have been first removed (for example a biopsy) from a human or animal body. Conventional immunoassays may be employed, including ELISA, Western blot, immunohistochemistry, or immunoprecipitation.

The antigen binding proteins may be provided in a diagnostic kit comprising one or more antigen binding proteins, a detectable label, and instructions for use of the kit. For convenience, the kit may comprise the reagents in predetermined amounts with instructions for use.

EXAMPLES

Example 1 - Sequencing of Hybridoma Variable domains: SAP-E and SAP-K

SAP-E and SAP-K are from two groups of anti-SAP monoclonals, each group having been tested separately for their binding to human SAP *in vitro*. SAP-E and SAP-K showed the strongest binding to SAP, within their groups, and were compared with each other in different assays.

The first group of antibodies comprised antibodies from 7 hybridomas generated in a single conventional immunization with purified human SAP (SEQ ID NO:43 shown below) (details of method for purifying human SAP are given in Hawkins *et al*. (1991) Clin. Exp. Immunol. 84, 308-316) and fusion protocol and are designated SAP-A to SAP-G. Two of these antibodies, SAP-E and SAP-B, are IgG2a isotype while the others are all IgG1 isotype (see Example 13, Table 11).

The second group of antibodies comprised 6 different IgG2a monoclonals (SAP-H to SAP-M) derived by standard techniques from immunization with purified human SAP (SEQ ID NO:43 shown below) (Hawkins *et al*. (1991) Clin. Exp. Immunol. 84, 308-316) and a conventional fusion to produce hybridomas which were cloned by routine methods.

homo sapiens SAP mature amino acid sequence (SEQ ID NO:43)

HTDLSGKVFVFPRESVTDHVNLITPLEKPLQNFTLCFRAYSDLSRAYSLFSYNTQGRDNELLVYKERVGEYS
LYIGRHKVTSKVIEKFPAPVHICVSWESSSGIAEFWINGTPLVKKGLRQGYFVEAQPKIVLGQEQDSYGGK
FDRSQSFVGEIGDLYMWDSVLPPENILSAYQGTPLPANILDWQALNYEIRGYVIIKPLVWV

For comparison purposes, the mouse SAP sequence, which has a 69.4% identity with human SAP, is given below.

mus musculus SAP mature protein (SEQ ID NO:44)

QTDLKRKVFVFPRESETDHVKLIPHLEKPLQNFTLCFRTYSDLSRSQSLFSYSVKGRDNELLIYKEKVGEYSLY
IGQSKVTVRGMEEYLSPVHLCTTWESSSGIVEFWVNGKPWVKKSLQREYTVKAPPSIVLGQEQDNYGG
GFQRSQSFVGEFSDLYMWDYVLTPQDILFVYRDSPVNPNILNWQALNYEINGYVVIRPRVW

Total RNA was extracted from hybridoma cell pellets of approximately 10^6 cells using the RNeasy kit from Qiagen (#74106). AccessQuick RT-PCR System (A1702) was used to produce cDNA of the variable heavy and light regions using degenerate primers specific for the murine immunoglobulin gene leader sequences and murine IgG2a/$_K$ constant regions. The purified RT-PCR fragments were cloned using the TA cloning kit from Invitrogen (K2000-01). A consensus sequence was obtained for each hybridoma by sequence alignment, and alignment with known immunoglobulin variable sequences listed in KABAT (Sequences of Proteins of Immunological Interest, 4th Ed., U.S. Department of Health and Human Services, National Institutes of Health (1987)). The consensus sequences for SAP-E and SAP-K are shown below.

SAP-E sequences

SAP-E CDRH1 (SEQ ID NO:1)

TYNMH

SAP-E CDRH2 (SEQ ID NO:2)

YIYPGDGNANYNQQFKG

SAP-E CDRH3 (SEQ ID NO:3)

GDFDYDGGYYFDS

SAP-E CDRL1 (SEQ ID NO:4)

RASENIYSYLA

SAP-E CDRL2 (SEQ ID NO:5)

NAKTLAE

SAP-E CDRL3 (SEQ ID NO:6)

QHHYGAPLT

SAP-E V_H amino acid sequence (SEQ ID NO:7) with CDRs underlined

QASLQQSGTELVRSGASVKMSCKASGFTFATYNMHWIKQTPGQGLEWIGYIYPGDGNANYNQQFKGK
ATLTADTSSNTAYMQISSLTSEDSAVYFCARGDFDYDGGYYFDSWGQGTTLTVSS

SAP-E V_H DNA sequence (SEQ ID NO:8)

CAGGCTTCTCTACAGCAGTCTGGGACTGAGCTGGTGAGGTCTGGGGCCTCAGTGAAGATGTCCTGC
AAGGCTTCTGGCTTCACATTTGCCACTTACAATATGCACTGGATTAAGCAGACACCCGGACAGGGCC
TGGAATGGATTGGGTATATTTATCCTGGAGATGGTAATGCTAACTACAATCAGCAGTTCAAGGGCAA
GGCCACATTGACTGCAGACACATCCTCCAACACAGCCTACATGCAGATCAGCAGCCTGACATCTGAA
GACTCTGCGGTCTATTTCTGTGCAAGAGGGGACTTTGATTACGACGGAGGGTACTACTTTGACTCCT
GGGGCCAGGGCACCACTCTCACAGTCTCCTCA

SAP-E V_L amino acid sequence (SEQ ID NO:9) with CDRs underlined

DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQGRSPQLLVHNAKTLAEGVPSRVSGSGSGTH
FSLKINGLQPEDFGNYYCQHHYGAPLTFGAGTKLELK

SAP-E V_L DNA sequence (SEQ ID NO:10)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTGTCACCATCACATG
TCGAGCAAGTGAGAATATTTACAGTTATTTAGCATGGTATCAGCAGAAACAGGGAAGATCCCCTCAG
CTCCTGGTCCATAATGCAAAAACCTTAGCAGAAGGTGTGCCATCAAGGGTCAGTGGCAGTGGATCA
GGCACACACTTTTCTCTGAAGATCAACGGCCTGCAGCCTGAAGATTTTGGGAATTATTACTGTCAAC
ATCATTATGGTGCTCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAACTGAAA

SAP-K sequences

SAP-K CDRH1 (SEQ ID NO:11)

SYWMH

SAP-K CDRH2 (SEQ ID NO:12)

MIHPNSVNTNYNEKFKS

SAP-K CDRH3 (SEQ ID NO:13)

RNDYYWYFDV

SAP-K CDRL1 (SEQ ID NO:14)

KASQNVNSNVA

SAP-K CDRL2 (SEQ ID NO:15)

SASYRYS

SAP-K CDRL3 (SEQ ID NO:16)

QQCNNYPFT

SAP-K V_H amino acid sequence (SEQ ID NO:17) with CDRs underlined

QVQLQQPGAELIKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGMIHPNSVNTNYNEKFKSK
ATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRNDYYWYFDVWGTGTTVTVSS

SAP-K V_H DNA sequence (SEQ ID NO:18)

CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTGATAAAGCCTGGGGCTTCAGTGAAGTTGTCCTGC
AAGGCTTCTGGCTACACTTTCACCAGCTACTGGATGCACTGGGTGAAGCAGAGGCCTGGACAAGGC
CTTGAGTGGATTGGAATGATTCATCCTAATAGTGTTAATACTAACTACAATGAGAAGTTCAAGAGTA
AGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACTCAACAGCCTGACATCTGA
GGACTCTGCGGTCTATTACTGTGCAAGACGGAATGATTACTACTGGTACTTCGATGTCTGGGGCACA
GGGACCACGGTCACCGTCTCCTCA

SAP-K V_L amino acid sequence (SEQ ID NO:19) with CDRs underlined

DIVMTQSQKFMSTSVGDRVSVTCKASQNVNSNVAWYQQKPGQSPKALIYSASYRYSGVPDRFTGSGSG
TDFTLTITNVQSEDLAEYFCQQCNNYPFTFGSGTKLEIK

SAP-K V_L DNA sequence (SEQ ID NO:20)

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCAGCGTCACCT
GCAAGGCCAGTCAGAATGTGAATTCTAATGTAGCCTGGTATCAACAGAAACCAGGGCAATCTCCTAA
AGCACTGATTTACTCGGCTTCCTACCGGTACAGTGGAGTCCCTGATCGCTTCACAGGCAGTGGATCT

GGGACAGATTTCACTCTCACCATCACCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAGC
AATGTAACAACTATCCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAAA

Example 2: Construction of chimeric antibodies

Chimeric antibodies, comprising parent murine variable domains grafted onto human IgG1/κ wild-type constant regions were constructed by PCR cloning for SAP-E and SAP-K. Based on the consensus sequence, primers to amplify the murine variable domains were designed, incorporating restriction sites required to facilitate cloning into mammalian expression vectors. Through introduction of the restriction site in FR4 (Framework Region 4 (V-region sequence following CDR3 and preceding first constant domain)) the V_H amino acid sequence in SAP-E was changed from TTLTVSS as shown in SEQ ID NO:7 to TLVTVSS and the V_H amino acid sequence in SAP-K was changed from TTVTVSS as shown in SEQ ID NO:17 to TLVTVSS. In the SAP-K variable light chain an internal EcoRI site was present in CDRL1 and mutagenesis primers were designed to remove this undesired internal EcoRI site by changing one base pair – this did not change the amino acid sequence.

The full length heavy and light chain protein sequences of the SAP-E chimeric antibody (cSAP-E) are given in SEQ ID NO:21 and SEQ ID NO:22 respectively. The full length heavy and light chain protein sequences of the SAP-K chimeric antibody (cSAP-K) are given in SEQ ID NO:23 and SEQ ID NO:24 respectively.

SAP-E VH chimera nucleotide sequence (SEQ ID NO:45)

CAGGCTTCTCTACAGCAGTCTGGGACTGAGCTGGTGAGGTCTGGGGCCTCAGTGAAGATGTCCTGC
AAGGCTTCTGGCTTCACATTTGCCACTTACAATATGCACTGGATTAAGCAGACACCCGGACAGGGCC
TGGAATGGATTGGGTATATTTATCCTGGAGATGGTAATGCTAACTACAATCAGCAGTTCAAGGGCAA
GGCCACATTGACTGCAGACACATCCTCCAACACAGCCTACATGCAGATCAGCAGCCTGACATCTGAA
GACTCTGCGGTCTATTTCTGTGCAAGAGGGGACTTTGATTACGACGGAGGGTACTACTTTGACTCCT
GGGGCCAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGG
CCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCC
CCGAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCG
TGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGC
ACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAG

CCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCTGCCCTGCCCCCGAGCTGCTGGGAGGCCCCA
GCGTGTTCCTGTTCCCCCCCAAGCCTAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTG
TGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGG
AGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCC
GTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAG
GCCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTG
TACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAG
GGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAA
GACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAG
AGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAATCACTAC
ACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SAP-E VH chimera amino acid sequence (SEQ ID NO:21)

QASLQQSGTELVRSGASVKMSCKASGFTFATYNMHWIKQTPGQGLEWIGYIYPGDGNANYNQQFKGK
ATLTADTSSNTAYMQISSLTSEDSAVYFCARGDFDYDGGYYFDSWGQGTLVTVSSASTKGPSVFPLAPSS
KSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVN
HKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVK
FNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQP
REPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDK
SRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SAP-E VL chimera nucleotide sequence (SEQ ID NO:46)

GACATCCAGATGACTCAGTCTCCAGCCTCCCTATCTGCATCTGTGGGAGAAACTGTCACCATCACATG
TCGAGCAAGTGAGAATATTTACAGTTATTTAGCATGGTATCAGCAGAAACAGGGAAGATCCCCTCAG
CTCCTGGTCCATAATGCAAAAACCTTAGCAGAAGGTGTGCCATCAAGGGTCAGTGGCAGTGGATCA
GGCACACACTTTTCTCTGAAGATCAACGGCCTGCAGCCTGAAGATTTTGGGAATTATTACTGTCAAC
ATCATTATGGTGCTCCGCTCACGTTCGGTGCTGGGACCAAGCTGGAACTGAAACGTACGGTGGCCG
CCCCCAGCGTGTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTGT
GTCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAGA
GCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAGC
ACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAGGTGACCCACCAG
GGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SAP-E VL chimera amino acid sequence (SEQ ID NO:22)

DIQMTQSPASLSASVGETVTITCRASENIYSYLAWYQQKQGRSPQLLVHNAKTLAEGVPSRVSGSGSGTH
FSLKINGLQPEDFGNYYCQHHYGAPLTFGAGTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYP
REAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNR
GEC

SAP-K VH chimera nucleotide sequence (SEQ ID NO:47)

CAGGTCCAACTGCAGCAGCCTGGGGCTGAGCTGATAAAGCCTGGGGCTTCAGTGAAGTTGTCCTGC
AAGGCTTCTGGCTACACTTTCACCAGCTACTGGATGCACTGGGTGAAGCAGAGGCCTGGACAAGGC
CTTGAGTGGATTGGAATGATTCATCCTAATAGTGTTAATACTAACTACAATGAGAAGTTCAAGAGTA
AGGCCACACTGACTGTAGACAAATCCTCCAGCACAGCCTACATGCAACTCAACAGCCTGACATCTGA
GGACTCTGCGGTCTATTACTGTGCAAGACGGAATGATTACTACTGGTACTTCGATGTCTGGGGCACA
GGGACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCCCCCAGC
AGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCCGAACCG
GTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTGCTGCAG
AGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCACCCAGAC
CTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCCCAAGA
GCTGTGACAAGACCCACACCTGCCCCCCCTGCCCTGCCCCCGAGCTGCTGGGAGGCCCCAGCGTGTT
CCTGTTCCCCCCCAAGCCTAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGTGTGGTG
GTGGATGTGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGAGGTGCA
CAATGCCAAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCGTGCTGAC
CGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGGCCCTGCC
TGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGTACACCCT
GCCCCCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGGGCTTCTA
CCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGACCACCC
CCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAGCAGAT
GGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACACCCAGA
AGAGCCTGAGCCTGTCCCCTGGCAAG

SAP-K VH chimera amino acid sequence (SEQ ID NO:23)

QVQLQQPGAELIKPGASVKLSCKASGYTFTSYWMHWVKQRPGQGLEWIGMIHPNSVNTNYNEKFKSK
ATLTVDKSSSTAYMQLNSLTSEDSAVYYCARRNDYYWYFDVWGTGTLVTVSSASTKGPSVFPLAPSSKST
SGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHKP
SNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SAP-K VL chimera nucleotide sequence (SEQ ID NO:48)

GACATTGTGATGACCCAGTCTCAAAAATTCATGTCCACATCAGTAGGAGACAGGGTCAGCGTCACCT
GCAAGGCCAGTCAGAATGTGAACTCTAATGTAGCCTGGTATCAACAGAAACCAGGGCAATCTCCTA
AAGCACTGATTTACTCGGCTTCCTACCGGTACAGTGGAGTCCCTGATCGCTTCACAGGCAGTGGATC
TGGGACAGATTTCACTCTCACCATCACCAATGTGCAGTCTGAAGACTTGGCAGAGTATTTCTGTCAG
CAATGTAACAACTATCCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAAACGTACGGTGGCC
GCCCCCAGCGTGTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGGCACCGCCAGCGTGGTG
TGTCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGCAG
AGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGCAG
CACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAGGTGACCCACCA
GGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SAP-K VL chimera amino acid sequence (SEQ ID NO:24)

DIVMTQSQKFMSTSVGDRVSVTCKASQNVNSNVAWYQQKPGQSPKALIYSASYRYSGVPDRFTGSGSG
TDFTLTITNVQSEDLAEYFCQQCNNYPFTFGSGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFY
PREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFN
RGEC

Example 3: Humanisation strategy

Humanised antibodies were generated by a process of grafting CDRH1, CDRH2, CDRH3, CDRL1, CDRL2 and CDRL3 from the murine antibody onto a suitable human framework sequence.

SAP-E Humanisation Strategy

SAP-E Heavy chain humanisation

For the SAP-E mouse variable heavy chain sequence a human germ line acceptor framework was selected (IGHV1-69, SEQ ID NO:25) which had 60% identity (including CDRs) with the mouse SAP-E variable heavy chain sequence (SEQ ID NO:7) together with the JH1 minigene (Kabat: AEYFQHWGQGTLVTVSS (SEQ ID NO:26)). The first six residues of the JH1 minigene residues fall within the CDR3 region and were replaced by the incoming CDR from the donor antibody.

Five humanised variants were generated on the basis of sequence comparison and possible impact on antibody function. Construct H0 was a straight graft of murine CDRs (using the Kabat definition) into the human acceptor framework selected above. Construct H1 has additional back-mutations at residues 27 and 30. Constructs H2 and H3 were based on H1 with additional back-mutations at residues 2 (H2), and 48 and 67 (H3). Construct H4 was based on H3 with additional back-mutations at residues 69, 73 and 91. See Table 3.

The sequences of the humanised variable heavy domains of H0, H1, H2, H3 and H4 are given below (SEQ ID NO:27, SEQ ID NO:28 SEQ ID NO:29, SEQ ID NO:30 and SEQ ID NO:31 respectively).

Table 3: Summary of SAP-E humanised VH variants generated

Construct	Acceptor/template Framework	Back-mutations@ aa# (Kabat)	Total number of back-mutations	Human acceptor framework	Original mouse sequence
H0 (SEQ ID NO:27)	IGHV1-69 (SEQ ID NO:25)	------	NONE	----	------
H1 (SEQ ID NO:28)	H0	27 30	2	G S	F A
H2 (SEQ ID NO:29)	H1	2	3	V	A
H3 (SEQ ID NO:30)	H1	48 67	4	M V	I A
H4 (SEQ ID NO:31)	H3	69 73 91	7	I K Y	L T F

SAP-E Light chain humanisation

For the SAP-E mouse variable light chain sequence a human germ line acceptor framework was selected (IGKV1-39, SEQ ID NO:32) which had 68% identity (including CDRs) with the mouse SAP-E variable light chain sequence (SEQ ID No:9) together with the J-region kappa 2 minigene (Kabat: YTFGQGTKLEIK, SEQ ID NO:33)) based on sequence similarity. The first two residues of the JK-2 minigene residues fall within the CDR3 region and were replaced by the incoming CDR from the donor antibody.

Three humanised variants were generated on the basis of sequence comparison and possible impact on antibody function. Construct L0 was a straight graft of murine CDRs (using the Kabat definition) into the human acceptor framework selected above. Construct L1 has a back-mutation at residue 49 and construct L2 has back mutations at positions 48 and 49. See Table 4.

The sequences of the humanised variable light domains of L0, L1 and L2 are given below (SEQ ID NO:34, SEQ ID NO:35 and SEQ ID NO:36 respectively).

Table 4: Summary of SAP-E humanised VL variants generated

Construct	Acceptor/template Framework	Back-mutations@ aa# (Kabat)	Total number of back-mutations	Human acceptor framework	Original mouse sequence
L0 (SEQ ID NO:34)	IGKV1-39 (SEQ ID NO:32)	------	NONE	----	------
L1 (SEQ ID NO:35)	L0	49	1	Y	H
L2 (SEQ ID NO:36)	L1	48 49	2	I Y	V H

SAP-K Humanisation Strategy

SAP-K Heavy chain humanisation

For the SAP-K mouse variable heavy chain sequence a human germ line acceptor framework was selected (IGHV1-69, SEQ ID NO:25) which had 65% identity (including CDRs) with the mouse SAP-K variable heavy chain sequence (SEQ ID NO:17) together with the JH1 minigene (Kabat: AEYFQHWGQGTLVTVSS (SEQ ID NO:26)). The first six residues of the JH1 minigene

residues fall within the CDR3 region and were replaced by the incoming CDR from the donor antibody.

Four humanised variants were generated on the basis of sequence comparison and possible impact on antibody function. Construct H0 was a straight graft of murine CDRs (using the Kabat definition) into the human acceptor framework selected above. Construct H1 has additional back-mutations at residues 27 and 30. Construct H2 was based on H1 with additional back-mutations at residues 48 and 67. Construct H3 was based on H2 with additional back-mutations at residues 69 and 71. See Table 5.

The sequences of the humanised variable heavy domains of H0, H1, H2 and H3 are given below (SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39 and SEQ ID NO:40 respectively).

Table 5: Summary of SAP-K humanised VH variants generated

Construct	Acceptor/template Framework	Back-mutations@ aa# (Kabat)	Total number of back-mutations	Human acceptor framework	Original mouse sequence
H0 (SEQ ID NO:37)	IGHV1-69 (SEQ ID NO: 25)	------	NONE	----	------
H1 (SEQ ID NO:38)	H0	27 30	2	G S	Y T
H2 (SEQ ID NO:39)	H1	48 67	4	M V	I A
H3 (SEQ ID NO:40)	H2	69 71	6	I A	L V

SAP-K Light chain humanisation

For the SAP-K mouse variable light chain sequence a human germ line acceptor framework was selected (IGKV1-39, SEQ ID NO:32) which had 63% identity (including CDRs) with the mouse SAP-K variable light chain sequence (SEQ ID NO:19) together with the J-region kappa 2 minigene (Kabat: YTFGQGTKLEIK, SEQ ID NO:33) based on sequence similarity. The first two residues of the JK-2 minigene residues fall within the CDR3 region and were replaced by the incoming CDR from the donor antibody.

Two humanised variants were generated on the basis of sequence comparison and possible impact on antibody function. Construct L0 was a straight graft of murine CDRs (using the Kabat definition) into the human acceptor framework selected above. Construct L1 has a back-mutation at residue 46.

The sequences of the humanised variable light domains of L0 and L1 are given below (SEQ ID NO:41 and SEQ ID NO:42 respectively).

Table 6: Summary of SAP-K humanised VL variants generated

Construct	Acceptor/template Framework	Back-mutations@ aa# (Kabat)	Total number of back-mutations	Human acceptor framework	Original mouse sequence
L0 (SEQ ID NO:41)	IGKV1-39 (SEQ ID NO:32)	------	NONE	----	------
L1 (SEQ ID NO:42)	L0	46	1	L	A

Construction of humanised antibody vectors

The humanised variable region DNA sequences were sequence optimised. DNA fragments encoding the humanised variable heavy and variable light regions were constructed de novo using a PCR-based strategy and overlapping oligonucleotides. The PCR product was cloned

into mammalian expression vectors containing the human gamma 1 constant region and the human kappa constant region respectively. This is the wild-type Fc region.

IGHV1-69 human variable heavy chain germline acceptor nucleotide sequence (SEQ ID NO:49)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTG
CAAGGCTTCTGGAGGCACCTTCAGCAGCTATGCTATCAGCTGGGTGCGACAGGCCCCTGGACAAGG
GCTTGAGTGGATGGGAGGGATCATCCCTATCTTTGGTACAGCAAACTACGCACAGAAGTTCCAGGG
CAGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATC
TGAGGACACGGCCGTGTATTACTGTGCGAGA

IGHV1-69 human variable heavy chain germline acceptor amino acid sequence (SEQ ID NO:25)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYAISWVRQAPGQGLEWMGGIIPIFGTANYAQKFQGRV
TITADKSTSTAYMELSSLRSEDTAVYYCAR

IGKV1-39 human variable heavy chain germline acceptor nucleotide sequence (SEQ ID NO:50)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTG
CCGGGCAAGTCAGAGCATTAGCAGCTATTTAAATTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATGCTGCATCCAGTTTGCAAAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACA
GAGTTACAGTACCCCT

IGKV1-39 human variable heavy chain germline acceptor amino acid sequence (SEQ ID NO:32)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSGSGSGTDF
TLTISSLQPEDFATYYCQQSYSTP

JH1 minigene (SEQ ID NO:26)

AEYFQHWGQGTLVTVSS

Jκ2 minigene (SEQ ID NO:33)

YTFGQGTKLEIK

SAP-E humanised heavy chain V region variant H0 nucleotide sequence non-codon optimised (SEQ ID NO:51)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTG
CAAGGCTTCTGGAGGCACCTTCAGCACTTACAATATGCACTGGGTGCGACAGGCCCCTGGACAAGG
GCTTGAGTGGATGGGATATATTTATCCTGGAGATGGTAATGCTAACTACAATCAGCAGTTCAAGGGC
AGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT
GAGGACACGGCCGTGTATTACTGTGCGAGAGGGGACTTTGATTACGACGGAGGGTACTACTTTGAC
TCCTGGGGCCAGGGCACCCTGGTCACCGTCTCCTCA

SAP-E humanised light chain V region variant L0 nucleotide sequence non-codon optimised (SEQ ID NO:52)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTG
CCGAGCAAGTGAGAATATTTACAGTTATTTAGCATGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATAATGCAAAAACCTTAGCAGAAGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAACA
TCATTATGGTGCTCCGCTCACGTTTGGCCAGGGGACCAAGCTGGAGATCAAA

SAP-E humanised heavy chain V region variant H0 nucleotide sequence (codon optimised) (SEQ ID NO:53)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGGGCACCTTCTCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATGGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTC
GACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGC

SAP-E humanised heavy chain V region variant H0 amino acid sequence (SEQ ID NO:27)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSTYNMHWVRQAPGQGLEWMGYIYPGDGNANYNQQFK
GRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSS

SAP-E humanised heavy chain V region variant H1 nucleotide sequence (codon optimised) (SEQ ID NO:54)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGTTCACCTTCGCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATGGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTC
GACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGC

SAP-E humanised heavy chain V region variant H1 amino acid sequence (SEQ ID NO:28)

QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWMGYIYPGDGNANYNQQFK
GRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSS

SAP-E humanised heavy chain V region variant H2 nucleotide sequence (codon optimised) (SEQ ID NO:55)

CAGGCGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGTTCACCTTCGCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATGGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTC
GACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGC

SAP-E humanised heavy chain V region variant H2 amino acid sequence SEQ ID NO:29

QAQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWMGYIYPGDGNANYNQQFK
GRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSS

SAP-E humanised heavy chain V region variant H3 nucleotide sequence (codon optimised) (SEQ ID NO:56)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGTTCACCTTCGCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATCGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGCCACCATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGGA
GCGAGGATACCGCCGTGTACTACTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTCG
ACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGC

SAP-E humanised heavy chain V region variant H3 amino acid sequence (SEQ ID NO:30)

QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWIGYIYPGDGNANYNQQFKG
RATITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSS

SAP-E humanised heavy chain V region variant H4 nucleotide sequence (codon optimised) (SEQ ID NO:57)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGTTCACCTTCGCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATCGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGCCACCCTGACCGCCGACACCAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGGA
GCGAGGATACCGCCGTGTACTTCTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTCG
ACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGC

SAP-E humanised heavy chain V region variant H4 amino acid sequence (SEQ ID NO:31)

QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWIGYIYPGDGNANYNQQFKG
RATLTADTSTSTAYMELSSLRSEDTAVYFCARGDFDYDGGYYFDSWGQGTLVTVSS

SAP-E humanised light chain V region variant L0 nucleotide sequence (codon optimised) (SEQ ID NO:58)

GACATCCAGATGACCCAGAGCCCCAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACC
TGCAGGGCCTCCGAGAACATCTACAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC
AAGCTGCTGATCTACAACGCCAAGACCCTCGCCGAGGGCGTCCCTAGCAGGTTCTCTGGAAGCGGC

AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTATTACTGCC
AGCACCACTACGGCGCCCCCCTGACCTTTGGCCAGGGCACCAAACTGGAGATCAAG

SAP-E humanised light chain V region variant L0 amino acid sequence SEQ ID NO:34

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIYNAKTLAEGVPSRFSGSGSGTDF
TLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIK

SAP-E humanised light chain V region variant L1 nucleotide sequence (codon optimised) (SEQ ID NO:59)

GACATCCAGATGACCCAGAGCCCCAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACC
TGCAGGGCCTCCGAGAACATCTACAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC
AAGCTGCTGATCCACAACGCCAAGACCCTCGCCGAGGGCGTCCCTAGCAGGTTCTCTGGAAGCGGC
AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTATTACTGCC
AGCACCACTACGGCGCCCCCCTGACCTTTGGCCAGGGCACCAAACTGGAGATCAAG

SAP-E humanised light chain V region variant L1 amino acid sequence (SEQ ID NO:35)

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIHNAKTLAEGVPSRFSGSGSGTDF
TLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIK

SAP-E humanised light chain V region variant L2 nucleotide sequence (codon optimised) (SEQ ID NO:60)

GACATCCAGATGACCCAGAGCCCCAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACC
TGCAGGGCCTCCGAGAACATCTACAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC
AAGCTGCTGGTGCACAACGCCAAGACCCTCGCCGAGGGCGTCCCTAGCAGGTTCTCTGGAAGCGGC
AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTATTACTGCC
AGCACCACTACGGCGCCCCCCTGACCTTTGGCCAGGGCACCAAACTGGAGATCAAG

SAP-E humanised light chain V region variant L2 amino acid sequence (SEQ ID NO:36)

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLVHNAKTLAEGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIK

SAP-E humanised heavy chain H1 full mature nucleotide sequence (codon optimised) (SEQ ID NO:61)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAGGTGAAGAAACCCGGCAGCAGCGTGAAGGTGAGCT
GCAAGGCTAGCGGGTTCACCTTCGCCACCTACAACATGCACTGGGTCAGGCAGGCACCCGGCCAGG
GCCTGGAGTGGATGGGCTATATCTACCCCGGCGACGGCAACGCCAACTACAACCAGCAGTTCAAGG
GCAGGGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTACATGGAACTGAGCAGCCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGGGCGACTTCGACTACGACGGCGGCTACTACTTC
GACAGCTGGGGACAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTT
CCCCCTGGCCCCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGG
ACTACTTCCCCGAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTT
CCCCGCCGTGCTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAG
CCTGGGCACCCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAA
GGTGGAGCCCAAGAGCTGTGACAAGACCCACACCTGCCCCCCCTGCCCTGCCCCCGAGCTGCTGGG
AGGCCCCAGCGTGTTCCTGTTCCCCCCCAAGCCTAAGGACACCCTGATGATCAGCAGAACCCCCGAG
GTGACCTGTGTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGA
CGGCGTGGAGGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCGGG
TGGTGTCCGTGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGT
CCAACAAGGCCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGC
CCCAGGTGTACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCT
GGTGAAGGGCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACA
ACTACAAGACCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGT
GGACAAGAGCAGATGGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACA
ATCACTACACCCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SAP-E humanised heavy chain H1 full mature amino acid sequence (SEQ ID NO:62)

QVQLVQSGAEVKKPGSSVKVSCKASGFTFATYNMHWVRQAPGQGLEWMGYIYPGDGNANYNQQFK
GRVTITADKSTSTAYMELSSLRSEDTAVYYCARGDFDYDGGYYFDSWGQGTLVTVSSASTKGPSVFPLAP
SSKSTSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICN
VNHKPSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPE
VKFNWYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKG

QPREPQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTV
DKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SAP-E humanised light chain L1 full mature nucleotide sequence (codon optimised) (SEQ ID NO:63)

GACATCCAGATGACCCAGAGCCCCAGCTCACTGAGCGCCAGCGTGGGCGACAGGGTGACCATTACC
TGCAGGGCCTCCGAGAACATCTACAGCTACCTGGCCTGGTACCAGCAGAAGCCCGGCAAGGCCCCC
AAGCTGCTGATCCACAACGCCAAGACCCTCGCCGAGGGCGTCCCTAGCAGGTTCTCTGGAAGCGGC
AGCGGCACCGACTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACCTATTACTGCC
AGCACCACTACGGCGCCCCCCTGACCTTTGGCCAGGGCACCAAACTGGAGATCAAGCGTACGGTGG
CCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGGCACCGCCAGCGTGG
TGTGTCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTGC
AGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAGC
AGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAGGTGACCCAC
CAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SAP-E humanised light chain L1 full mature amino acid sequence (SEQ ID NO:64)

DIQMTQSPSSLSASVGDRVTITCRASENIYSYLAWYQQKPGKAPKLLIHNAKTLAEGVPSRFSGSGSGTDF
TLTISSLQPEDFATYYCQHHYGAPLTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREA
KVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

SAP-K humanised heavy chain V region variant H0 nucleotide sequence non-codon optimised (SEQ ID NO:65)

CAGGTGCAGCTGGTGCAGTCTGGGGCTGAGGTGAAGAAGCCTGGGTCCTCGGTGAAGGTCTCCTG
CAAGGCTTCTGGAGGCACCTTCAGCAGCTACTGGATGCACTGGGTGCGACAGGCCCCTGGACAAGG
GCTTGAGTGGATGGGAATGATTCATCCTAATAGTGTTAATACTAACTACAATGAGAAGTTCAAGAGT
AGAGTCACGATTACCGCGGACAAATCCACGAGCACAGCCTACATGGAGCTGAGCAGCCTGAGATCT
GAGGACACGGCCGTGTATTACTGTGCGAGACGGAATGATTACTACTGGTACTTCGATGTCTGGGGC
CAGGGCACCCTGGTCACCGTCTCCTCA

SAP-K humanised light chain V region variant L0 nucleotide sequence non-codon optimised (SEQ ID NO:66)

GACATCCAGATGACCCAGTCTCCATCCTCCCTGTCTGCATCTGTAGGAGACAGAGTCACCATCACTTG
CAAGGCCAGTCAGAATGTGAACTCTAATGTAGCCTGGTATCAGCAGAAACCAGGGAAAGCCCCTAA
GCTCCTGATCTATTCGGCTTCCTACCGGTACAGTGGGGTCCCATCAAGGTTCAGTGGCAGTGGATCT
GGGACAGATTTCACTCTCACCATCAGCAGTCTGCAACCTGAAGATTTTGCAACTTACTACTGTCAGCA
ATGTAACAACTATCCATTCACGTTTGGCCAGGGGACCAAGCTGGAGATCAAA

SAP-K humanised heavy chain V region variant H0 nucleotide sequence (codon optimised) (SEQ IS NO:67)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCAGCGTGAAAGTGAGCT
GCAAGGCCAGCGGCGGAACCTTCAGCAGCTACTGGATGCACTGGGTGAGGCAGGCACCCGGCCAG
GGCCTGGAGTGGATGGGCATGATCCACCCCAACAGCGTGAACACCAACTACAACGAGAAGTTCAAG
AGCAGAGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTATATGGAGCTGAGCTCTCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGAGGAACGACTACTACTGGTACTTCGACGTCTGG
GGCCAGGGCACACTAGTGACCGTGTCCAGC

SAP-K humanised heavy chain V region variant H0 amino acid sequence (SEQ ID NO:37)

QVQLVQSGAEVKKPGSSVKVSCKASGGTFSSYWMHWVRQAPGQGLEWMGMIHPNSVNTNYNEKFK
SRVTITADKSTSTAYMELSSLRSEDTAVYYCARRNDYYWYFDVWGQGTLVTVSS

SAP-K humanised heavy chain V region variant H1 nucleotide sequence (codon optimised) (SEQ ID NO:68)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCAGCGTGAAAGTGAGCT
GCAAGGCCAGCGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAGGCAGGCACCCGGCCAG
GGCCTGGAGTGGATGGGCATGATCCACCCCAACAGCGTGAACACCAACTACAACGAGAAGTTCAAG
AGCAGAGTGACCATCACCGCCGACAAGAGCACCAGCACCGCCTATATGGAGCTGAGCTCTCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGAGGAACGACTACTACTGGTACTTCGACGTCTGG
GGCCAGGGCACACTAGTGACCGTGTCCAGC

SAP-K humanised heavy chain V region variant H1 amino acid sequence (SEQ ID NO:38)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWMGMIHPNSVNTNYNEKFK
SRVTITADKSTSTAYMELSSLRSEDTAVYYCARRNDYYWYFDVWGQGTLVTVSS

SAP-K humanised heavy chain V region variant H2 nucleotide sequence (codon optimised) (SEQ ID NO:69)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCAGCGTGAAAGTGAGCT
GCAAGGCCAGCGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAGGCAGGCACCCGGCCAG
GGCCTGGAGTGGATCGGCATGATCCACCCCAACAGCGTGAACACCAACTACAACGAGAAGTTCAAG
AGCAGAGCCACCATCACCGCCGACAAGAGCACCAGCACCGCCTATATGGAGCTGAGCTCTCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGAGGAACGACTACTACTGGTACTTCGACGTCTGG
GGCCAGGGCACACTAGTGACCGTGTCCAGC

SAP-K humanised heavy chain V region variant H2 amino acid sequence (SEQ ID NO:39)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWIGMIHPNSVNTNYNEKFKS
RATITADKSTSTAYMELSSLRSEDTAVYYCARRNDYYWYFDVWGQGTLVTVSS

SAP-K humanised heavy chain V region variant H3 nucleotide sequence (codon optimised) (SEQ ID NO:70)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCAGCGTGAAAGTGAGCT
GCAAGGCCAGCGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAGGCAGGCACCCGGCCAG
GGCCTGGAGTGGATCGGCATGATCCACCCCAACAGCGTGAACACCAACTACAACGAGAAGTTCAAG
AGCAGAGCCACCCTGACCGTGGACAAGAGCACCAGCACCGCCTATATGGAGCTGAGCTCTCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGAGGAACGACTACTACTGGTACTTCGACGTCTGG
GGCCAGGGCACACTAGTGACCGTGTCCAGC

SAP-K humanised heavy chain V region variant H3 amino acid sequence (SEQ ID NO:40)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWIGMIHPNSVNTNYNEKFKS
RATLTVDKSTSTAYMELSSLRSEDTAVYYCARRNDYYWYFDVWGQGTLVTVSS

SAP-K humanised light chain V region variant L0 nucleotide sequence (codon optimised) SEQ ID NO:71)

GACATCCAGATGACCCAGAGCCCCTCTTCACTGAGCGCTAGCGTGGGCGACAGGGTGACCATCACC
TGCAAGGCCAGCCAGAACGTGAACAGCAACGTGGCCTGGTACCAGCAGAAGCCCGGCAAAGCCCC
CAAGCTCCTGATCTACAGCGCCAGCTACAGATATAGCGGCGTGCCTAGCAGGTTTAGCGGCAGCGG
AAGCGGGACCGATTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACTTACTACTGC
CAGCAGTGCAACAACTACCCCTTCACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

SAP-K humanised light chain V region variant L0 amino acid sequence (SEQ ID NO:41)

DIQMTQSPSSLSASVGDRVTITCKASQNVNSNVAWYQQKPGKAPKLLIYSASYRYSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQCNNYPFTFGQGTKLEIK

SAP-K humanised light chain V region variant L1 nucleotide sequence (codon optimised) (SEQ ID NO:72)

GACATCCAGATGACCCAGAGCCCCTCTTCACTGAGCGCTAGCGTGGGCGACAGGGTGACCATCACC
TGCAAGGCCAGCCAGAACGTGAACAGCAACGTGGCCTGGTACCAGCAGAAGCCCGGCAAAGCCCC
CAAGGCCCTGATCTACAGCGCCAGCTACAGATATAGCGGCGTGCCTAGCAGGTTTAGCGGCAGCGG
AAGCGGGACCGATTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACTTACTACTGC
CAGCAGTGCAACAACTACCCCTTCACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

SAP-K humanised light chain V region variant L1 amino acid sequence (SEQ ID NO:42)

DIQMTQSPSSLSASVGDRVTITCKASQNVNSNVAWYQQKPGKAPKALIYSASYRYSGVPSRFSGSGSGT
DFTLTISSLQPEDFATYYCQQCNNYPFTFGQGTKLEIK

SAP-K humanised H3 heavy chain nucleotide sequence (codon optimised) (SEQ ID NO:75)

CAGGTGCAGCTGGTGCAGAGCGGCGCCGAAGTGAAGAAGCCCGGCAGCAGCGTGAAAGTGAGCT
GCAAGGCCAGCGGCTACACCTTCACCAGCTACTGGATGCACTGGGTGAGGCAGGCACCCGGCCAG
GGCCTGGAGTGGATCGGCATGATCCACCCCAACAGCGTGAACACCAACTACAACGAGAAGTTCAAG
AGCAGAGCCACCCTGACCGTGGACAAGAGCACCAGCACCGCCTATATGGAGCTGAGCTCTCTGAGG
AGCGAGGATACCGCCGTGTACTACTGCGCCAGGAGGAACGACTACTACTGGTACTTCGACGTCTGG
GGCCAGGGCACACTAGTGACCGTGTCCAGCGCCAGCACCAAGGGCCCCAGCGTGTTCCCCCTGGCC

CCCAGCAGCAAGAGCACCAGCGGCGGCACAGCCGCCCTGGGCTGCCTGGTGAAGGACTACTTCCCC
GAACCGGTGACCGTGTCCTGGAACAGCGGAGCCCTGACCAGCGGCGTGCACACCTTCCCCGCCGTG
CTGCAGAGCAGCGGCCTGTACAGCCTGAGCAGCGTGGTGACCGTGCCCAGCAGCAGCCTGGGCAC
CCAGACCTACATCTGTAACGTGAACCACAAGCCCAGCAACACCAAGGTGGACAAGAAGGTGGAGCC
CAAGAGCTGTGACAAGACCCACACCTGCCCCCCCTGCCCTGCCCCCGAGCTGCTGGGAGGCCCCAG
CGTGTTCCTGTTCCCCCCCAAGCCTAAGGACACCCTGATGATCAGCAGAACCCCCGAGGTGACCTGT
GTGGTGGTGGATGTGAGCCACGAGGACCCTGAGGTGAAGTTCAACTGGTACGTGGACGGCGTGGA
GGTGCACAATGCCAAGACCAAGCCCAGGGAGGAGCAGTACAACAGCACCTACCGGGTGGTGTCCG
TGCTGACCGTGCTGCACCAGGATTGGCTGAACGGCAAGGAGTACAAGTGTAAGGTGTCCAACAAGG
CCCTGCCTGCCCCTATCGAGAAAACCATCAGCAAGGCCAAGGGCCAGCCCAGAGAGCCCCAGGTGT
ACACCCTGCCCCCTAGCAGAGATGAGCTGACCAAGAACCAGGTGTCCCTGACCTGCCTGGTGAAGG
GCTTCTACCCCAGCGACATCGCCGTGGAGTGGGAGAGCAACGGCCAGCCCGAGAACAACTACAAGA
CCACCCCCCCTGTGCTGGACAGCGATGGCAGCTTCTTCCTGTACAGCAAGCTGACCGTGGACAAGAG
CAGATGGCAGCAGGGCAACGTGTTCAGCTGCTCCGTGATGCACGAGGCCCTGCACAATCACTACAC
CCAGAAGAGCCTGAGCCTGTCCCCTGGCAAG

SAP-K humanised H3 heavy chain amino acid sequence (SEQ ID NO:76)

QVQLVQSGAEVKKPGSSVKVSCKASGYTFTSYWMHWVRQAPGQGLEWIGMIHPNSVNTNYNEKFKS
RATLTVDKSTSTAYMELSSLRSEDTAVYYCARRNDYYWYFDVWGQGTLVTVSSASTKGPSVFPLAPSSKS
TSGGTAALGCLVKDYFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTYICNVNHK
PSNTKVDKKVEPKSCDKTHTCPPCPAPELLGGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVKFN
WYVDGVEVHNAKTKPREEQYNSTYRVVSVLTVLHQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPRE
PQVYTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPVLDSDGSFFLYSKLTVDKSR
WQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

SAP-K humanised L0 light chain nucleotide sequence (codon optimised) (SEQ ID NO:77)

GACATCCAGATGACCCAGAGCCCCTCTTCACTGAGCGCTAGCGTGGGCGACAGGGTGACCATCACC
TGCAAGGCCAGCCAGAACGTGAACAGCAACGTGGCCTGGTACCAGCAGAAGCCCGGCAAAGCCCC
CAAGCTCCTGATCTACAGCGCCAGCTACAGATATAGCGGCGTGCCTAGCAGGTTTAGCGGCAGCGG
AAGCGGGACCGATTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACTTACTACTGC
CAGCAGTGCAACAACTACCCCTTCACCTTCGGCCAGGGCACCAAGCTGGAGATCAAGCGTACGGTG
GCCGCCCCCAGCGTGTTCATCTTCCCCCCCAGCGATGAGCAGCTGAAGAGCGGCACCGCCAGCGTG

GTGTGTCTGCTGAACAACTTCTACCCCCGGGAGGCCAAGGTGCAGTGGAAGGTGGACAATGCCCTG
CAGAGCGGCAACAGCCAGGAGAGCGTGACCGAGCAGGACAGCAAGGACTCCACCTACAGCCTGAG
CAGCACCCTGACCCTGAGCAAGGCCGACTACGAGAAGCACAAGGTGTACGCCTGTGAGGTGACCCA
CCAGGGCCTGTCCAGCCCCGTGACCAAGAGCTTCAACCGGGGCGAGTGC

SAP-K humanised L0 light chain amino acid sequence (SEQ ID NO:78)

DIQMTQSPSSLSASVGDRVTITCKASQNVNSNVAWYQQKPGKAPKLLIYSASYRYSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQCNNYPFTFGQGTKLEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPRE
AKVQWKVDNALQSGNSQESVTEQDSKDSTYSLSSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

Leader sequence for immunoglobulin chains (SEQ ID: 79)

MGWSCIILFLVATATGVHS

Example 4: - Antibody expression

Recombinant antibody expression

Expression plasmids encoding the heavy and light chains respectively of chimeric or humanised antibodies were transiently co-transfected into HEK2936E cells by lipid transfection using Fectin 293. Cells were grown in Freestyle expression media 293 with 10% pluronic F68 and 50mg/ml geneticin, 37 degrees C, 5% CO2 for 72 – 120 hrs, supernatant was harvested by centrifugation. In some instances the supernatant material was used as the test article in binding assays. In other instances, the supernatant material was filter sterilised and the antibody recovered by affinity chromatography using Protein A MAbSelect SuRE column followed by dialysis into PBS.

Hybridoma antibody expression

The hybridoma cells were grown in shake flasks in Ex620 medium supplemented with 4mM glutamax and 10% low IgG FCS. The cells were passaged and weaned off serum until growing well in serum free medium. The cells were then used as a seed for a 10L wavebag. The cells were grown in the wavebag at 22 rocks/min, 37 degrees C, 5% CO2 @ 0.1L/min

until viability dropped to 30%. The conditioned medium was collected by sterile filtration. Antibody was recovered by affinity chromatography using recombinant Protein A followed by dialysis into PBS.

Examples 5-7: Comparative data between hybridomas and/or chimeric mAbs and/or humanised Mabs

Example 5: Comparison of SAP-K and SAP-E hybridomas in human SAP binding ELISA

1 µg/mL or 5 µg/mL human SAP was directly immobilised onto an ELISA plate and blocked with 1%BSA/TBS plus 0.05% TWEEN20. Anti-SAP antibodies from purified material were titrated across the plate. Bound antibody was detected by treatment with a horse-radish peroxidase (HRP) -conjugated rabbit-anti-mouse IgG antibody (Dako, P0260). The ELISA was developed using O-phenylenediamine dihydrochloride (OPD) peroxidase substrate (Sigma, P9187).

Figure 1 shows the binding curves for murine antibodies SAP-E and SAP-K at a 1 µg/mL coating concentration of human SAP.

Figure 2 shows the binding curves for murine antibodies SAP-E and SAP-K at a 5 µg/mL coating concentration of human SAP.

At the 5 µg/mL coating concentration, SAP-K and SAP-E showed similar binding to the immobilised human SAP, whereas at the 1 µg/mL lower density coating SAP-K showed greater binding than the SAP-E. All subsequent human SAP binding ELISAs using this format used the lower density 1 µg/mL coating concentration to distinguish between the binding properties of the two antibodies.

Example 6: Comparison of SAP-K and SAP-E chimeric/humanised mAbs in human SAP binding ELISA

1µg/mL human SAP was directly immobilised onto an ELISA plate and blocked with 1%BSA/TBS plus 0.05% TWEEN20. Anti-SAP antibodies from the test supernatants or

purified material were titrated across the plate. Bound antibody was detected by treatment with goat anti-human Kappa Light Chains peroxidase conjugate (Sigma, A7164). The ELISA was developed using O-phenylenediamine dihydrochloride (OPD) peroxidase substrate (Sigma, P9187).

Figure 3 shows the binding curves for chimeric antibodies cSAP-E and cSAP-K. The profile of the curves for the chimeric antibodies is the same as that of the equivalent hybridomas.

Figure 4 shows the binding curves for SAP-K H0L0, SAP-K H1L0, SAP-K H2L0 and SAP-K H3L0 compared to the SAP-K chimera and the SAP-E H1L1 compared to the SAP-E chimera. An irrelevant human IgG1 kappa antibody was also tested as a negative control. The data shows that humanisation of the SAP-K antibody resulted in a loss of human SAP binding activity of approximately 2-fold compared to the parental SAP-K chimera, whilst the humanised SAP-E antibody retained binding activity compared to the parental SAP-E chimera.

Example 7 - Competition ELISA

ELISA plates were coated with human SAP at either 1µg/mL (for competition with SAP-K chimera) or 5µg/mL (for competition with SAP-E chimera) and blocked with 1% BSA/PBS. A constant concentration of chimeric anti-SAP mAb was mixed with serial diluted (1:1) amounts of mouse anti-SAP mAbs. Plates were washed and the amount of chimeric antibody bound to the immobilised human SAP was detected using goat anti-human Kappa Light chain peroxidase conjugate (Sigma, A7164). The ELISA was developed using O-phenylenediamine dihydrochloride (OPD) peroxidase substrate (Sigma, P9187).

Figure 5 shows purified SAP-K and SAP-E murine monoclonal antibodies in the competition ELISA with the SAP-E chimera.

Figure 6 shows purified SAP-K and SAP-E murine monoclonal antibodies in the competition ELISA with the SAP-K chimera.

In both figures 5 and 6 no competition is observed between the SAP-E and SAP-K antibodies showing that the two antibodies bind to distinct epitopes on the human SAP molecule.

Example 8: Determination of kinetics of binding

Biacore analysis of binding of humanised anti-SAP antibody variants to purified human and purified cynomologus monkey SAP.

Human and cynomologus monkey SAP were immobilised on a Biacore C1 chip by primary amine coupling in accordance with the manufacturer's instructions. Humanised anti-SAP antibody contained in culture supernatants and purified chimeric antibodies at 512nM were passed over both human and cynomologus monkey SAP surfaces and binding sensograms obtained. All runs were double referenced with a buffer injection for purified sample or media for the supernatant samples over the human and cyno SAP surfaces. Analysis was carried out at 25°C using HBS-EP buffer. Regeneration of surface was done in the presence of 3M MgCl2 and did not affect the ability of antibodies to rebind to human SAP in a subsequent cycle. Data were analysed using the 1 to 1 dissociation model within the Biacore T100 evaluation software.

The data generated in Tables 6a and 6b show off-rates (kd) of the humanised SAP-E and SAP-K antibody supernatants respectively. The values were based on a single curve and used for ranking purposes between the different constructs for binding to human SAP. Humanised SAP-E antibodies showed better off-rates than the humanised SAP-K antibodies for binding human SAP. A number of the SAP-K humanised antibody variants showed binding to cynomologus monkey SAP (N.B. the SAP-K chimera bound cynomologus monkey SAP) whilst none of the humanised SAP-E antibody variants bound cynomologus monkey SAP (N.B. the SAP-E chimera likewise did not bind cynomologous monkey SAP). Humanised SAP-E variants which contained either the straight graft humanised heavy chain (H0) or the straight graft humanised light chain (L0) or a combination of both showed the poorest off-rates. The SAP-E humanised L1 light chain was the best light chain variant and combination of the L1 with the H1 heavy chain variant gave a humanised antibody with an acceptable off-rate whilst keeping the number of back mutations to a minimum. Off-rate ranking of the humanised SAP-K variants showed the L0 straight graft to be the best humanised light chain variant and the H0 straight graft to be the poorest humanised heavy chain variant.

Table 6a

SAP-E Variant	Kd for human SAP (s^{-1})
SAP-E chimera	3.83E-03
SAP-E H1L1	4.80E-03
SAP-E H4L1	5.43E-03
SAP-E H1L2	5.51E-03
SAP-E H3L1	5.76E-03
SAP-E H4L2	5.80E-03
SAP-E H2L1	6.09E-03
SAP-E H3L2	6.31E-03
SAP-E H2L2	6.52E-03
SAP-E H1L0	8.09E-03
SAP-E H3L0	9.10E-03
SAP-E H2L0	9.79E-03
SAP-E H4L0	9.81E-03
SAP-E H0L1	4.02E-02
SAP-E H0L2	4.29E-02
SAP-E H0L0	5.35E-02

Table 6b

N.B. Kd is for human SAP

	kd (s^{-1})	Binding to cyno SAP
SAP-K chimera	6.64E-03	Yes
SAP-K H1L0	1.71E-02	poor
SAP-K H3L0	1.84E-02	Yes
SAP-K H2L0	2.04E-02	Yes
SAP-K H3L1	2.36E-02	yes
SAP-K H0L0	2.63E-02	no
SAP-K H1L1	2.96E-02	poor
SAP-K H2L1	3.21E-02	poor
SAP-K H0L1	4.79E-02	no

Biacore analysis of binding of anti-SAP antibodies to purified human SAP directly immobilised on a solid phase support

Human SAP was immobilised on a Biacore CM3 chip by primary amine coupling in accordance with the manufacturer's instructions. Anti SAP antibodies were passed over this surface at 512, 128, 32, 8, 2, 0.5nM and binding sensorgrams obtained. All runs were double referenced with a buffer injection over the human SAP surface. Analysis was carried out at 25°C using HBS-EP buffer. Regeneration of surface was done by allowing buffer to flow over the surface for several minutes and did not affect the ability of human SAP to rebind antibodies in a subsequent cycle. Data were analysed from the 128 – 0.5nM runs using the bivalent analyte model inherent to the Biacore T100 evaluation software.

The data generated and compiled in table 7 were meant for comparison between the constructs and show that SAP-K antibodies have a better association rate in this assay while

SAP-E antibodies show better dissociation rates. Furthermore, humanization had not altered the binding kinetics of SAP-E antibody whilst for SAP-K a loss in association and dissociation rate was observed following humanisation.

Table 7

	Ka ($M^{-1}.s^{-1}$)	Kd (s^{-1})	KD (nM)
SAP-K chimera	4.06E+5	7.59E-03	18.7
SAP-K H0L0	6.08E+4	4.49E-02	739
SAP-K H1L0	1.15E+5	1.78E-02	155
SAP-K H2L0	1.15E+5	2.20E-02	191
SAP-K H3L0	1.50E+5	1.92E-02	128
SAP-E chimera	2.64E+4	2.18E-03	82.6
SAP-E H1L1	2.64E+4	2.07E-03	78.3

Biacore analysis of binding of anti-SAP antibodies to purified human SAP captured on immobilised O-phosphoethanolamine

O-phosphoethanolamine was immobilised on a Biacore CM5 chip by primary amine coupling in accordance with the manufacturer's instructions. Human SAP was then captured on the surface in the presence of calcium chloride, in order to replicate in the Biacore system *in vitro*, the precise orientation of SAP molecules bound to amyloid fibrils *in vivo*. Anti SAP antibodies were then passed over this surface at 256, 64, 16, 4, 1nM and a binding sensorgrams obtained. Analysis was carried out at 25°C using 4% BSA, 10mM Tris, 140mM NaCl, 2mM $CaCl_2$, 0.05% surfactant P20, 0.02% NaN_3, pH 8.0 as running buffer. Regeneration was achieved using two pulses of Tris-EDTA (10mM Tris, 140mM NaCl, 10mM EDTA, pH 8.0) which removed the bound human SAP but did not significantly affect subsequent binding of SAP to the immobilised phosphoethanolamine. Data generated were double referenced

with a buffer injection over the human SAP surface and analyzed using the bivalent analyte model in the Biacore T100 evaluation software.

The data generated, as shown in Table 8, are intended only for comparison between the constructs. They do not constitute accurate kinetic values, due to possible modification of binding by the avidity effect inherent in the assay format. Avidity is more likely to have affected antibody dissociation rates, leading to lower calculated KD values. Furthermore, for all the SAP-E antibodies, the dissociation rate (kd) obtained is outside the limit of the Biacore measurement range. Nevertheless, the results indicate tight binding of the anti-SAP antibodies to human SAP immobilised by interaction of the SAP with a solid phase ligand, just as it is in amyloid deposits *in vivo*, which is the therapeutic target of the present invention.

Table 8

	ka ($M^{-1}.s^{-1}$)	kd (s^{-1})	KD (nM)
SAP-K chimera	3.32E+5	2.97E-4	0.895
SAP-E chimera	2.03E+4	9.12E-7	4.49E-11
Mouse SAP-K	3.00E+5	2.19E-4	0.730
Mouse SAP-E	3.15E+4	1.51E-8	4.79E-13
SAP-K H3L0	1.36E+5	5.01E-3	36.8
SAP-E H1L1	1.94E+4	1.58E-7	8.14E-12

Example 9: Amino acid scan at position 91 of SAP-K L0 humanised light chain

Site-directed saturation mutagenesis was used to generate a panel of variants where the cysteine residue at position 91 (Kabat numbering) was potentially substituted with all other

19 amino acids in a single reaction by using a mutagenesis primer encoding NNK at this position (where N codes for adenosine or cytidine or guanosine or thymidine and K codes for guanisine or thymidine). From Biacore off-rate ranking carried out on antibody supernatant for the variants generated, four were selected for scale up in the HEK2936E cells and purification. Biacore kinetic analysis using the O-phosphoethanolamine method as detailed in Example 7 showed that the variant with alanine at position 91 (SEQ ID NO:43) had an improved affinity compared to the wild-type; KD values of 0.436 nM and 36.8 nM were measured respectively. N.B. all variants were tested in the same experiment used to produce the results shown in table 7.

Other variants, for example glycine, serine and valine improved binding with respect to H3L0, but to a lesser extent than alanine. In addition, the fact that these four variants had better binding properties than L0 was also observed in a binding ELISA and a Biacore off-rate ranking experiment when the light chains were paired with H1.

SAP-K humanised light chain V region variant L0 91A nucleotide sequence (codon optimised) (SEQ ID NO:73)

GACATCCAGATGACCCAGAGCCCCTCTTCACTGAGCGCTAGCGTGGGCGACAGGGTGACCATCACC
TGCAAGGCCAGCCAGAACGTGAACAGCAACGTGGCCTGGTACCAGCAGAAGCCCGGCAAAGCCCC
CAAGCTCCTGATCTACAGCGCCAGCTACAGATATAGCGGCGTGCCTAGCAGGTTTAGCGGCAGCGG
AAGCGGGACCGATTTCACCCTGACCATCAGCAGCCTGCAGCCCGAGGACTTCGCCACTTACTACTGC
CAGCAGGCGAACAACTACCCCTTCACCTTCGGCCAGGGCACCAAGCTGGAGATCAAG

SAP-K humanised light chain V region variant L0 91A amino acid sequence (SEQ ID NO:74)

DIQMTQSPSSLSASVGDRVTITCKASQNVNSNVAWYQQKPGKAPKLLIYSASYRYSGVPSRFSGSGSGTD
FTLTISSLQPEDFATYYCQQANNYPFTFGQGTKLEIK

Example 10: Complement dependence of amyloid clearance by anti-SAP antibody.

The role of complement in amyloid clearance by anti-SAP antibody was investigated by comparing the efficiency of the treatment between mice with complement deficiency and normal, complement sufficient, animals. Targeted deletion of the gene for C1q blocks

activation of the classical complement pathway, which is initiated by binding of C1q to antibody-antigen complexes, but C3 activation, the pivotal functional step responsible for chemotaxis and opsonisation, the major biological functions of complement, can still proceed via the alternative and lectin pathways as well as by direct C3 cleavage by non-complement serine proteinases. Targeted deletion of the gene for C3 completely abrogates these functions.

Induction of AA amyloidosis

AA amyloidosis was induced and confirmed in two groups of complement deficient mice: C3 knockouts (n=14) and C1q knockouts (n=12), and in 15 wild-type mice. All mice were pure line C57BL/6. Each mouse received a single dose of amyloid enhancing factor, an extract of amyloidotic tissue containing amyloid fibrils (Baltz et al, (1986) Plenum Press, New York, pp. 1 15-121), by intravenous injection followed 4 days later by 10 daily subcutaneous injections of 10% w/v casein in solution in 0.1M $NaHCO_3$ administered over a 12 day period (Botto et al, (1997) *Nature Med.,* 3: 855-859). Casein elicits persistent acute inflammation and a sustained increase in serum amyloid A protein (SAA) production leading to AA amyloid deposition in all animals. Seven days after the last casein injection, KI was introduced into the drinking water of all mice and 3 days later each mouse received an intravenous injection of a standard dose of ^{125}I-labelled human SAP (Hawkins et al, (1990) *J. Clin. Invest.,* 86: 1862-1 869 and Hawkins et al, (1988) *J. Exp. Med.,* 167: 903-913). All mice underwent whole body counting 24h and 48h after the tracer injection to determine retention of radioactivity, a precise index of whole body amyloid load. Ten days after the ^{125}I-SAP tracer injection, all mice were 'loaded' with human SAP by a single intraperitoneal injection of 10 mg per mouse of isolated pure human SAP. Human SAP injected into amyloidotic mice localises in the amyloid deposits and persists there with a half life of about 3-4 days whilst any human SAP not bound to amyloid is cleared from the circulation with a half life of about 3-4 hours (Hawkins et al, (1988) *J. Exp. Med,,* 167: 903-913 and Pepys et al, (2002) *Nature,* 41 7: 254-259).

Immunohistochemical staining with anti-human SAP antibody in spleen of an amyloidotic mouse after injection of isolated pure human SAP shows that there is strong positive staining of all the amyloid deposits in their typical marginal zone distribution. This bound

human SAP is the target of the therapeutic anti-SAP antibody according to the present invention.

Anti-SAP treatment

Three days after the human SAP injection, when human SAP was no longer detectable in the circulation, all mice except two in each of the complement knockout groups received a single intraperitoneal injection of 1 ml of the whole IgG fraction (batch no. 2866) of monospecific sheep anti-human SAP antiserum at 50 mg/ml in solution in phosphate buffered saline (PBS), containing 7 mg/ml of actual anti-SAP antibody. The antiserum was produced by The Binding Site Ltd, Birmingham, UK, using human SAP (rigorously purified to 100% in the University College London Centre for Amyloidosis and Acute Phase Proteins) and proprietary immunisation procedures. All animals were then killed 15 days after anti-SAP administration for histological estimation of amyloid load by alkaline alcoholic Congo red staining (Puchtler, H., Sweat, F. and Levine, M. (1962) On the binding of Congo red by amyloid. *J. Histochem. Cytochem.,* **10:** 355-364). Congo red sections of spleen and liver of all animals were independently examined by one or more expert observers, blinded to the treatment each mouse had received, and scored for the amount of amyloid present as previously reported (Botto et al, (1997) *Nature Med.,* 3 : 855-859). The scores of 1-5 represent an approximately log base 10 ranking scale from 1, corresponding to one or two tiny specks of amyloid among several sections of a particular organ, to 5, corresponding to abundant widespread deposits comprising about 10,000 times more amyloid than grade 1 (Botto et al, (1997) *Nature Med.,* 3: 855-859). The scores of the different observers were always highly concordant although some observers also used intermediate integer.5 scores. The arithmetic mean of the scores of all observers for each organ in each animal were used for statistical analysis.

Results

In marked contrast to the effective clearance of amyloid deposits in the complement sufficient wild-type mice, there was still abundant amyloid present in both groups of complement deficient animals although it tended to have a more fragmented appearance than in the two control complement deficient mice of each type. The median, range, spleen amyloid scores were: wild type, 1.17, 0.0-1.5, n=15; C3 knockout, 1.92, 1.17-4.33, n=12; C1q

knockout, 1.25, 1.17-3.5, n=10 (Kruskal-Wallis non-parametric ANOVA, P<0.001). The differences between the wild type controls and both complement deficient groups were significant, P<0.001 for the C3 knockouts and P=0.036 (with Bonferroni correction for multiple comparisons) for the C1q knockouts, but the difference between the C3 and C1q knockouts was not significant, P=0.314 (Mann-Whitney U tests).

Discussion

In mice lacking either C1q or C3, anti-SAP treatment did not clear amyloid deposits as effectively as in complement sufficient wild-type mice. The therapeutic efficacy of anti-SAP is thus very substantially complement dependent and is not mediated by IgG antibody binding alone which could, in theory, engage phagocytic cells via their Fc(γ) receptors. Nevertheless the more fragmented appearance of the persistent amyloid deposits in the complement deficient mice suggested at least some effect of antibody alone. Also the trend to more clearance in C1q deficient compared to C3 deficient animals suggested that C3 activation is critical and that some complement activation may be taking place in the absence of C1q.

Example 11: Requirement for intact IgG anti-SAP antibody

Complement activation by IgG antibody requires the whole intact molecule, including the Fc region, and proceeds via the classical pathway initiated by binding of C1q. However, in some antibody-antigen systems, complement activation via the alternative pathway can be mediated by the $F(ab)_2$ fragment. In order to confirm the complement dependence of amyloid clearing by anti-SAP antibody and to investigate the potential requirement for the Fc region of the antibody, the effect was tested of $F(ab)_2$ anti-SAP antibody which was produced by pepsin cleavage at pH 4.0 of the IgG fraction of the sheep polyclonal anti-human SAP antiserum (batch 2866) and purified by standard methods.

Induction and treatment of AA amyloidosis

AA amyloidosis was induced and confirmed in wild-type C57BL/6 mice as detailed in Example 10 above. After loading the amyloid deposits with human SAP also as detailed in

Example 10, groups of mice were treated with whole IgG fraction of the sheep polyclonal anti-human SAP antiserum, with buffer vehicle alone or with the $F(ab)_2$ fragment of the IgG fraction. The dose of anti-SAP antibody activity injected was 7.28 mg per mouse receiving $F(ab)_2$ and 7 mg (50 mg of total IgG as usual) per mouse receiving whole IgG. All mice were killed 14 days later for estimation of amyloid load by Congo red staining.

Results

Clearance of amyloid deposits was almost complete in mice receiving IgG anti-SAP antibody compared to the massive amyloid deposits in the control mice receiving vehicle alone. The mice receiving $F(ab)_2$ had less amyloid than untreated controls, but still substantially more than the mice treated with whole IgG anti-SAP antibody (Table 9).

Table 9. Reduced efficacy of $F(ab)_2$ anti-SAP compared to intact IgG antibody in clearing amyloid deposits.

Group (treatment, group size)	Amyloid score median, range	
	Spleen	Liver
1 (no antibody, n=10)	4.0, 4.0-4.33	3.5, 2.67-4.67
2 (IgG anti-SAP antibody, n=8)	1.0, 1.0-3.67*	1.25, 1.0-1.5
3 ($F(ab)_2$ anti-SAP antibody, n=5)	2.17, 1.33-3.0	1.67, 1.33-1.67

Kruskal-Wallis test: spleen, $P<0.001$; liver $P<0.001$

Mann-Whitney tests**: 1 vs 2, spleen & liver both, $P<0.001$; 1 vs 3, spleen & liver both, $P=0.001$; 2 vs 3, spleen, $P=0.284$; liver, $P=0.019$

*Single outlier in group 2 with heavy spleen amyloid despite IgG anti-SAP treatment. Excluding this animal gives a highly significant difference between efficacy of IgG and $F(ab)_2$ anti-SAP antibody treatment. **Due to the multiple comparisons, a P value of 0.01 or less is required for significance

Discussion

The molar dose of $F(ab)_2$ anti-SAP antibody used in this study was about one third greater than that of IgG antibody, due to the smaller molecular weight of the $F(ab)_2$ fragment compared to whole IgG. For optimal effect on amyloid clearance the Fc is required. This is not because of direct involvement of cellular recognition by Fc(γ) receptors since the whole IgG was even less effective in complement deficient mice than was $F(ab)_2$ in complement sufficient mice. It is likely that the high dose of $F(ab)_2$ that was administered was able to activate some complement via the alternative pathway.

Example 12: Requirement for macrophages

The histological and histochemical studies described in US 2009/0191196 show that the cells which infiltrate, surround and phagocytose the amyloid deposits in mice treated with anti-SAP antibody are macrophages. In order to confirm that macrophages are indeed responsible for the clearance of the amyloid, the effect of treatment with the whole IgG fraction of the sheep polyclonal anti-human SAP antiserum (batch 2866) was tested in mice in which all macrophage activity had been inhibited by administration of liposomal clodronate. The reagents, experimental protocol and effects on macrophage function of liposomal clodronate are well established and extensively documented (Van Rooijen et al, (2002) *J. Liposome Research.* Vol. 12. Pp, 81-94).

Induction and treatment of AA amyloidosis

After induction and confirmation of AA amyloidosis in wild-type mice, using the protocol detailed in Example 10 above, all animals received a single intraperitoneal dose of 10 mg of isolated pure human SAP to load their deposits with human SAP. The test group then received 0.3 ml of liposomal clodronate intraperitoneally immediately and on days 2, 7 and 14 thereafter. One control group and the test group received a single intraperitoneal dose of 50 mg of the IgG fraction of sheep anti-human SAP antiserum on day 3 after the human SAP injection. A second control group received no anti-SAP and no other additional treatment. All mice were killed for estimation of amyloid load by Congo red staining 14 days after administration of the anti-SAP to the test and antibody control groups.

Results

Treatment with anti-SAP produced almost complete clearance of amyloid deposits compared to the group which received no antibody. In contrast, in mice which received the liposomal clodronate in a regime known to completely ablate macrophage function, there was no clearance of amyloid deposits (Table 10).

Table 10. Macrophage depletion inhibits clearance of amyloid deposits by anti-SAP antibody.

Group (treatment, group size)	Amyloid score median, range	
	Spleen	Liver
1 (clodronate plus anti-SAP, n=13)	4.83, 2.0-5.0	3.17, 2.0-3.5
2 (anti-SAP only, n=12)	1.33, 0.67-3.5	1.0, 0.67-2.5
3 (none, n=12)	4.0, 3.5-4.5	2.83, 1.0-3.17

Kruskal-Wallis test: spleen, $P<0.001$; liver $P<0.001$

Mann-Whitney tests with Bonferroni correction: 1 vs 2: spleen & liver both, $P<0.003$; 1 vs 3: spleen, $P=0.078$; liver, $P=0.411$; 2 vs 3, spleen & liver both, $P<0.003$.

Discussion

The result in this particular experiment confirmed that macrophage function is required for clearance of amyloid deposits by anti-human SAP antibody.

Example 13: Efficacy of mouse monoclonal anti-human SAP antibody, SAP-E, in clearing mouse systemic AA amyloid deposits.

The capacity of various monoclonal antibodies to mediate clearance of murine AA amyloid deposits containing human SAP was sought in comparison with the standard sheep polyclonal anti-human SAP antibody as a positive control.

Induction of AA amyloidosis and treatment

SAP knockout C57BL/6 mice transgenic for human SAP were created by crossing pure line C57BL/6 animals in which the mouse SAP gene has been deleted (Botto et al, (1997) *Nature Med.,* 3: 855-859) with C57BL/6 mice bearing a human SAP transgene (Yamamura et al, (1993) *Mol. Reprod. Dev.,* 36: 248-250 and Gillmore et al, (2004) *Immunology,* 112: 255-264). These mice thus lack mouse SAP but express human SAP at concentrations significantly greater than those seen in man. Systemic AA amyloidosis was induced in the human SAP transgenic mouse SAP knockout mice as described in Example 10, and 9 days after the final injection of casein into the mice, the presence and extent of amyloid deposition were confirmed as usual by whole body counting of amyloid after injection of a tracer dose of ^{125}I-labelled human SAP. All mice had substantial and comparable amounts of amyloid, and were allocated into closely matched groups to receive the different treatments. One week after the tracer injection, each mouse received a single dose of 5 mg CPHPC by intraperitoneal injection, to deplete their circulating human SAP, followed 5h later via the same route by either the standard sheep polyclonal anti-human SAP IgG fraction (batch 2866, 1 ml at 50 mg/ml total protein containing 7 mg/ml anti-human SAP antibody) or 5 mg of one of nine different isolated pure monoclonal anti-human SAP antibodies (Table 11). All mice were killed 21 days after the antibody injection and amyloid load was determined by Congo red histology of their spleens.

Table 11. The presence of amyloid in spleen of mice with systemic AA amyloidosis after treatment with CPHPC and various anti-human SAP antibodies.

Antibody treatment	Antibody isotype	Amyloid score median, range
none		**3, 3-5**
polyclonal	**NA**	**1, 1-1**
monoclonal SAP-A	IgG1	3, 2-4
monoclonal SAP-B	IgG2a	3, 2-4
monoclonal SAP-C	IgG1	4, 2-4
monoclonal SAP-D (n=1)	IgG1	4
monoclonal SAP-E	**IgG2a**	**1, 1-1**
monoclonal SAP-F (n=1)	IgG1	2
monoclonal SAP-G	IgG1	3, 2-4

Among the monoclonal antibodies tested, only SAP-E produced clearance of the amyloid deposits but its effect was the same as the highly reproducible and dramatic action of the sheep polyclonal antibody. Importantly SAP-E is of the mouse IgG2a isotype which is known to activate mouse complement while all the other monoclonals except SAP-B were mouse IgG1 isotype which is not complement activating. Although SAP-B is a mouse IgG2a isotype, its binding to SAP *in vitro* was notably less than that of SAP-E and evidently was not sufficient *in vivo* to be effective.

Discussion

These results demonstrate that a sufficiently avid, complement activating, IgG2a mouse monoclonal anti-human SAP antibody mediates amyloid clearance *in vivo* as effectively as sheep polyclonal anti-human SAP antibody.

Example 14: Comparative characterisation of monoclonal mouse anti-human SAP antibodies, SAP-K and SAP-E, *in vitro*.

SAP-K was selected from among the 6 different, most avidly binding, mouse IgG2a monoclonals, derived by standard techniques from immunization with purified human SAP and a conventional fusion to produce hybridomas which were cloned by routine methods. Among these IgG2a antibodies, SAP-K showed the greatest binding to immobilised human SAP. This was the case regardless of whether the human SAP had been directly immobilised on plastic surfaces by non-specific adherence or by covalent attachment, or by the specific calcium dependent binding of SAP to immobilised ligands, whether amyloid fibrils or the small molecule ligand, phosphoethanolamine. SAP-K also bound well to directly immobilised SAP in the presence or absence of calcium, and if the SAP had previously been complexed with CPHPC and then covalently 'fixed' in the decameric SAP-CPHPC complex (Pepys, M.B. *et al* (2002) Targeted pharmacological depletion of serum amyloid P component for treatment of human amyloidosis. *Nature,* 417**:** 254-259; Kolstoe, S.E. *et al* (2009) Molecular dissection of Alzheimer's disease neuropathology by depletion of serum amyloid P component. *Proc. Natl. Acad. Sci. USA,* 106: 7619-7623). SAP-E also bound well to human SAP in all these different configurations. However the two antibodies differ significantly in that much more SAP-K than SAP-E became bound when human SAP was only sparsely available, for example when plates were exposed to just 1 μg/ml of human SAP for coating, whereas when there was more abundant immobilised SAP, for example when the coating solution contained 100 μg/ml of SAP, then there was more binding of SAP-E than SAP-K. This difference suggest that SAP-E binds optimally when more than one SAP molecule lies closely associated with another whilst SAP-K binds avidly to single isolated SAP molecules. This mechanism is supported by the finding that when human SAP was immobilised by capture on plates coated with polyclonal sheep anti-human SAP (batch

2866), which provides pairs of SAP molecules held closely together in the two arms of each sheep IgG antibody molecule, SAP-E bound better than SAP-K at all levels of human SAP input (Figure 7).

Figure 7 shows immunoradiometric assay for binding of monoclonal mouse antibodies to human SAP captured by immobilised sheep polyclonal anti-human SAP antibody. Substantially more SAP-E than SAP-K bound at all concentrations of human SAP offered. Each point is the mean of 3 replicates.

Very importantly, both SAP-E and SAP-K bound apparently equally well to native human SAP, shown by the similar immunoprecipitation of both antibodies in double immunodiffusion in agarose gel against both isolated pure human SAP and whole human serum. The similar binding of these two mouse monoclonal antibodies was reflected in the similar parameters measured in the Biacore instrument (BIAcoreX, Pharmacia Biosensor AB, Uppsala, Sweden) using human SAP covalently immobilised on the chip (Table 12).

Table 12. Affinity of monoclonal antibodies for human SAP determined by Biacore

	k_a (M^{-1} sec^{-1})	k_d (sec^{-1})	K_D (M)
SAP-E	$2 \pm 5 \times 10^{4}$	$6 \pm 4 \times 10^{-5}$	$5 \pm 4 \times 10^{-9}$
SAP-K	$3.18 \pm 5 \times 10^{4}$	$1.7 \pm 0.9 \times 10^{-5}$	$1 \pm 1.7 \times 10^{-9}$

Values shown are mean and SD of 3 replicate measurements

In contrast, although both antibodies bound to native human SAP in western blotting after agarose gel electrophoresis in physiological buffers, only SAP-E bound to human SAP in western blotting from reduced SDS-PAGE. SAP-E thus recognises denatured human SAP while SAP-K only recognises native human SAP and must be binding to a conformational epitope.

CNBr digestion of human SAP results in cleavage between 159M and 160W resulting in a new peptide where position 159 has been converted from methionine to homoserine lactone (termed 150-158-homoserine lactone). In western blotting from SDS-PAGE, SAP-E

bound to the *N*-terminal 1-158-homoserine lactone polypeptide released by CNBr cleavage of SAP at residue Met159, but scarcely reacted with the 1-140 fragment released by chymotrypsin digestion in the absence of calcium (Figure 8). The epitope recognised by SAP-E must therefore be in the region 140-158 which evidently comprises some denaturation resistant secondary structure since SAP-E binding is not potently inhibited by the peptides 136-147, 138-149, 140-151 and 112-119 in solution. This is consistent with the kinetic stability and resistance to denaturation of SAP (Manning, M. and Colón, W. (2004) *Biochemistry,* 43**:** 11248-11254).

Figure 8 shows epitope mapping for monoclonal anti-human SAP antibody, SAP-E. **A**, complete amino acid sequence of human SAP showing the points at which it is cleaved by CNBr in 70%TFA (residue 159M) and by chymotrypsin, without reduction/carbamidomethylation, in ammonium bicarbonate in the absence of calcium, (residues 140Y and 144F). **B**, SDS-PAGE analysis of SAP cleaved with CNBr. Left panel: Coomassie blue stain; lane 1, untreated control SAP; lane 2, SAP after CNBr cleavage, showing trace residual uncleaved intact protomer and the expected fragments at approximately 20kD (residues 1-158-homoserine-lactone) and 5kD (160-204) respectively. These were precisely confirmed by mass spectrometry. Right panel: Western blot with SAP-5 showing intense staining of intact untreated SAP in lanes 1 (100 ng loaded) and 2 (10 ng), and also residual intact SAP and the larger residue 1-158-homoserine-lactone fragment in CNBr cleaved SAP in lanes 3 (600 ng), 4 (130 ng) and 5 (64 ng). Lane 6 contained isolated pure human CRP with which the SAP-5 did not react at all. **C**, SDS-PAGE analysis of SAP digested with chymotrypsin. Left panel: Coomassie blue stain; lane 1, untreated control SAP; lane 2, SAP after chymotrypsin digestion, showing the expected major fragments corresponding to residues 1-140 and 145-204. These were precisely confirmed by mass spectrometry. Right panel: Western blot with SAP-E showing intense staining of intact untreated SAP in lanes 1 (500 ng loaded) and 2 (100 ng), and also residual intact SAP in lanes 3 and 4 which contained the chymotrypsin digested SAP at different loadings. Very weak binding of SAP-E to the residue 1-140 fragment is seen only in lane 3 which was most heavily loaded. Lanes 5 (500 ng) and 6 (100 ng) contained isolated pure human CRP with which the SAP-E did not react at all. **D**, Sequence comparison between human SAP (h) and mouse SAP (m) for residues 136-147. Top panel, differences indicated above by residues shown in black

in the murine sequence. Bottom panel, position of this extended loop with 140Y at its apex shown in white in the 3D subunit structure of human SAP. The different residues in the murine sequence are shown in black. The grey spheres represent the calcium atoms bound in the ligand binding pocket.

The conformational epitope recognised by SAP-K was identified by CLIPS® technology epitope mapping (Pepscan Presto BV) as the exposed peripheral loop, residues 121-131, at the circumference of the disc like pentameric native SAP molecule.

Figure 9 shows the location of the epitopes on human SAP recognised by SAP-K (A, highlighted in black, as determined by CLIPS® technology) and SAP-E (B, shown in white, 140-158 as determined by binding results with the CNBr cleavage product of SAP and the fragment released by chymotrypsin digestion in the absence of calcium).

Example 15: Efficacy of SAP-K mouse monoclonal anti-human SAP antibody in clearing amyloid deposits *in vivo* in the mouse AA amyloidosis model.

The potency of SAP-K was compared with the action of the standard sheep polyclonal antibody in clearing established systemic AA amyloid deposits in mice.

Induction of AA amyloidosis and treatment

AA amyloidosis was induced and confirmed in wild-type C57BL/6 mice as detailed in Example 10 above. After loading the amyloid deposits with human SAP also detailed in Example 10, groups of mice were treated with 50 mg per mouse of total IgG as the whole IgG fraction (batch 2866) of the sheep polyclonal anti-human SAP antiserum providing a dose of 7 mg of actual anti-SAP antibody, isolated purified SAP-K at a dose of 5 mg per mouse, isolated purified SAP-K at a dose of 1 mg per mouse, and, as a negative control, isolated purified monoclonal mouse IgG2a antibody specific for an unrelated human antigen and unreactive with either human SAP or any murine antigen. All mice were killed 17 days later for estimation of amyloid load by Congo red staining.

Results

The mice treated with 5 mg of SAP-K showed the same remarkable clearance of splenic and hepatic amyloid deposits as seen with the 7 mg dose of sheep polyclonal antibody. Only trace specks of amyloid remained in the spleens of the treated mice and none at all was detected in many of the livers, contrasting sharply with the extensive splenic and hepatic amyloid deposits in all animals which received the irrelevant control mouse IgG2a antibody (Table 13). At the lower doses of 1 mg, 0.5 mg and 0.1 mg (data not shown for 0.5 mg and 0.1 mg) of SAP-K per mouse, there was no significant effect.

Table 13. Effect of monoclonal mouse IgG2a anti-human SAP antibody SAP-K on visceral amyloid deposits in mice with systemic AA amyloidosis.

	Amyloid score median, range	
Group (treatment, group size)	Spleen	Liver
1 (negative control mouse IgG2a, n=8)	4.08, 1.5-4.50	2.42, 2.0-2.67
2 (7 mg sheep polyclonal IgG anti-human SAP antibody, n=5)	1.17, 1.0-1.5	1.0, 0.67-1.17
3 (1 mg monoclonal mouse IgG2a anti-human SAP antibody, SAP-K, n=10)	3.5, 2.83-4.5	1.83, 1.0-2.83
4 (5 mg monoclonal mouse IgG2a anti-human SAP antibody, SAP-K, n=10)	1.25, 1.0-2.0	1.0, 1.0-1.33

Kruskal-Wallis test: spleen, $P<0.001$; liver P,0.001

Mann-Whitney tests*: 1 vs 2, spleen, P=0.002; liver, P=0.002; 1 vs 3, spleen, P=0.173; liver, P=0.083; 1 vs 4, spleen, $P<0.001$; liver, $P<0.001$; 2 vs 3, spleen, P=0.0.001; liver, P=0.019; 2 vs

4, spleen, P=0.513; liver, P=0.768; 3 vs 4, spleen, P<0.001; liver, P=0.004. *Due to the multiple comparisons, a P value of 0.01 or less is required for significance.

Discussion

These results demonstrate the efficacy in clearing amyloid deposits *in vivo* of a monoclonal anti-human SAP antibody, of the complement activating mouse IgG2a isotype, which specifically recognizes a conformational epitope. Thus monoclonal anti-human SAP antibodies for use according to the present invention can be directed at either predominantly sequence epitopes, such as antibody SAP-E, or at entirely conformational epitopes, such as SAP-K.

Example 16: Comparison of efficacy of SAP-E and SAP-K in clearing systemic AA amyloid deposits in mice, and estimation of plasma anti-SAP antibody concentrations.

Induction of AA amyloidosis and treatment

AA amyloidosis was induced and confirmed in wild-type C57BL/6 mice as detailed in Example 10 above. After loading the amyloid deposits with human SAP also detailed in Example 10, groups of mice were treated with 3 mg and 1 mg per mouse of the two different antibodies. A control group, in which amyloid was also induced, received just PBS instead of antibody and two further groups were given the known effective dose of 5 mg/mouse of each antibody. All mice were bled for assay of circulating anti-SAP antibody at days 1, 5 and 15 after dosing with antibody, and all were killed on day 21 for estimation of amyloid load by Congo red staining. All sera were assayed for anti-SAP activity using a robust immunoradiometric assay standardised with purified SAP-E and SAP-K respectively, spiked at known concentrations into normal mouse serum.

Results

Amyloid load was scored by four independent expert observers all blinded to the identity of each tissue examined. The scores of all observers were, as usual highly concordant and for statistical analysis, the total scores of all observers for both spleen and liver for each mouse were summed. Both antibodies were efficacious, as previously demonstrated, and there

was a clear dose dependent effect but SAP-E was apparently more potent than SAP-K at the lower doses.

Table 14. Comparison of potency between SAP-E and SAP-K in clearing visceral AA amyloid deposits

Group (treatment, no. of mice)	Spleen plus liver amyloid score median, range
C (negative control, PBS only)	6.81, 4.25-8.0
K5 (SAP-K 5 mg, n=5)	2.25, 2.25-2.5
K3 (SAP-K 3 mg, n=10)	2.81, 2.0-4.25
K1 (SAP-K 1 mg, n=10)	5.63, 4.0-6.5
E5 (SAP-E 5 mg, n=5)	2.0, 1.5-2.38
E3 (SAP-E 3 mg, n=10)	2.5, 2.0-5.0
E1 (SAP-E 1 mg, n=10)	3.38, 2.5-5.63

Kruskal-Wallis test: $P<0.001$

Mann-Whitney tests*: K5 vs E5, P=0.095; K3 vs E3, P=0.684; K1 vs E1, P=0.001; K5 vs K3, P=0.594; K5 vs K1, P=0.001; K3 vs K1, $P<0.001$; E5 vs E3, P=0.008; E5 vs E1, P=0.001; E3 vs E1, P=0.004; K5 vs C, P=0.001; E5 vs C, P=0.001; K3 vs C, $P<0.001$; E3 vs C, $P<0.001$; K1 vs C, P=0.043; E1 vs C, $P<0.001$. *Due to the multiple comparisons, a P value of 0.01 or less is required for significance.

The concentrations of circulating anti-SAP antibody activity were strongly and consistently dose dependent after the single dose administered to all animals, apart from a single outlying individual in each of the lower dose groups. After the 1 mg per mouse dose, nothing above background was generally detectable even at day 1 in most mice. In

contrast, after the 5 mg dose abundant antibody was still present at 15 days, and after 3 mg most mice had circulating antibody at day 5 but few after 15 days (Table 15). There was no significant difference between the patterns for SAP-E and SAP-K.

Table 15. Serum concentration of anti-SAP antibody after single intraperitoneal doses.

	anti-SAP concentration after dosing median, range (μg/ml)*		
Group (dose of anti-SAP antibody)	**1 day**	**5 days**	**15 days**
K5 (SAP-K 5 mg)	950, 840-1200	400, 300-480	45, 25-90
E5 (SAP-E 5 mg)	1000, 800-1500	600, 360-700	80, 15-113
K3 (SAP-K 3 mg)	240, 50-600	40, 8-280	8, 6-30
E3 (SAP-E 3 mg)	275, 4-480	48, 0-240	4, 2-68
K1 (SAP-K 1mg)	7, 7-90	6, 5-38	4, 2-9
E1 (SAP-E 1mg)	7, 6-280	7, 6-120	5, 3-12
C (PBS only)	5, 5-7	5, 5-13	5, 5-16

*Apparent anti-SAP antibody concentrations below 17 μg/ml are background for the assay and represent no genuine activity.

Discussion

In direct head to head comparison there was consistent evidence that SAP-E was slightly but significantly more potent than SAP-K. After administration of 1 mg per mouse no circulating anti-SAP antibody activity was detectable one day later, having evidently all localised to human SAP within the amyloid deposits. After the 3 mg dose abundant anti-SAP was present in the circulation at day 1 and was still present at day 5. After 5 mg per mouse there was still a significant concentration of anti-SAP in the blood after 15 days. These

observations suggest that repeated small doses of anti-SAP antibody may be sufficient to trigger amyloid clearance.

Example 17: Comparison of efficacy of low dose SAP-E and SAP-K in clearing systemic AA amyloid deposits in mice.

Induction of AA amyloidosis and treatment

AA amyloidosis was induced and confirmed in wild-type C57BL/6 mice as detailed in Example 10 above. After loading the amyloid deposits with human SAP as also detailed in Example 10, groups of mice (n=10 each) were treated with single doses of either 0.5 mg and 1 mg per mouse of the two different antibodies, or 6 repeated doses of 0.15 mg, given at 3 or 4 day intervals. A control group (n=9), in which amyloid was also induced, received just PBS instead of antibody and two further groups (n=3 each) were given the known effective dose of 5 mg/mouse of each antibody. All were killed on day 29 for estimation of amyloid load by Congo red staining.

Results

The low doses, including the repeated very low dose, showed significant efficacy in reducing amyloid load, especially in the liver. SAP-E was again apparently more potent than SAP-K.

Table 16. Comparison of potency between low doses of SAP-E and SAP-K in clearing visceral AA amyloid deposits

	Amyloid score, (median, range)	
Group	Spleen	Liver
C, negative control PBS only	4.5, 4.0-4.75	3.25, 2.0-4.0
E1, SAP-E 1 mg	1.25, 1.0-4.25	1.0, 0.5-1.25
E0.5, SAP-E 0.5 mg	4.75, 1.0-5.0	1.0, 0.5-3.5
Erep, SAP-E 6x 0.15 mg	3.5, 2.0-4.5	0.5, 0.0-3.25
K1, SAP-K 1 mg	4.13, 1.0-5.0	1.0, 0.0-4.0
K0.5, SAP-K 0.5 mg	4.25, 1.75-4.5	1.13, 0.0-2.75

Krep, SAP-K 6x 0.15 mg	4.38, 1.5-4.75	1.0, 0.0-2.25

Kruskal-Wallis test: spleen, P<0.001; liver, P=0.001

Mann-Whitney tests*: E1 vs C: spleen, P<0.001; liver P<0.001; E0.5 vs C: spleen, P=0.604; liver P=0.004; Erep vs C: spleen, P0.002; liver, P<0.001; K1 vs C: spleen, P=0.065; liver, P=0.001; K0.5 vs C: spleen, P=0.022; liver, P=0.001; Krep vs C: spleen, P=0.079; liver, P<0.001; E1 vs E0.5: spleen, P=0.005; liver P=0.143; E1 vs Erep: spleen, P=0.043; liver, P=0.280; E0.5 vs Erep: spleen, P=0.019; liver, P=0.043; K1 vs K0.5: no significant differences; K1 vs Krep: no significant differences; K0.5 vs Krep: no significant differences; E1 vs K1: spleen, P=0.015; liver, P=0.353; E0.5 vs K0.5: no significant differences; Erep vs Krep: no significant differences. *Due to the multiple comparisons, a P value of 0.01 or less is required for significance.

Discussion

The significantly greater potency of SAP-E than SAP-K appears to be reproducible. The efficacy of even very low doses when administered repeatedly and the suggestion of greater effects on liver than spleen amyloid deposits are of interest and potential clinical significance.

Example 18: Activation of complement by humanised monoclonal anti-human SAP antibodies *in vitro.*

Complement activation is essential for efficacy of amyloid clearing by anti-human SAP antibodies according to the present invention. The capacity of the humanised monoclonal antibodies, SAP-E H1L1 and SAP-K H3L0, to activate C3 in human and mouse serum was compared *in vitro* by adding different amounts of the isolated pure antibodies to either whole human serum containing a SAP concentration of 30 mg/l, or to whole mouse serum which had been spiked with isolated pure human SAP to this same concentration. In both cases the serum was fresh and complement sufficient and experimental conditions were optimal for complement activation with complement fixation test buffer (CFT) as the diluent.

The following mixtures were made (Table 17):

Tube no.	Serum	Monoclonal anti-SAP antibody	Final concentrations (μg/ml)	
			Anti-SAP	Human SAP
M1	Mouse + human SAP	SAP-E H1L1	15	30
M2	Mouse + human SAP	SAP-E H1L1	30	30
M3	Mouse + human SAP	SAP-E H1L1	60	30
M4	Mouse + human SAP	SAP-E H1L1	120	30
M5	Mouse + human SAP	SAP-K H3L0	15	30
M6	Mouse + human SAP	SAP-K H3L0	30	30
M7	Mouse + human SAP	SAP-K H3L0	60	30
M8	Mouse + human SAP	SAP-K H3L0	120	30
M9	Mouse + human SAP	None	0	30
H1	Human	SAP-E H1L1	15	30
H2	Human	SAP-E H1L1	30	30
H3	Human	SAP-E H1L1	60	30
H4	Human	SAP-E H1L1	120	30
H5	Human	SAP-K H3L0	15	30
H6	Human	SAP-K H3L0	30	30
H7	Human	SAP-K H3L0	60	30
H8	Human	SAP-K H3L0	120	30
H9	Human	None	0	30

All tubes were incubated at 37°C for 2 hours to enable complement activation to proceed. Since slow spontaneous activation always occurs in serum, two additional controls were provided, replicates of M9 and H9, designated M10 and H10, which were not incubated but were frozen at -80°C immediately after mixing and then thawed just before assaying for C3

cleavage. Comparison between M/H9 and M/H10 enables distinction between spontaneous C3 cleavage and any additional activation produced by the anti-SAP antibody, as well as any effect of addition of human SAP alone t mouse serum.

C3 cleavage in human serum was assayed by two dimensional electroimmunophoresis using monospecific antibody against human C3. This method is of low sensitivity for mouse C3 cleavage because the different electrophoretic mobilities of mouse C3 are more difficult to distinguish reliable than is the case with human C3. Mouse C3 cleavage was therefore assayed by agarose gel electrophoresis followed by immunoblotting with monospecific anti-mouse C3 antibody.

Results

Both humanised antibodies efficiently activated human complement, evidenced by major dose dependent cleavage of C3, producing reduction in the size of the slower mobility native C3 immunoprecipitation peak and increase in the size of the faster cleaved C3c peak (Figure 10).

Figure 10 shows C3 activation by humanised monoclonal anti-human SAP antibodies in whole human serum.

In an assay including the control for baseline C3 cleavage in sample H10, it is clear that even the lowest dose of both anti-SAP antibodies produces more C3 cleavage than seen in the no antibody, spontaneous cleavage, control (Figure 11).

Figure 11 shows C3 activation by low dose humanised monoclonal anti-human SAP antibodies in whole human serum.

Very similar results were obtained for cleavage of mouse C3 in whole mouse serum supplemented with human SAP. Both antibodies showed dose dependent cleavage of native mouse C3 leading to decreased intensity of the slow mobility native C3 band and increased intensity of the faster mobility activated form. Also even the lowest dose of each antibody produced more C3 cleavage than was seen in the no antibody, spontaneous activation, control (Figure 12).

Figure 12 shows C3 activation by humanised monoclonal anti-human SAP antibodies in whole mouse serum supplemented with pure human SAP.

Discussion

Both humanised monoclonal anti-human SAP antibodies efficiently activate complement in the presence of human SAP and are thus suitable candidates for use in treatment of systemic amyloidosis, and any other disease caused by extracellular amyloid deposits in the tissues, according to the present invention.

SEQUENCE CONCORDANCE

SEQ ID NO	Sequence description
1	SAP-E CDRH1 amino acid sequence
2	SAP-E CDRH2 amino acid sequence
3	SAP-E CDRH3 amino acid sequence
4	SAP-E CDRL1 amino acid sequence
5	SAP-E CDRL2 amino acid sequence
6	SAP-E CDRL3 amino acid sequence
7	SAP-E V_H amino acid sequence
8	SAP-E V_H DNA sequence
9	SAP-E V_L amino acid sequence
10	SAP-E V_L DNA sequence
11	SAP-K CDRH1 amino acid sequence
12	SAP-K CDRH2 amino acid sequence
13	SAP-K CDRH3 amino acid sequence
14	SAP-K CDRL1 amino acid sequence
15	SAP-K CDRL2 amino acid sequence
16	SAP-K CDRL3 amino acid sequence
17	SAP-K V_H amino acid sequence
18	SAP-K V_H DNA sequence
19	SAP-K V_L amino acid sequence
20	SAP-K V_L DNA sequence
21	SAP-E V_H chimera amino acid sequence
22	SAP-E V_L chimera amino acid sequence
23	SAP-K V_H chimera amino acid sequence
24	SAP-K V_L chimera amino acid sequence
25	IGHV1-69 human variable heavy chain germline acceptor amino acid sequence
26	JH1 minigene
27	SAP-E humanised V_H variant H0 amino acid sequence
28	SAP-E humanised V_H variant H1 amino acid sequence
29	SAP-E humanised V_H variant H2 amino acid sequence
30	SAP-E humanised V_H variant H3 amino acid sequence
31	SAP-E humanised V_H variant H4 amino acid sequence
32	IGKV1-39 human variable light chain germline acceptor amino acid sequence
33	JK2 minigene
34	SAP-E humanised V_L variant L0 amino acid sequence
35	SAP-E humanised V_L variant L1 amino acid sequence

36	SAP-E humanised V_L variant L2 amino acid sequence
37	SAP-K humanised V_H variant H0 amino acid sequence
38	SAP-K humanised V_H variant H1 amino acid sequence
39	SAP-K humanised V_H variant H2 amino acid sequence
40	SAP-K humanised V_H variant H3 amino acid sequence
41	SAP-K humanised V_L variant L0 amino acid sequence
42	SAP-K humanised V_L variant L1 amino acid sequence
43	Homo sapiens SAP amino acid sequence
44	Mus musculus SAP amino acid sequence
45	SAP-E VH chimera nucleotide sequence
46	SAP-E VL chimera nucleotide sequence
47	SAP-K VH chimera nucleotide sequence
48	SAP-K VL chimera nucleotide sequence
49	IGHV1-69 human variable heavy chain germline acceptor nucleotide sequence
50	IGHV1-39 human variable heavy chain germline acceptor nucleotide sequence
51	SAP-E humanised heavy chain V region variant H0 nucleotide sequence non-codon optimised
52	SAP-E humanised light chain V region variant L0 nucleotide sequence non-codon optimised
53	SAP-E humanised heavy chain V region variant H0 nucleotide sequence (codon optimised)
54	SAP-E humanised heavy chain V region variant H1 nucleotide sequence (codon optimised)
55	SAP-E humanised heavy chain V region variant H2 nucleotide sequence (codon optimised)
56	SAP-E humanised heavy chain V region variant H3 nucleotide sequence (codon optimised)
57	SAP-E humanised heavy chain V region variant H4 nucleotide sequence (codon optimised)
58	SAP-E humanised light chain V region variant L0 nucleotide sequence (codon optimised)
59	SAP-E humanised light chain V region variant L1 nucleotide sequence (codon optimised)
60	SAP-E humanised light chain V region variant L2 nucleotide sequence (codon optimised)
61	SAP-E humanised heavy chain H1 full mature nucleotide sequence (codon optimised)
62	SAP-E humanised heavy chain H1 full mature amino acid sequence

63	SAP-E humanised light chain L1 full mature nucleotide sequence (codon optimised)
64	SAP-E humanised light chain L1 full mature amino acid sequence
65	SAP-K humanised heavy chain V region variant H0 nucleotide sequence non-codon optimised
66	SAP-K humanised light chain V region variant L0 nucleotide sequence non-codon optimised
67	SAP-K humanised heavy chain V region variant H0 nucleotide sequence (codon optimised)
68	SAP-K humanised heavy chain V region variant H1 nucleotide sequence (codon optimised)
69	SAP-K humanised heavy chain V region variant H2 nucleotide sequence (codon optimised)
70	SAP-K humanised heavy chain V region variant H3 nucleotide sequence (codon optimised)
71	SAP-K humanised light chain V region variant L0 nucleotide sequence (codon optimised)
72	SAP-K humanised light chain V region variant L1 nucleotide sequence (codon optimised)
73	SAP-K humanised light chain V region variant L0 91A nucleotide sequence (codon optimised)
74	SAP-K humanised light chain V region variant L0 91A amino acid sequence
75	SAP-K humanised H3 heavy chain nucleotide sequence (codon optimised)
76	SAP-K humanised H3 heavy chain amino acid sequence
77	SAP-K humanised L0 light chain nucleotide sequence (codon optimised)
78	SAP-K humanised L0 light chain amino acid sequence
79	Signal sequence for immunoglobulin chains

CLAIMS

1. A non-murine antigen binding protein which specifically binds to SAP and competes for binding to SAP with a reference antibody which comprises a heavy chain variable region sequence of SEQ ID NO:7, and a light chain variable region sequence of SEQ ID NO:9.

2. A non-murine antigen binding protein which binds to SAP and comprises CDRH3 set forth in SEQ ID NO: 3 or a functional variant of CDRH3.

3. An antigen binding protein according to claim 2, which further comprises one or more or all CDRs selected from: CDRH1 (SEQ ID NO:1), CDRH2 (SEQ ID NO:12, CDRL1 (SEQ ID NO:4), CDRL2 (SEQ ID NO:5), and CDRL3 (SEQ ID NO:6); or a functional variant of CDRH1, CDRH2, CDRL1, CDRL2 or CDRL3.

4. An antigen binding protein according to claim 2 or 3, wherein the CDRH3 functional variant is a variant of SEQ ID NO:3 wherein Ser 102 is substituted for Tyr, His, Val, Ile, Asp or Gly.

5. An antigen binding protein according to claim 3 or 4, wherein:

(a) the CDRH1 functional variant is a variant of SEQ ID NO:1 wherein Tyr 32 is substituted for Ile, His, Phe, Thr, Asn, Cys, Glu or Asp; Asn 33 is substituted for Tyr, Ala, Trp, Gly, Thr, Leu or Val; Met 34 is substituted for Ile, Val or Trp; and/or His 35 is substituted for Glu, Asn, Gln, Ser, Tyr or Thr;

(b) the CDRH2 functional variant is a variant of SEQ ID NO:2 wherein Tyr 50 is substituted for Arg, Glu, Trp, Gly, Gln, Val, Leu, Asn, Lys or Ala; Ile51 is substituted for Leu, Val, Thr, Ser or Asn; Tyr 52 is substituted for Asp, Leu, Asn or Ser, Gly 53 is substituted for Ala, Tyr, Ser, Lys, Thr or Asn, Asp 54 is substituted for Asn, Ser, Thr, Lys or Gly; Asn 56 is substituted for Tyr, Arg, Glu, Asp, Gly, Val, Ser or Ala; and/or Asn 58 is substituted for Lys, Thr, Ser, Asp, Arg, Gly, Phe or Tyr;

(c) the CDRL1 functional variant is a variant of SEQ ID NO:4 wherein Asn 28 is substituted for Ser, Asp, Thr or Glu; Ile 29 is substituted for Val; Tyr 30 is substituted for Asp, Leu, Val, Ile, Ser, Asn, Phe, His, Gly or Thr; Ser 31 is substituted for Asn, Thr, Lys or Gly; Tyr

32 is substituted for Phe, Asn, Ala, His, Ser or Arg; Leu 33 is substituted for Met, Val, Ile or Phe; and/or Ala 34 is substituted for Gly, Asn, Ser, His, Val or Phe;

(d) the CDRL2 functional variant is a variant of SEQ ID NO:5 wherein Ala 51 is substituted for Thr, Gly or Val; and/or

(e) the CDRL3 functional variant is a variant of SEQ ID NO:6 wherein Gln 89 is substituted for Ser, Gly, Phe or Leu; His 90 is substituted for Gln or Asn; His 91 is substituted for Asn, Phe, Gly, Ser, Arg, Asp, Thr, Tyr or Val; Tyr 92 is substituted for Asn, Trp, Thr, Ser, Arg, Gln, His, Ala or Asp; Gly 93 is substituted for Glu, Asn, His, Thr, Ser, Arg or Ala; Ala 94 is substituted for Asp, Tyr, Thr, Val, Leu, His, Asn, Ile, Trp, Pro or Ser; and/or Leu 96 is substituted for Pro, Tyr, Arg, Ile, Trp or Phe.

6. An antigen binding protein which specifically binds to SAP, wherein the antigen binding protein is a chimeric or a humanised antibody comprising the corresponding CDRH3 of the variable domain sequence of SEQ ID NO:7, or a functional variant of CDRH3.

7. An antigen binding protein according to claim 6, which further comprises one or more or all of corresponding CDRs selected from CDRH1 or CDRH2 of the variable domain sequence of SEQ ID NO:7; or CDRL1, CDRL2, CDRL3 of the variable domain sequence of SEQ ID NO:9; or a functional variant of CDRH1, CDRH2, CDRL1, CDRL2 or CDRL3.

8. An antigen binding protein which specifically binds to SAP, and comprises a binding unit H3 comprising Kabat residues 95-101 of SEQ ID NO:7, or a functional variant of binding unit H3.

9. An antigen binding protein according to claim 8, which further comprises one or more or all binding units selected from: H1 comprising Kabat residues 31-32 of SEQ ID NO:7, H2 comprising Kabat residues 52-56 of SEQ ID NO:7, L1 comprising Kabat residues 30-34 of SEQ ID NO:9, L2 comprising Kabat residues 50-55 of SEQ ID NO:9; and L3 comprising Kabat residues 89-96 of SEQ ID NO:9; or a functional variant of binding unit H1, H2, L1, L2 or L3.

10. An antigen binding protein according to any one of claims 1-9, wherein the antigen binding protein comprises a heavy chain and/or a light chain wherein:

(a) the heavy chain framework comprises the following residues: Val, Ile or Gly at position 2; Leu or Val at position 4; Leu, Ile, Met or Val at position 20; Cys at position 22; Thr, Ala, Val, Gly or Ser at position 24; Gly at position 26; Ile, Phe, Leu or Ser at position 29; Trp at position 36; Trp or Tyr at position 47; Ile, Met, Val or Leu at position 48; Ile, Leu, Phe, Met or Val at position 69; Val, Ala or Leu at position 71; Ala, Leu, Val, Tyr or Phe at position 78; Leu or Met at position 80; Tyr or Phe at position 90; Cys at position 92; and/or Arg, Lys, Gly, Ser, His or Asn at position 94; and/or

(b) the light chain framework comprises the following residues: Ile, Leu or Val at position 2; Val, Gln, Leu or Glu at position 3; Met or Leu at position 4; Cys at position 23; Trp at position 35; Tyr, Leu or Phe at position 36; Leu, Arg or Val at position 46; Tyr, His, Phe or Lys at position 49; Tyr or Phe at position 71; Cys at position 88; and/or Phe at position 98.

11. An antigen binding protein according to any one of claims 1-10, wherein: the heavy chain framework comprises the following residues: Val at position 2, Leu at position 4, Val at position 20, Cys at position 22, Ala at position 24, Gly at position 26, Phe at position 29, Trp at position 36, Trp at position 47, Met at position 48, Ile at position 69, Ala at position 71, Ala at position 78, Met at position 80, Tyr at position 90, Cys at position 92, and Arg at position 94, and/or the light chain framework comprises the following residues: Ile at position 2, Gln at position 3, Met at position 4, Cys at position 23, Trp at position 35, Tyr at position 36, Leu at position 46, His at position 49, Phe at position 71, Cys at position 88, and Phe at position 98.

12. An antigen binding protein according to any one of claims 1-11, which further comprises a heavy chain variable domain antibody framework having 75% or greater sequence identity to the framework regions as shown in SEQ ID NO:25; and/or a light chain variable domain antibody framework having 75% or greater sequence identity to the framework regions as shown in SEQ ID NO:32.

13. An antigen binding protein which specifically binds to SAP and comprises a heavy chain variable region selected from SEQ ID NO:27-31; and/or a light chain variable region selected from SEQ ID NO:34-36; or a variant heavy chain variable region or light chain variable region with 75% or greater sequence identity.

14. An antigen binding protein which specifically binds to SAP and comprises a heavy chain of SEQ ID NO:62; and/or a light chain of SEQ ID NO:64; or a variant heavy chain or light chain with 75% or greater sequence identity.

15. An antigen binding protein as claimed in any one of claims 1-14, wherein the SAP is human SAP which is bound to amyloid fibrils *in vivo.*

16. An antigen binding protein as claimed in any one of claims 1-15, wherein the antigen binding protein binds to the A face of human SAP.

17. An antigen binding protein as claimed in any one of claims 1-16, wherein the antigen binding protein activates the human complement system.

18. An antigen binding protein according to any one of claims 1-5, 8, 9 or 15-17, which is chimeric, humanised, or human.

19. An antigen binding protein according to any one of the previous claims, wherein the antigen binding protein comprises a human IgG1 or IgG3 human constant domain.

20. A nucleic acid molecule which encodes an antigen binding protein as defined in any one of claims 1-19.

21. A nucleic acid molecule as claimed in claim 20, wherein the nucleic acid sequence comprises SEQ ID NO:54 and/or SEQ ID NO:59.

22. A nucleic acid molecule as claimed in claim 21, wherein the nucleic acid sequence comprises SEQ ID NO:61 and/or SEQ ID NO:63.

23. An expression vector comprising a nucleic acid molecule as defined in any one of claims 20-22.

24. A recombinant host cell comprising an expression vector as defined in claim 23.

25. A method for the production of an antigen binding protein as defined in any one of claims 1-19, which method comprises the step of culturing a host cell as defined in claim 24 and recovering the antigen binding protein.

26. A pharmaceutical composition comprising an antigen binding protein as defined in any one of claims 1-19 and a pharmaceutically acceptable carrier.

27. A method of treating a subject afflicted with a disease associated with amyloid deposition, which method comprises the step of administering to said subject a therapeutically effective amount of an antigen binding protein as defined in any one of claims 1-19 or the composition of claim 26.

28. A method of preventing a disease associated with amyloid deposition in a subject, which method comprises the step of administering to said subject a prophylactically effective amount of an antigen binding protein as defined in any one of claims 1-19 or the composition of claim 26.

29. A method according to claim 27 or 28, wherein the antigen binding protein is to be administered with a SAP depleting compound.

30. An antigen binding protein as defined in any one of claims 1-19 for use in treating or preventing a disease associated with amyloid deposition, wherein said antigen binding protein is to be administered with a SAP depleting compound.

31. A SAP depleting compound for use in treating or preventing a disease associated with amyloid deposition, wherein said SAP depleting compound is to be administered with an antigen binding protein as defined in any one of claims 1-19.

32. A method according to claim 27, 28 or 29, an antigen binding protein according to claim 29, or a SAP depleting compound according to claim 31, wherein the administration of the antigen binding protein and SAP depleting compound is sequential.

33. A method, an antigen binding protein, or a SAP depleting compound according to claim 32, wherein the SAP depleting compound is to be administered first.

34. A method, an antigen binding protein, or a SAP depleting compound according to claim 33, wherein the antigen binding protein is to be administered when substantially all of the SAP circulating in the subject has been cleared.

35. A method according to claim 27, 28, 29, 31, 33, or 34, an antigen binding protein according to claim 30, 32, 33, or 34, or a SAP antagonist compound according to claim 31, 32, 33, or 34, wherein the disease is selected from the group consisting of: systemic amyloidosis, local amyloidosis, Alzheimer's disease, type 2 diabetes, dialysis-related amyloidosis, monoclonal immunoglobulin chain (AL) amyloidosis and cerebral amyloid angiopathy.

36. A method according to claim 27, 28, 29, 32, 33, 34, or 35, an antigen binding protein according to claim 30, 32, 33, 34, or 35, or a SAP depleting compound according to claim 31, 32, 33, 34, or 35, wherein the SAP depleting compound is a D-proline derivative or a glycerol cyclic pyruvate derivative.

37. A method, antigen binding protein or SAP depleting compound according to claim 36, wherein the D-proline derivative is CPHPC.

FIGURES

Figure1

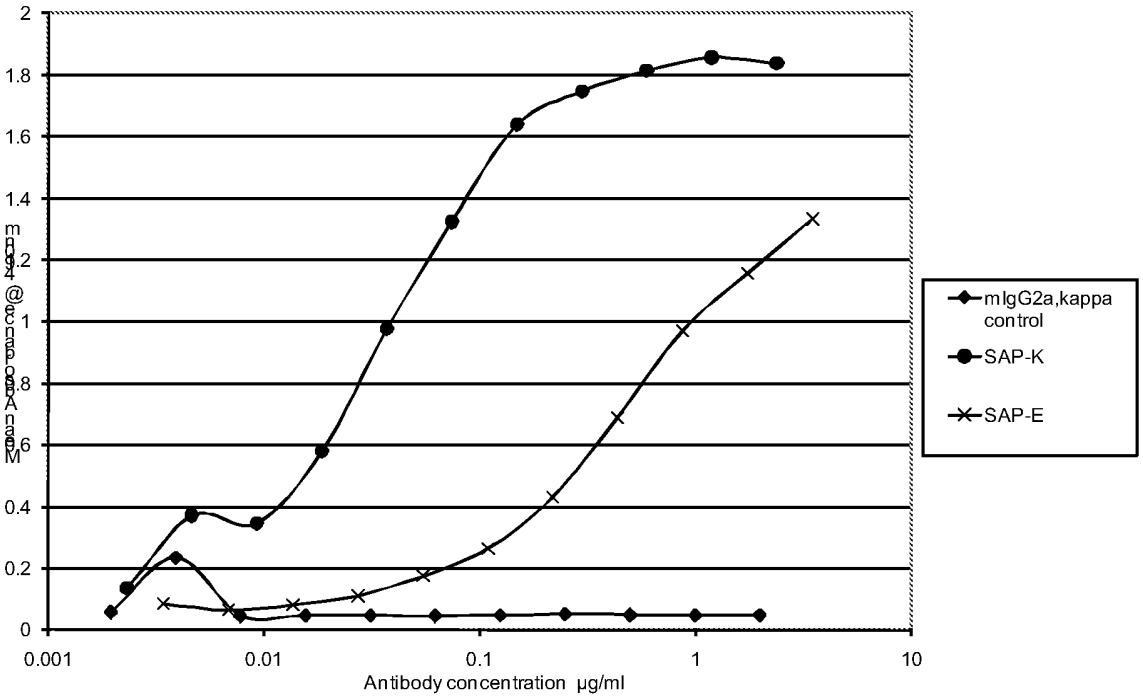


Figure 2

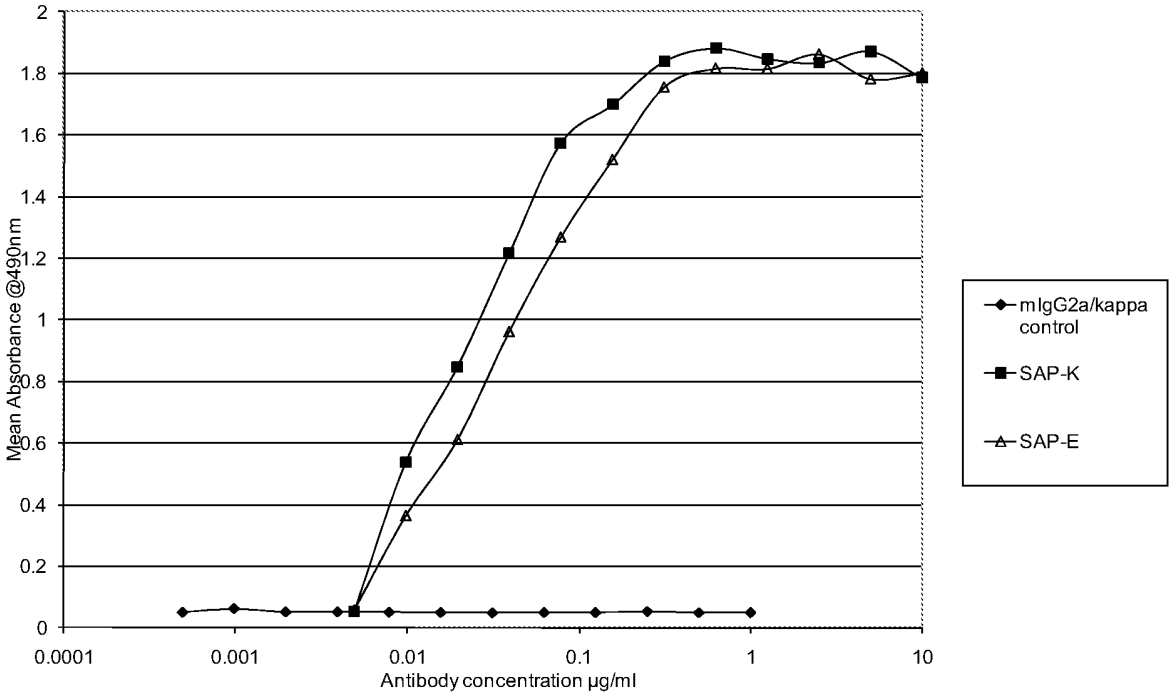


Figure 3

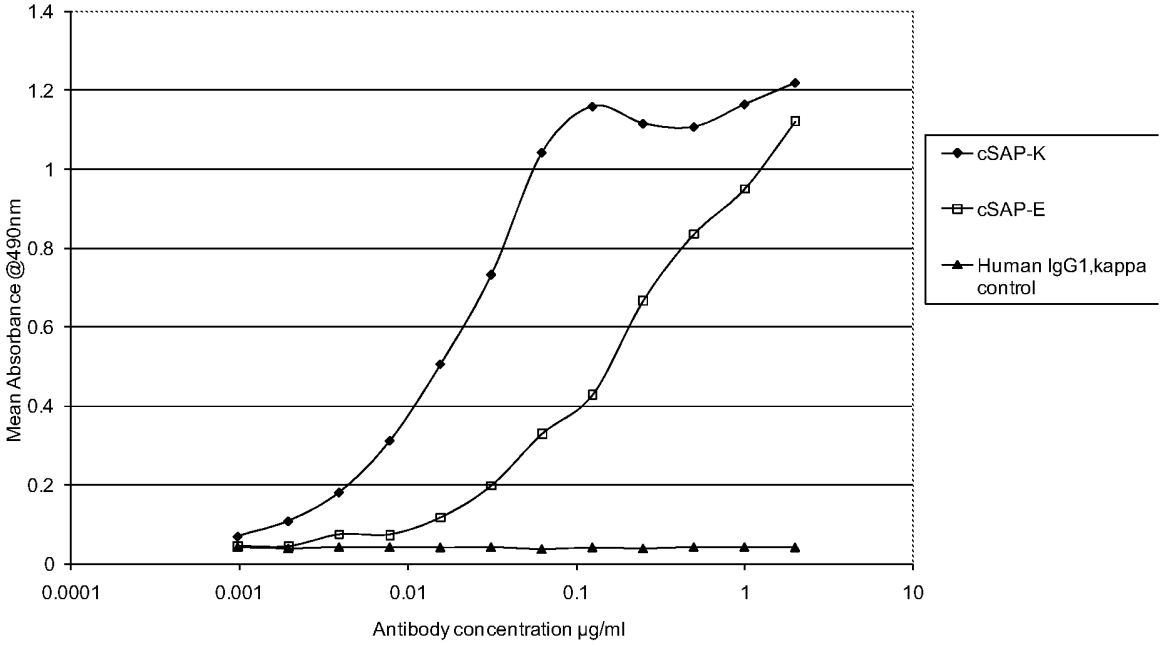


Figure 4

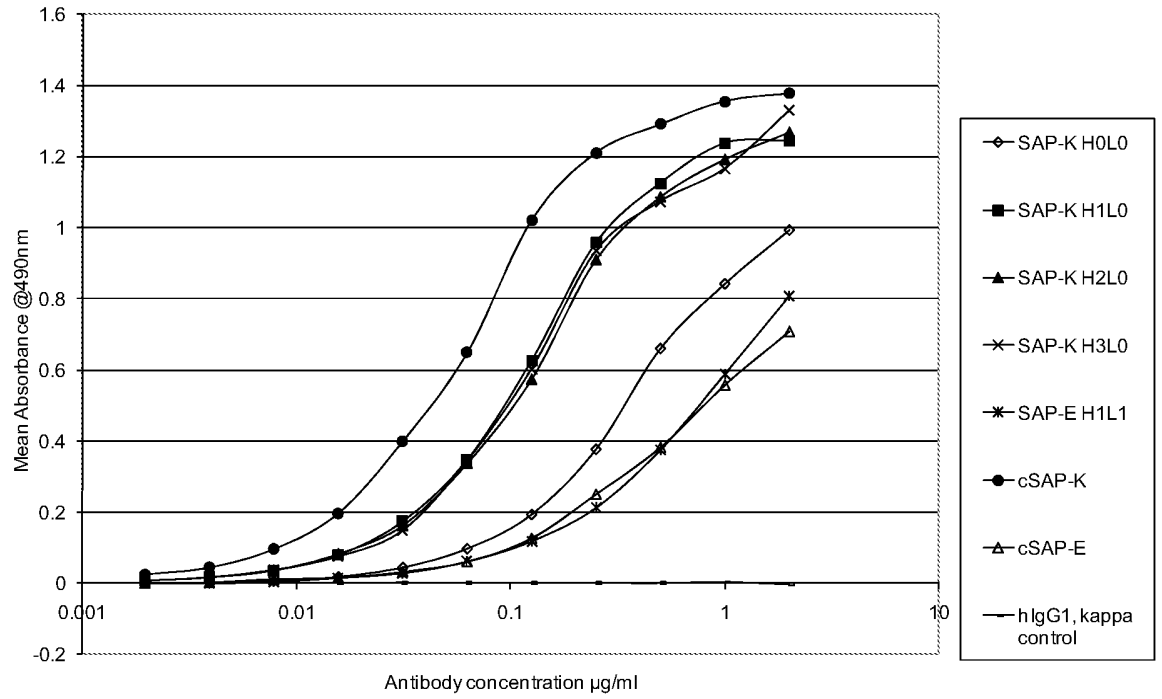


Figure 5

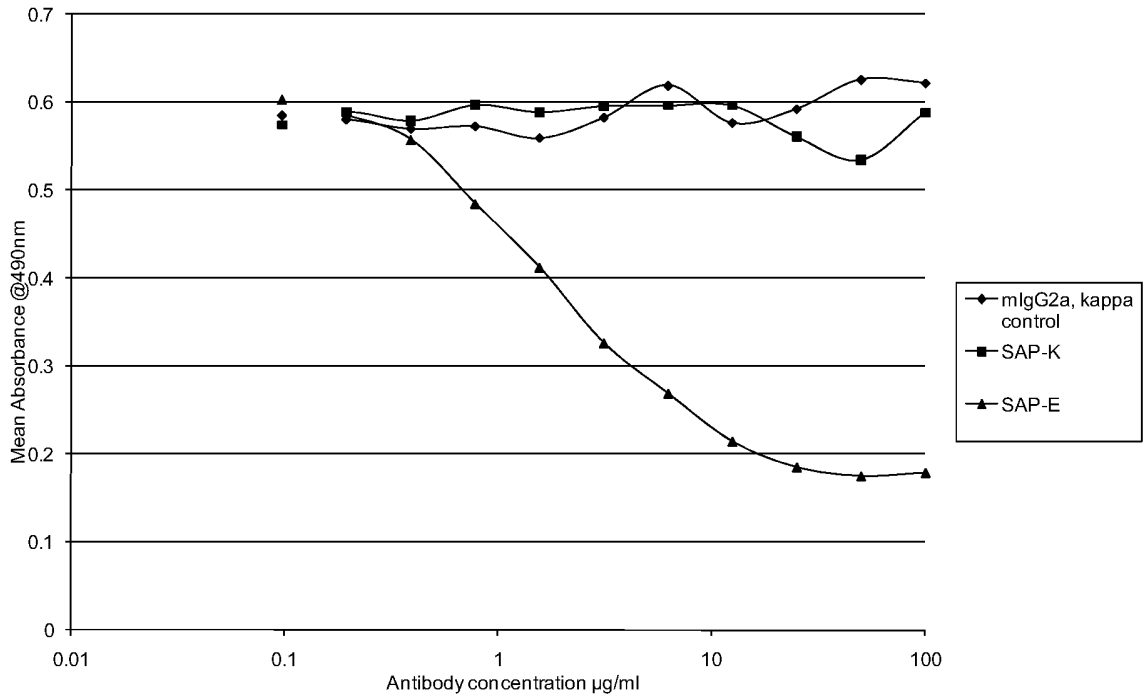


Figure 6

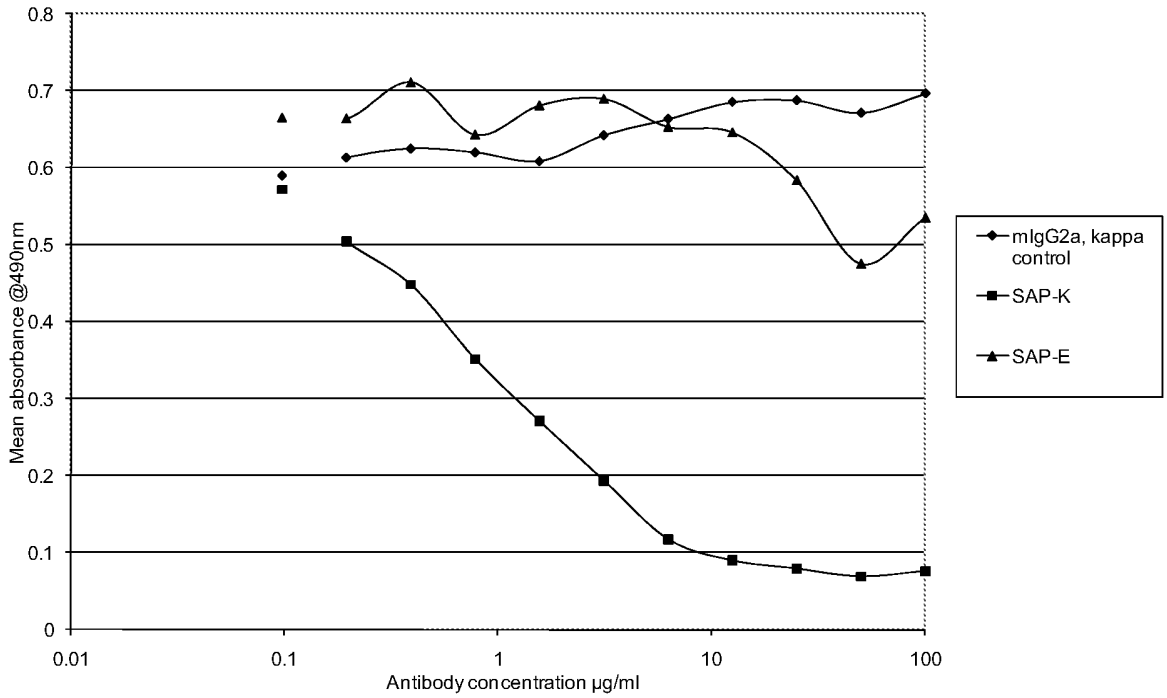
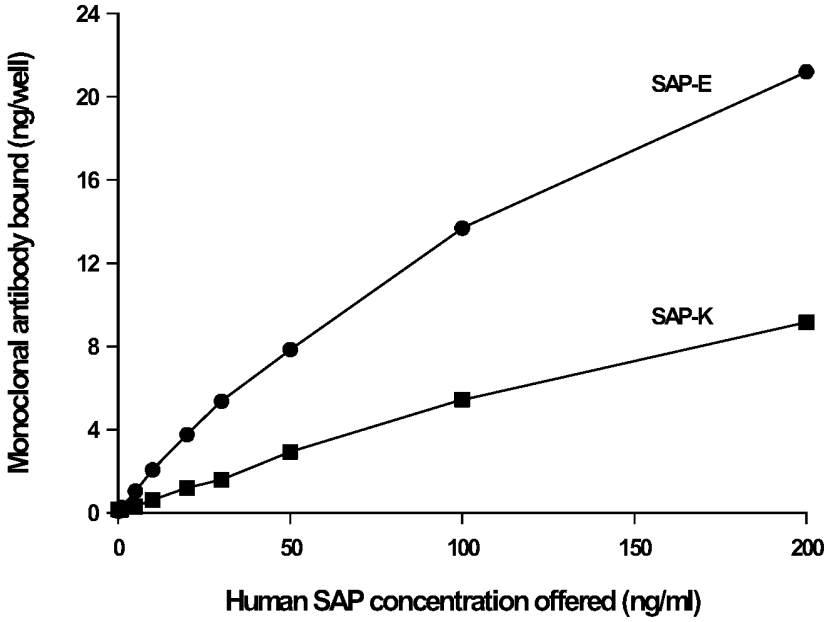
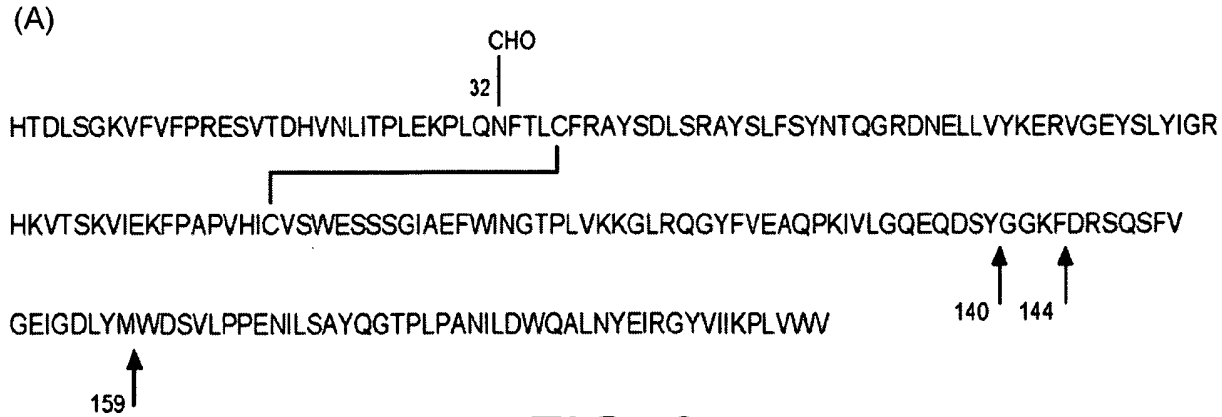


Figure 7


Monoclonal antibody bound (ng/well)
24
20
16
12
8
4
0
0
50
100
150
200
Human SAP concentration offered (ng/ml)
SAP-E
SAP-K


(A)
CHO
32
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140
144
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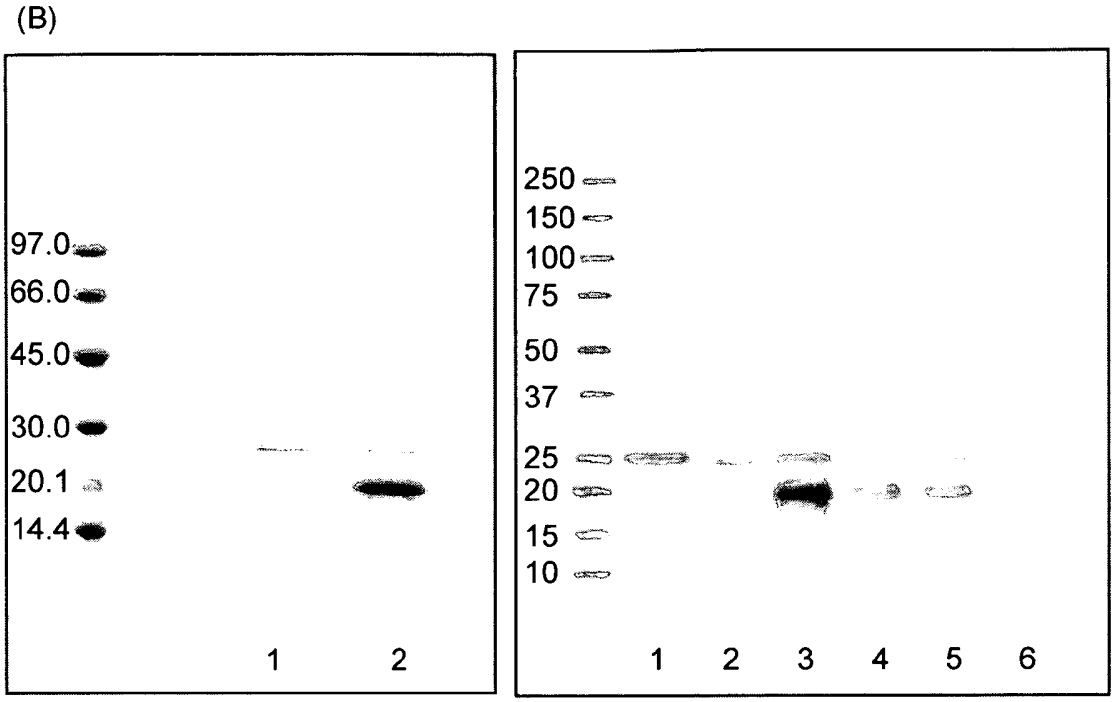
159

FIG. 8


(B)
97.0
66.0
45.0
30.0
20.1
14.4
1
2
250
150
100
75
50
37
25
20
15
10
1
2
3
4
5
6

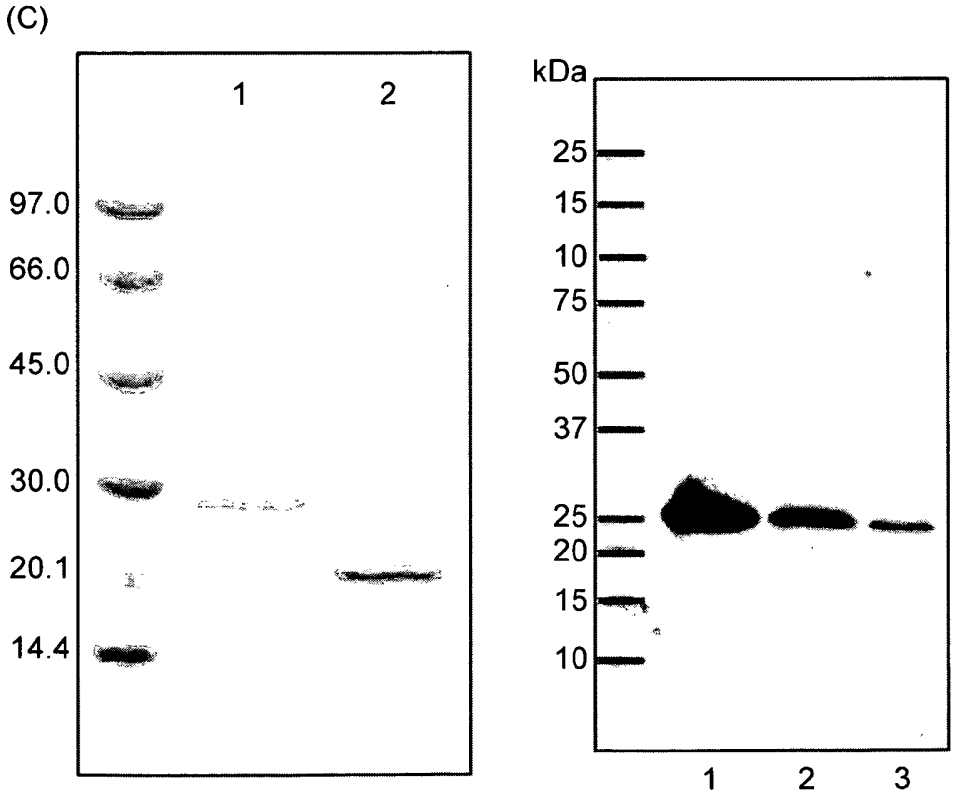

(C)
1
2
97.0
66.0
45.0
30.0
20.1
14.4
kDa
25
15
10
75
50
37
25
20
15
10
1
2
3

FIG. 8 Cont'd

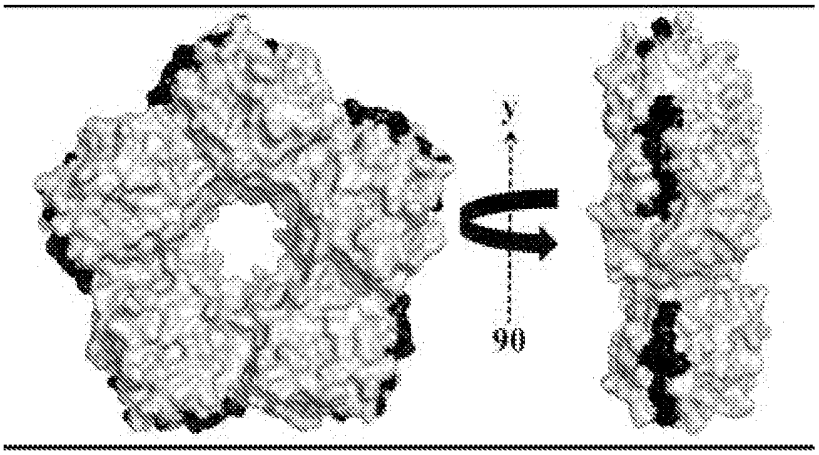
(D)

```
 136 140  147
h EQDSYGGKFDRS
m EQDNYGGGFQRS
```

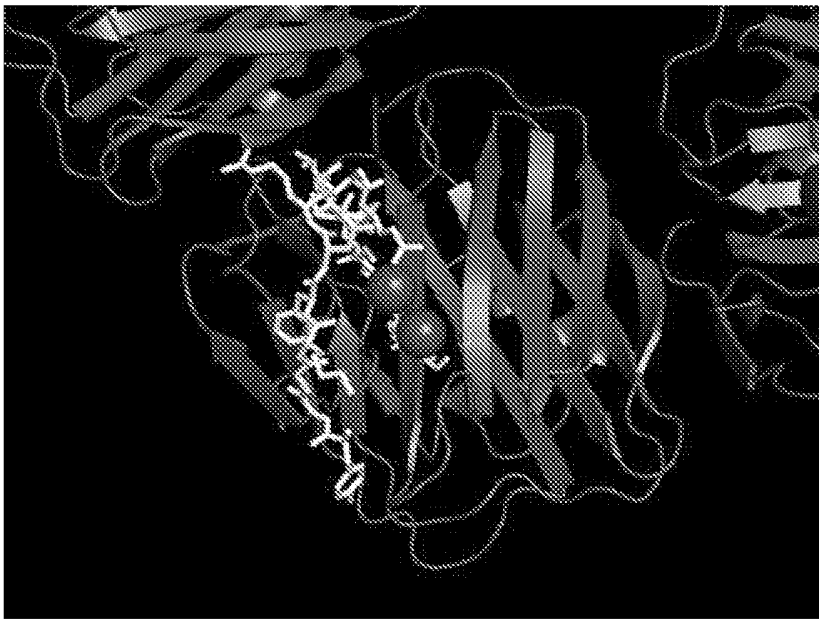
FIG. 8 Cont'd

Figure 9

(A)



(B)



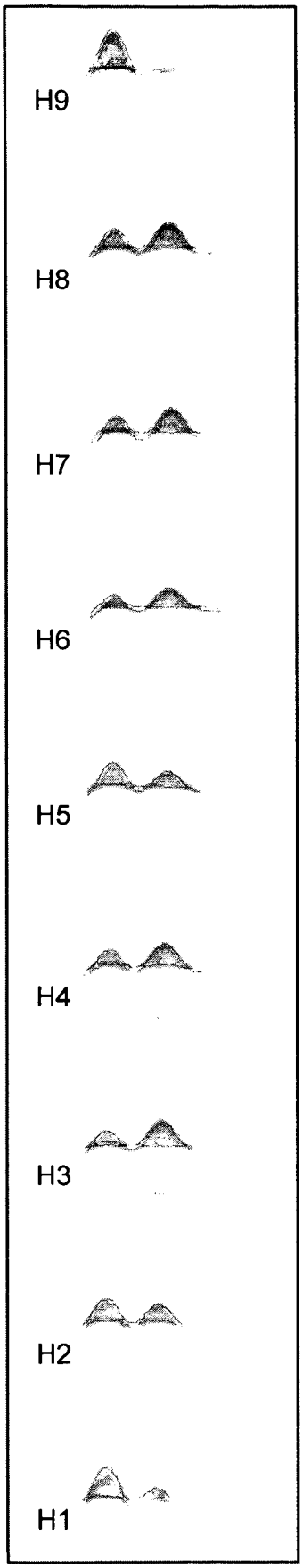


FIG. 10

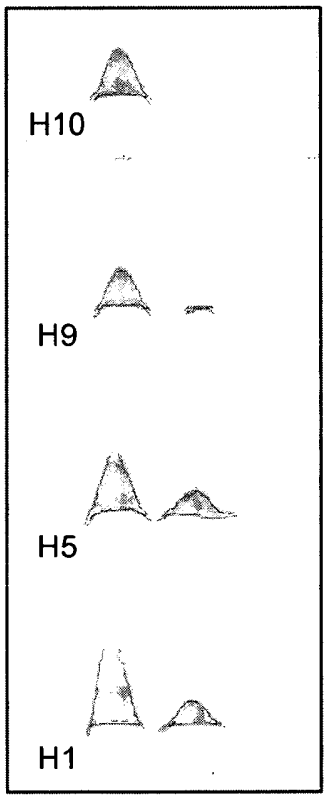
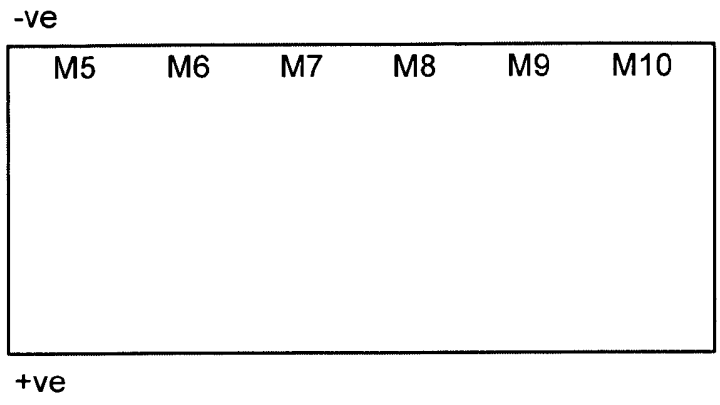
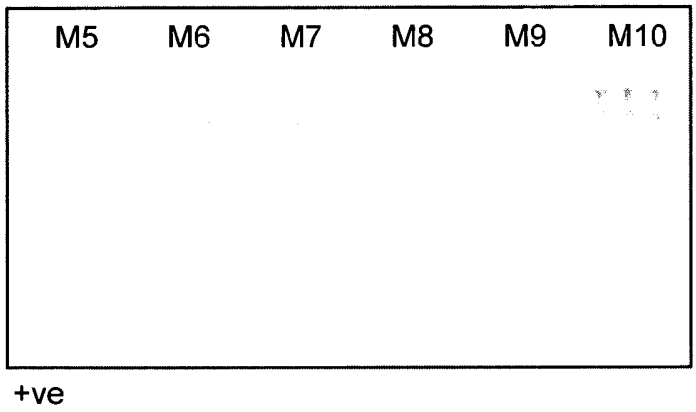


FIG. 11

(A)



(B) Immunoblot probed with anti-mouse C3 at 1:5000



(C) Immunoblot probed with anti-mouse C3 at 1:10000

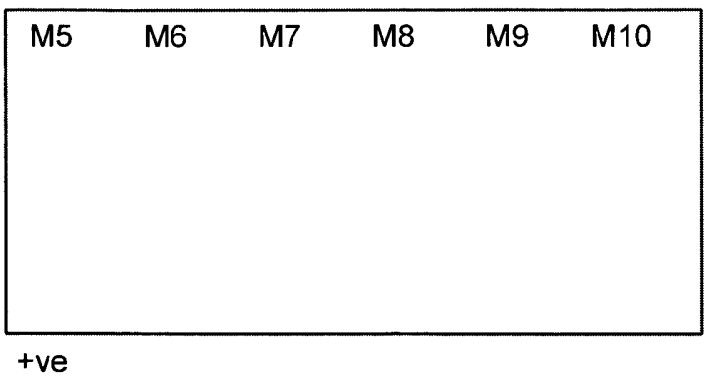


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2011/053038

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K39/395 A61P25/28 C07K16/18
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2009/155962 A1 (PENTRAXIN THERAPEUTICS LTD [GB]; PEPYS MARK BRIAN [GB]) 30 December 2009 (2009-12-30) examples 1-11	1-37
X	WO 2009/000926 A1 (PENTRAXIN THERAPEUTICS LTD [GB]; PEPYS MARK BRIAN [GB]) 31 December 2008 (2008-12-31) examples 1-8	1-37
X	WO 95/05394 A1 (ROYAL POSTGRAD MED SCHOOL [GB]; BIRKBECK COLLEGE [GB]; PEPYS MARK BRIA) 23 February 1995 (1995-02-23) example 3	1-37

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 April 2011	09/05/2011

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Cilensek, Zoran

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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US009328167B2

(12) **United States Patent**
Poulsen et al.

(10) **Patent No.: US 9,328,167 B2**
(45) **Date of Patent: *May 3, 2016**

(54) **METHODS OF TREATING CHRONIC PAIN**

(71) Applicant: **Labrys Biologics, Inc.**, Redwood City, CA (US)

(72) Inventors: **Kristian Todd Poulsen**, San Francisco, CA (US); **David Louis Shelton**, Oakland, CA (US); **Joerg Zeller**, Ann Arbor, MI (US); **Ian Machin**, Sandwich (GB); **Laura Corradini**, Sandwich (GB)

(73) Assignee: **LABRYS BIOLOGICS, INC.**, Redwood City, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **14/612,110**

(22) Filed: **Feb. 2, 2015**

(65) **Prior Publication Data**

US 2015/0307607 A1 Oct. 29, 2015

Related U.S. Application Data

(60) Continuation of application No. 13/892,121, filed on May 10, 2013, now abandoned, which is a continuation of application No. 13/623,206, filed on Sep. 20, 2012, now abandoned, which is a division of application No. 12/920,621, filed as application No. PCT/IB2009/050852 on Mar. 3, 2009, now Pat. No. 8,293,239.

(60) Provisional application No. 61/033,558, filed on Mar. 4, 2008.

(51) **Int. Cl.**

A61K 39/395	(2006.01)
C12P 21/08	(2006.01)
C07K 16/00	(2006.01)
C07K 16/26	(2006.01)
C07K 16/18	(2006.01)
A61K 45/06	(2006.01)
A61K 39/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/26*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61K 45/06*** (2013.01); ***C07K 16/18*** (2013.01); *A61K 2039/505* (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/24* (2013.01); *C07K 2317/56* (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/92* (2013.01); *C07K 2317/94* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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Primary Examiner — Christine J Saoud
Assistant Examiner — Jon M Lockard
(74) *Attorney, Agent, or Firm* — Wilson Sonsini Goodrich & Rosati

(57) **ABSTRACT**

The invention relates to an anti-CGRP antibody for use in the prevention and/or treatment of chronic pain and/or symptoms of chronic pain, and to a method of treating and/or preventing chronic pain and/or symptoms of chronic pain using an anti-CGRP antibody.

20 Claims, 10 Drawing Sheets

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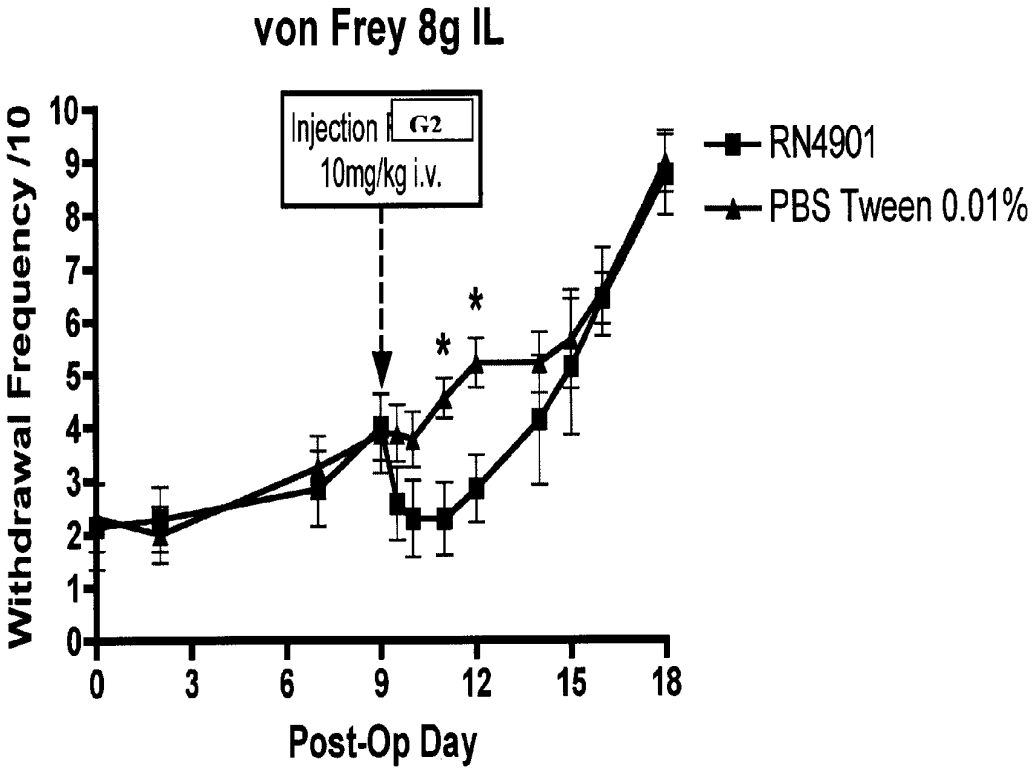
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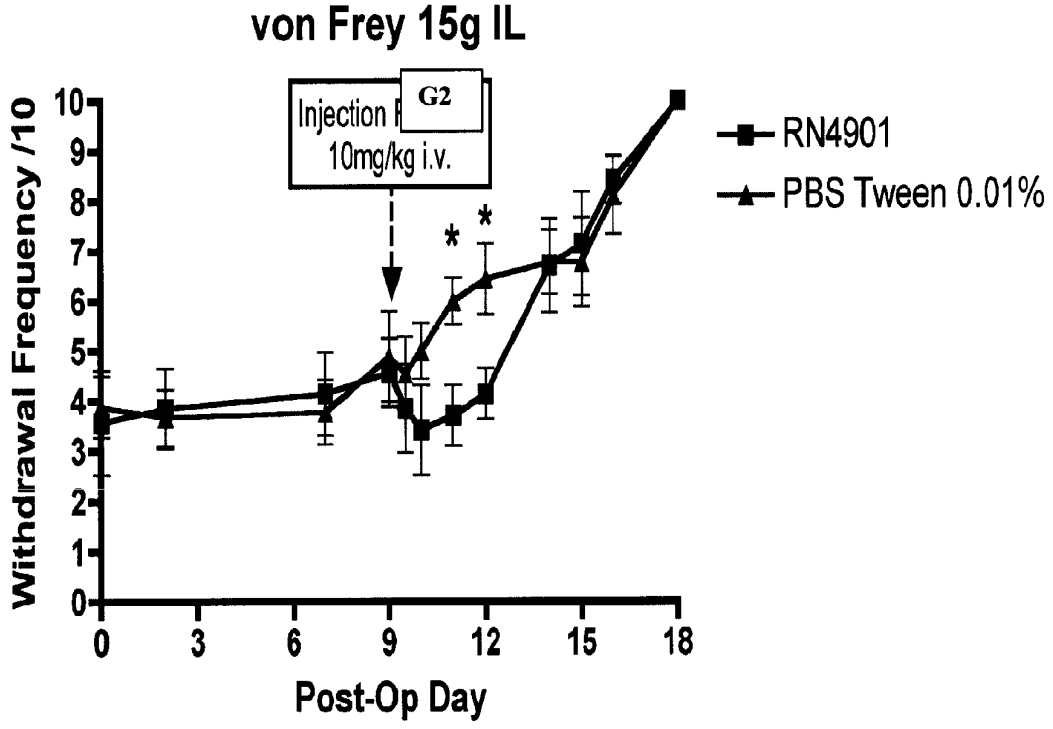
RN4901
PBS Tween 0.01%
Withdrawal Frequency /10
Post-Op Day
0
1
2
3
4
5
6
7
8
9
10
0
3
6
9
12
15
18
*
*

Figure 1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10mg/kg i.v.
G2
RN4901
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Withdrawal Frequency /10
Post-Op Day
0
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Figure 2

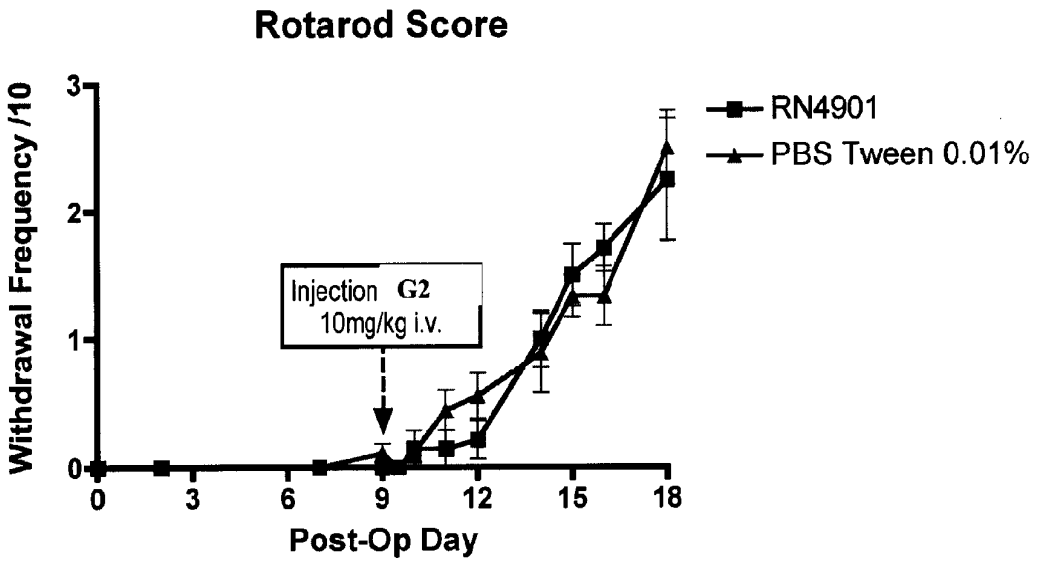
Rotarod Score
Withdrawal Frequency /10
3
2
1
0
0
3
6
9
12
15
18
Post-Op Day
Injection G2
10mg/kg i.v.
RN4901
PBS Tween 0.01%

Figure 3

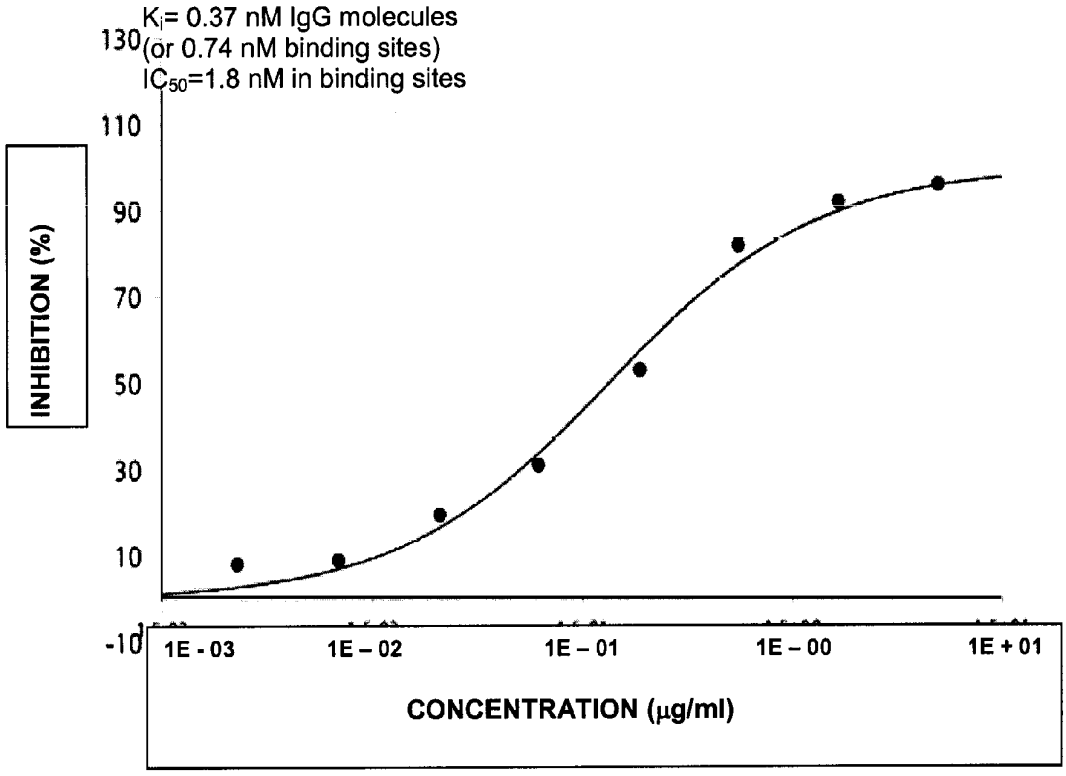
Ki= 0.37 nM IgG molecules
(or 0.74 nM binding sites)
IC50=1.8 nM in binding sites
130
110
90
70
50
30
10
-10
INHIBITION (%)
1E - 03
1E – 02
1E – 01
1E – 00
1E + 01
CONCENTRATION (µg/ml)

Figure 4:

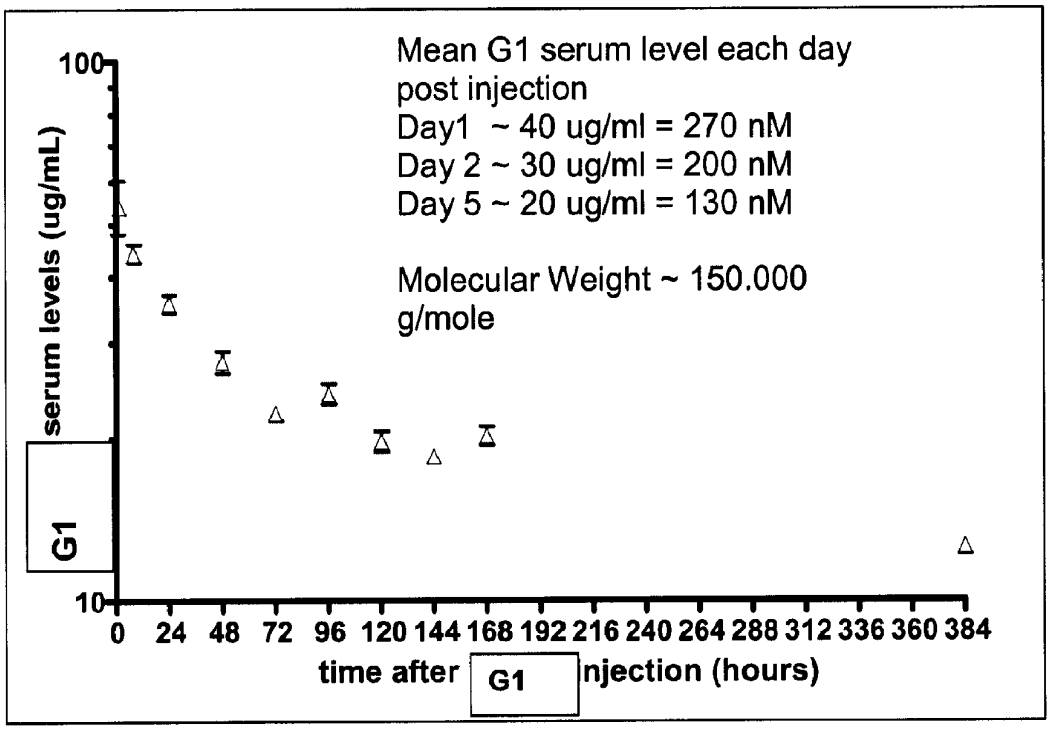
Mean G1 serum level each day post injection
Day1 ~ 40 ug/ml = 270 nM
Day 2 ~ 30 ug/ml = 200 nM
Day 5 ~ 20 ug/ml = 130 nM
Molecular Weight ~ 150.000 g/mole
serum levels (ug/mL)
100
10
G1
0 24 48 72 96 120 144 168 192 216 240 264 288 312 336 360 384
time after G1 injection (hours)

Figure 5a

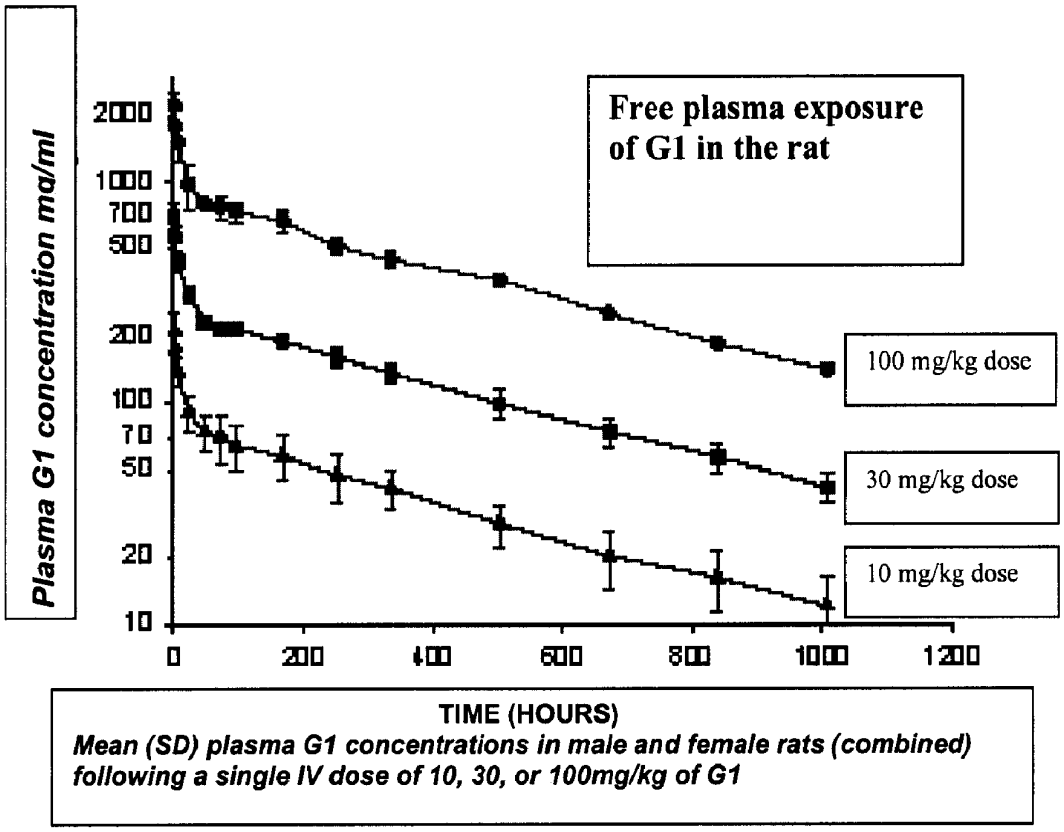
Plasma G1 concentration mg/ml
2000
1000
700
500
200
100
70
50
20
10
0
200
400
600
800
1000
1200
Free plasma exposure of G1 in the rat
100 mg/kg dose
30 mg/kg dose
10 mg/kg dose
TIME (HOURS)
Mean (SD) plasma G1 concentrations in male and female rats (combined) following a single IV dose of 10, 30, or 100mg/kg of G1

Figure 5b

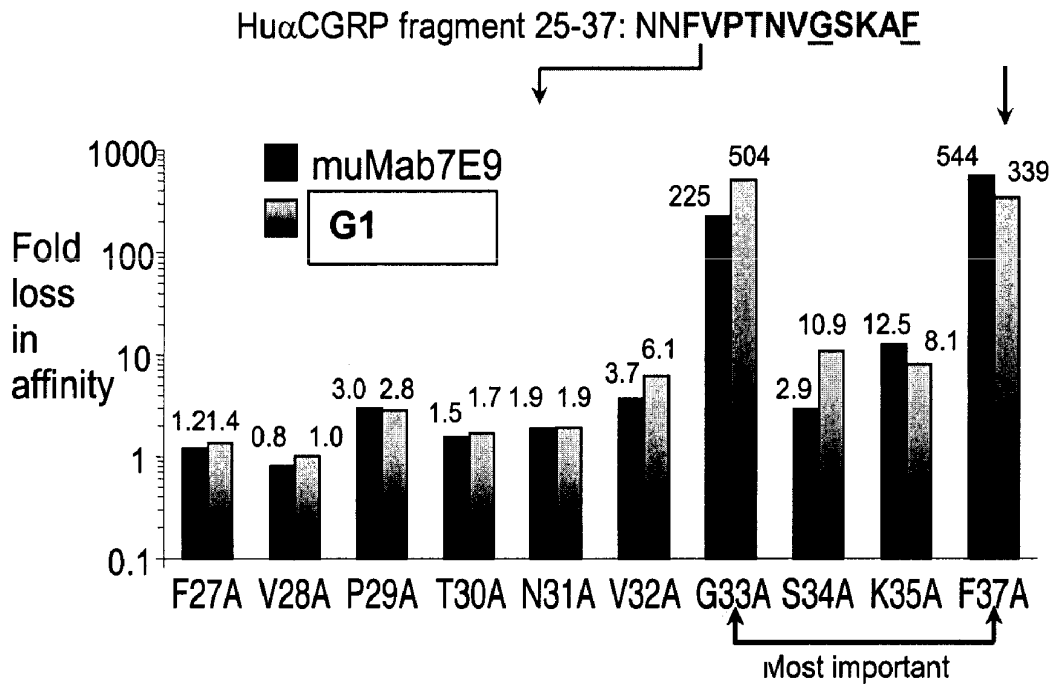
HuαCGRP fragment 25-37: NNFVPTNVGSKAF
muMab7E9
G1
Fold loss in affinity
1000
100
10
1
0.1
1.2
1.4
0.8
1.0
3.0
2.8
1.5
1.7
1.9
1.9
3.7
6.1
225
504
2.9
10.9
12.5
8.1
544
339
F27A
V28A
P29A
T30A
N31A
V32A
G33A
S34A
K35A
F37A
Most important

Figure 6

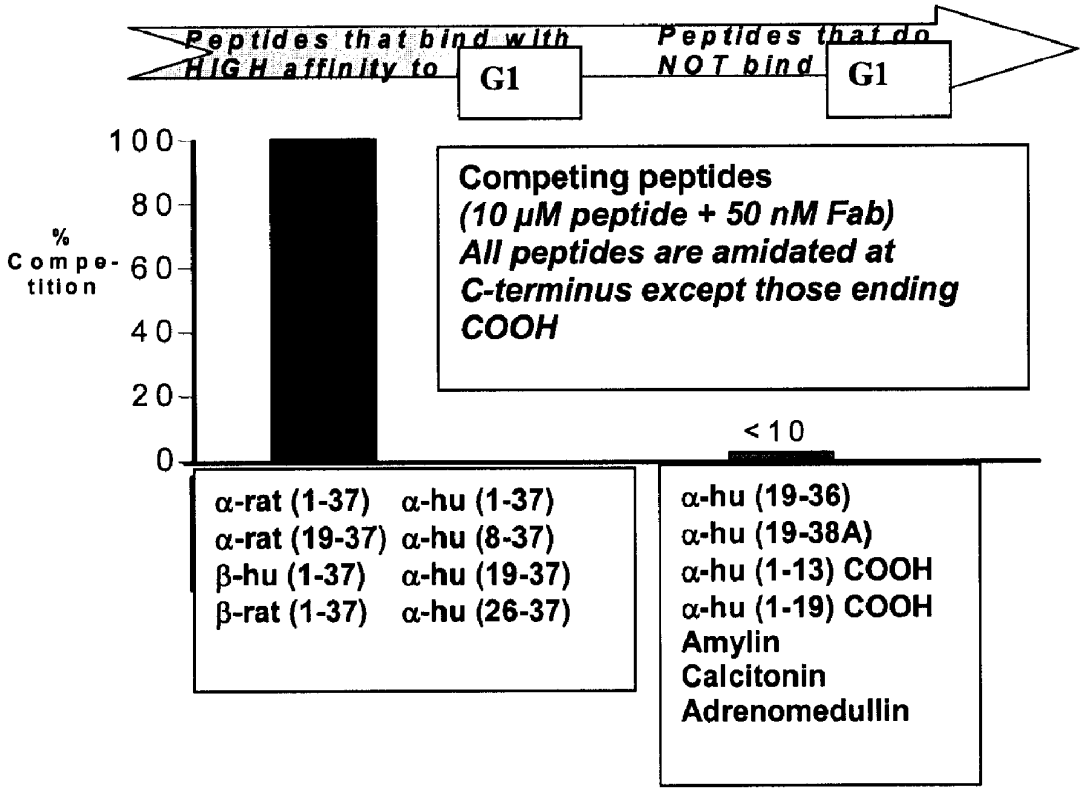
Peptides that bind with HIGH affinity to G1
Peptides that do NOT bind G1
% Competition
100
80
60
40
20
0
Competing peptides
(10 µM peptide + 50 nM Fab)
All peptides are amidated at C-terminus except those ending COOH
α-rat (1-37)
α-rat (19-37)
β-hu (1-37)
β-rat (1-37)
α-hu (1-37)
α-hu (8-37)
α-hu (19-37)
α-hu (26-37)
< 10
α-hu (19-36)
α-hu (19-38A)
α-hu (1-13) COOH
α-hu (1-19) COOH
Amylin
Calcitonin
Adrenomedullin

Figure 7

*NH2-ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNV**GSKAF**-CONH2*
Human α-CGRP (identical to *cynomolgus* α-CGRP)

*NH2-ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNV**GSKAF**-CONH2*
Human β-CGRP (identical to *cynomolgus* β-CGRP)

*NH2-SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNV**GSEAF**-CONH2*
Rat α-CGRP (identical to mouse and dog α-CGRP)

*NH2-SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNV**GSKAF**-CONH2*
Rat β-CGRP

*NH2-SCNTATCVTHRLADLLSRSGGVLKDNFVPTDV**GSEAF**-CONH2*
Mouse β-CGRP

*NH2-GCNTATCVTHRLAGLLSRSGGMVKSNFVPTNV**GSEAF**-CONH2*
Rabbit CGRP

Figure 8

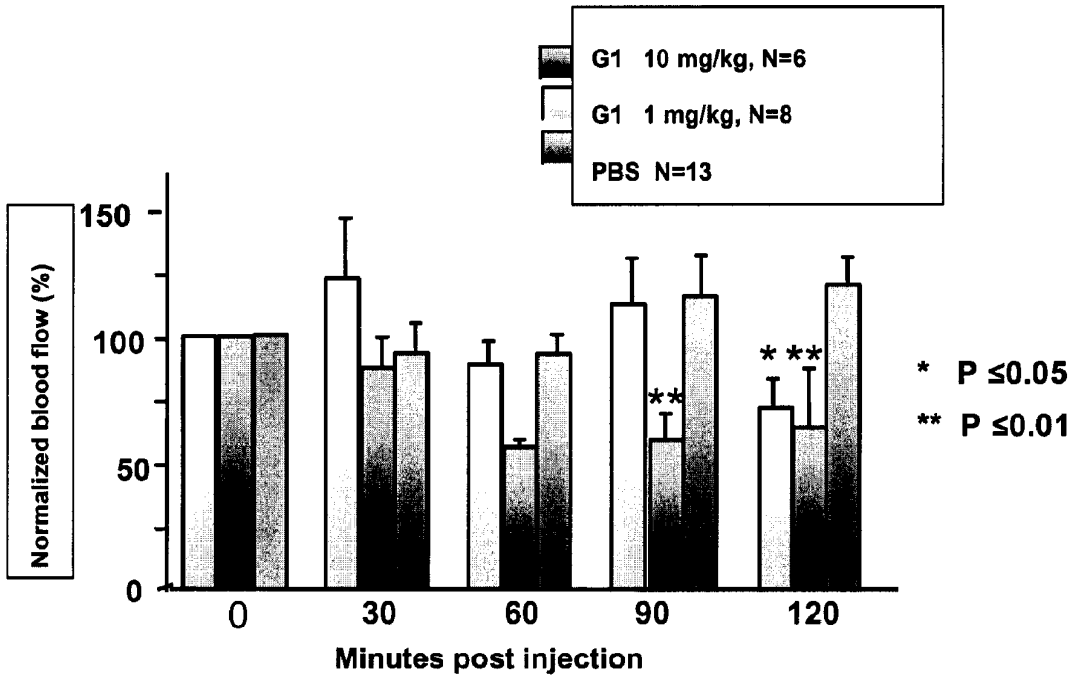
G1 10 mg/kg, N=6
G1 1 mg/kg, N=8
PBS N=13
Normalized blood flow (%)
150
100
50
0
0
30
60
90
120
Minutes post injection
* P ≤0.05
** P ≤0.01

Figure 9

METHODS OF TREATING CHRONIC PAIN

This application is a continuation of U.S. patent application Ser. No. 13/892,121 filed on May 10, 2013, now abandoned, which is a continuation of U.S. patent application Ser. No. 13/623,206 filed on Sep. 20, 2012, now abandoned, which is a divisional of U.S. patent application Ser. No. 12/920,621 (now U.S. Pat. No. 8,293,239) filed on Sep. 2, 2010, which is a National Stage Application under 35 U.S.C. §371 of PCT/IB2009/050852, filed on Mar. 3, 2009, which claims the benefit of U.S. Patent Application No. 61/033,558, filed on Mar. 4, 2008.

REFERENCE TO SEQUENCE LISTING

The instant application contains a Sequence Listing which has been submitted in ASCII format via EFS-Web and is hereby incorporated by reference in its entirety. The sequence listing contains no new matter. Said ASCII copy, created on Dec. 11, 2015, is named 44306702303USL.txt and is 28,591 bytes in size.

FIELD OF THE INVENTION

The invention relates to an anti-CGRP antibody for use in the prevention and/or treatment of chronic pain and/or symptoms of chronic pain, and to a method of treating and/or preventing chronic pain and/or symptoms of chronic pain using an anti-CGRP antibody.

BACKGROUND OF THE INVENTION

Chronic pain is a long lasting pain that persists longer than the temporal course of natural healing of the underlying causative injury or disease. It serves no beneficial or protective function and an estimated 2.7 million people in the UK are invalided due to chronic pain conditions.

Cancer pain is one of the most common types of chronic pain and demonstrates nociceptive components due to tumour growth and neuropathic components due to tumour induced nerve damage. It further involves structural damage, nerve entrapment and damage, inflammatory processes which lead to the disruption of normal tissue metabolism, the production of inflammatory prostaglandins and cytokines, and tissue damage.

To date, the main analgesics employed for treatment of chronic pain are opiates and non-steroidal anti-inflammatory drugs (NSAIDS). Both classes of drugs can produce severe side-effects; NSAIDS can cause gastric ulceration and renal damage, opiates can cause nausea, constipation, confusion and dependency problems. Opioids fail to produce pain relief in all individuals suffering chronic pain, even at high doses and development of analgesic resistance to opioids complicates their utility for long term therapy. In particular cancer pain treatment requires the use of unacceptably high levels of opiates bringing with it side-effects and at least 20% of treated patients still have uncontrolled pain.

Accordingly, there is a critical medical need to identify new pharmaceutically active compounds that interfere with key steps of the chronic pain process and particularly for the treatment and/or prevention of chronic nociceptive pain and/or symptoms of chronic nociceptive pain.

Surprisingly we have found that administration of an anti-CGRP antibody is effective, with a peripheral site of action, in the prevention and/or treatment of chronic pain and in particular chronic nociceptive pain such as cancer pain.

CGRP (calcitonin gene-related peptide) is a 37 amino acid neuropeptide which acts as a neurotransmitter in the central nervous system. It binds with high affinity to the CGRP receptor, Calcitonin receptor-like receptor (CRLR), activating adenylate cyclase and protein kinase A production.

Centrally penetrating spinally administered, small molecule selective CGRP antagonists have been shown to be useful in the treatment of neuropathic and nociceptive pain conditions (Adwanikar et al, Pain 2007) suggesting that removal of endogenous CGRP in the spinal cord has an anti-nociceptive effect. Additionally intrathecal administration of antiserum against CGRP has been shown to reduce nociceptive behaviour in rodent models of arthritis (Kuraishi, Y., et. al Neurosci. lett (1998) 92, 325-329).

Surprisingly we have found that administration of an anti-CGRP antibody is effective, with a peripheral site of action, in the prevention and/or treatment of chronic pain and in particular chronic nociceptive pain when administered peripherally. This peripheral administration route provides a distinct advantage over the requirement to administer antibodies intrathecally or spinally, a more high risk and inconvenient procedure.

BRIEF DESCRIPTION OF THE INVENTION

The present invention provides the use of an anti-CGRP antagonist antibody for the manufacture of a medicament for the prevention and/or treatment of chronic pain and/or symptoms of chronic pain, wherein the medicament is prepared to be peripherally administered.

The present invention further provides a method of prevention and/or treatment of chronic pain and/or symptoms of chronic pain, in an individual, which comprises peripherally administering to said individual a therapeutically effective amount of an anti-CGRP antagonist antibody.

In one embodiment, the anti-CGRP antagonist antibody acts peripherally on administration.

DESCRIPTION OF THE FIGURES

FIG. **1**. Effect of antibody G2 on mechanical hypersensitivity to 8 gram von Frey stimuli in a bone cancer pain model. MRMT-1 injected rats were treated with antibody G2 or vehicle (PBS+0.01% Tween20) at day 9 post surgery. Groups were healthy throughout the post-operative period at all times, shown by increasing post-operative weight gain (data not shown). Data are mean±SEM of 7-9 rats per group. *$p<0.05$ versus vehicle treated group at each time point.

FIG. **2**. Effect of antibody G2 on mechanical hypersensitivity to 15 gr von Frey stimuli in the bone cancer pain model. MRMT-1 injected rats were treated with G2 or vehicle (PBS+0.01% Tween20) at day 9 post surgery. Data are mean±SEM of 7-9 rats per group. *$p<0.05$ versus vehicle treated group at each time point.

FIG. **3**. Effect of antibody G2 on ambulation measured by rota rod. Two end points were explored. The latency to fall as measurements of compound induced impairments in motor co-ordination (A), and rota rod score, as measurements of ambulation evoked pain (B) in the bone cancer pain model. MRMT-1 injected rats were treated with antibody G2 or vehicle (PBS+0.01% Tween20) at day 9 post surgery. Data are mean±SEM of 7-9 rats per group. *$p<0.05$ versus vehicle treated group at each time point.

FIG. **4**: Binding assay data demonstrating antibody G1 inhibits the binding of α-CGRP to the CGRP1 receptor.

FIG. **5***a*: serum level of anti-CGRP concentration (ug/ml) vs time after IV administration of 10 mg/kg, measured by anti-IgG ELISA.

FIG. **5***b*: serum level of anti-CGRP concentration (ug/ml) vs time after IV administration of 10, 30, 100 mg/kg, measured by anti-IgG ELISA.

FIG. **6**: Alanine scan using a C-terminal CGRP fragment (CGRP 25-37; residues 25-37 of SEQ ID NO: 15). The change in affinity is expressed in fold loss of affinity and which shows that anti-CGRP antibody G1 binds to the C-terminal region of human α-CGRP.

FIG. **7**: Solution competition by Biacore: CGRP, CGRP fragments or peptides related in sequence to CGRP were used to determine the specificity of antibody G1.

FIG. **8**: CGRP sequences from human, cynomolgus monkey, rat, mouse, dog and rabbit. Non-conserved residues between species are underlined, the epitope of antibody G1 is in bold (SEQ ID NO: 15, 16, 17, 18, and 34-35, respectively, in order of appearance).

FIG. **9**: Data showing G1 inhibits neurogenic flare in the skin starting from 90 min post-treatment. G1 was administered by intravenous administration (1 ml/kg). Data are from 6-8 or 13 rats per group. *p=0.05, **p=0.01 vs vehicle (phosphate buffered saline) treated group at each time point (AVOVA).

Table 1: Kd and IC50 of anti-CGRP antibodies measured at 25° C. against human α-CGRP [muMab7E9=murine precursor of G1. Its K_D for rat β-CGRP=1 nM. RN4901=murine tool, recognising same epitope as G1 but showed same affinities and selectivity in rats (β-CGRP K_D=17 nM); G1=antibody humanized from muMab7E9 (K_D for rat□β□CGRP=0.1 nM).]

Table 2: G1 binding affinities as determined by Biacore

DESCRIPTION OF THE INVENTION

General Techniques

The practice of the present invention will employ, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are within the skill of the art. Such techniques are explained fully in the literature, such as, Molecular Cloning: A Laboratory Manual, second edition (Sambrook et al., 1989) Cold Spring Harbor Press; Oligonucleotide Synthesis (M. J. Gait, ed., 1984); Methods in Molecular Biology, Humana Press; Cell Biology: A Laboratory Notebook (J. E. Cellis, ed., 1998) Academic Press; Animal Cell Culture (R. I. Freshney, ed., 1987); Introduction to Cell and Tissue Culture (J. P. Mather and P. E. Roberts, 1998) Plenum Press; Cell and Tissue Culture: Laboratory Procedures (A. Doyle, J. B. Griffiths, and D. G. Newell, eds., 1993-1998) J. Wiley and Sons; Methods in Enzymology (Academic Press, Inc.); Handbook of Experimental Immunology (D. M. Weir and C. C. Blackwell, eds.); Gene Transfer Vectors for Mammalian Cells (J. M. Miller and M. P. Calos, eds., 1987); Current Protocols in Molecular Biology (F. M. Ausubel et al., eds., 1987); PCR: The Polymerase Chain Reaction, (Mullis et al., eds., 1994); Current Protocols in Immunology (J. E. Coligan et al., eds., 1991); Short Protocols in Molecular Biology (Wiley and Sons, 1999); Immunobiology (C. A. Janeway and P. Travers, 1997); Antibodies (P. Finch, 1997); Antibodies: a practical approach (D. Catty., ed., IRL Press, 1988-1989); Monoclonal antibodies: a practical approach (P. Shepherd and C. Dean, eds., Oxford University Press, 2000); Using antibodies: a laboratory manual (E. Harlow and D. Lane (Cold Spring Harbor Laboratory Press, 1999); The Antibodies (M. Zanetti and J. D. Capra, eds., Harwood Academic Publishers, 1995); and Cancer: Principles and Practice of Oncology (V. T. DeVita et al., eds., J. B. Lippincott Company, 1993).

DEFINITIONS

An "antibody" is an immunoglobulin molecule capable of specific binding to a target, such as a carbohydrate, polynucleotide, lipid, polypeptide, etc., through at least one antigen recognition site, located in the variable region of the immunoglobulin molecule. As used herein, the term encompasses not only intact polyclonal or monoclonal antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$, Fv, dAb), single chain antibodies (ScFv), mutants thereof, chimeric antibodies, diabodies, fusion proteins comprising an antibody portion, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site. An antibody includes an antibody of any class, such as IgG, IgA, or IgM (or sub-class thereof), and the antibody need not be of any particular class. Depending on the antibody amino acid sequence of the constant domain of its heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e.g., IgG1, IgG2, IgG3, IgG4, IgA1 and IgA2. The heavy-chain constant domains that correspond to the different classes of immunoglobulins are called alpha, delta, epsilon, gamma, and mu, respectively. The subunit structures and three-dimensional configurations of different classes of immunoglobulins are well known

"Fv" is an antibody fragment that contains a complete antigen-recognition and -binding site. In a two-chain Fv species, this region consists of a dimer of one heavy and one light chain variable domain in tight, non-covalent association. In a single-chain Fv species, one heavy and one light chain variable domain can be covalently linked by a flexible peptide linker such that the light and heavy chains can associate in a dimeric structure analogous to that in a two-chain Fv species. It is in this configuration that the three CDRs of each variable domain interact to define an antigen-binding specificity on the surface of the VH-VL dimer. However, even a single variable domain (or half of a Fv comprising only 3 CDRs specific for an antigen) has the ability to recognize and bind antigen, although generally at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain (CH1) of the heavy chain. Fab' fragments differ from Fab fragments by the addition of a few residues at the carboxy terminus of the heavy chain CH1 domain including one or more cysteines from the antibody hinge regions. A F(ab)2 fragment is a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region.

An antibody can have one or more binding sites (for combining with antigen). If there is more than one binding site, the binding sites may be identical to one another or may be different. For instance, a naturally-occurring immunoglobulin has two identical binding sites, a single chain antibody or Fab fragment has one binding site, while a "bispecific" or "bifunctional" antibody (diabody) has two different binding sites, in terms of sequence and/or antigen/epitope recognition.

An "isolated antibody" is an antibody that (1) is not associated with naturally-associated components, including other naturally-associated antibodies, that accompany it in its

native state, (2) is free of other proteins from the same species, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

A "monoclonal antibody" refers to a homogeneous antibody population wherein the monoclonal antibody is comprised of amino acids (naturally occurring and non-naturally occurring) that are involved in the selective binding of an antigen. A population of monoclonal antibodies is highly specific, being directed against a single antigenic site. The term "monoclonal antibody" encompasses not only intact monoclonal antibodies and full-length monoclonal antibodies, but also fragments thereof (such as Fab, Fab', $F(ab')_2$, Fv), single chain (ScFv), mutants thereof, fusion proteins comprising an antibody portion, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity and the ability to bind to an antigen. It is not intended to be limited as regards to the source of the antibody or the manner in which it is made (e.g., by hybridoma, phage selection, recombinant expression, transgenic animals, etc.).

As used herein, "humanized" antibodies refer to forms of non-human (e.g. murine) antibodies that are specific chimeric immunoglobulins, immunoglobulin chains, or fragments thereof (such as Fv, Fab, Fab', F(ab')2 or other antigen-binding subsequences of antibodies) that contain minimal sequence derived from non-human immunoglobulin. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a complementarity determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat, or rabbit having the desired specificity, affinity, and .biological activity. In some instances, Fv framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, the humanized antibody may comprise residues that are found neither in the recipient antibody nor in the imported CDR or framework sequences, but are included to further refine and optimize antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region or domain (Fc), typically that of a human immunoglobulin. Antibodies may have Fc regions modified as described in WO 99/58572. Other forms of humanized antibodies have one or more CDRs (one, two, three, four, five, six) which are altered with respect to the original antibody, which are also termed one or more CDRs "derived from" one or more CDRs from the original antibody.

As used herein, "human antibody" means an antibody having an amino acid sequence corresponding to that of an antibody produced by a human and/or has been made using any of the techniques for making human antibodies known in the art or disclosed herein. This definition of a human antibody includes antibodies comprising at least one human heavy chain polypeptide or at least one human light chain polypeptide. One such example is an antibody comprising murine light chain and human heavy chain polypeptides. Human antibodies can be produced using various techniques known in the art. In one embodiment, the human antibody is selected from a phage library, where that phage library expresses human antibodies (Vaughan et al., 1996, Nature Biotechnology, 14:309-314; Sheets et al., 1998, PNAS, (USA) 95:6157-6162; Hoogenboom and Winter, 1991, J. Mol. Biol., 227:381; Marks et al., 1991, J. Mol. Biol., 222:581). Human antibodies can also be made by introducing human immunoglobulin loci into transgenic animals, e.g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. This approach is described in U.S. Pat. Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; and 5,661,016. Alternatively, the human antibody may be prepared by immortalizing human B lymphocytes that produce an antibody directed against a target antigen (such B lymphocytes may be recovered from an individual or may have been immunized in vitro). See, e.g., Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985); Boerner et al., 1991, J. Immunol., 147 (1):86-95; and U.S. Pat. No. 5,750,373.

A single chain antibody (scFc) is an antibody in which VL and VH regions are paired to form a monovalent molecule via a synthetic linker that enables them to be made as a single protein chain (Bird et al Science, 242: 423-426 (1988) and Huston et al., Proc. Natl. Acad. Sci. USA, 85:5879-5883 (1988)).

Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites.

"Chimeric antibodies" refers to those antibodies wherein one portion of each of the amino acid sequences of heavy and light chains is homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular class, while the remaining segment of the chains is homologous to corresponding sequences in another. Typically, in these chimeric antibodies, the variable region of both light and heavy chains mimics the variable regions of antibodies derived from one species of mammals, while the constant portions are homologous to the sequences in antibodies derived from another. One clear advantage to such chimeric forms is that, for example, the variable regions can conveniently be derived from presently known sources using readily available hybridomas or B cells from non human host organisms in combination with constant regions derived from, for example, human cell preparations. While the variable region has the advantage of ease of preparation, and the specificity is not affected by its source, the constant region being human, is less likely to elicit an immune response from a human subject when the antibodies are injected than would the constant region from a non-human source. However, the definition is not limited to this particular example.

A "functional Fc region" possesses at least one effector function of a native sequence Fc region. Exemplary "effector functions" include C1q binding; complement dependent cytotoxicity (CDC); Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down-regulation of cell surface receptors (e.g. B cell receptor; BCR), etc. Such effector functions generally require the Fc region to be combined with a binding domain (e.g. an antibody variable domain) and can be assessed using various assays known in the art for evaluating such antibody effector functions.

A "native sequence Fc region" comprises an amino acid sequence identical to the amino acid sequence of an Fc region found in nature. A "variant Fc region" comprises an amino acid sequence which differs from that of a native sequence Fc region by virtue of at least one amino acid modification, yet retains at least one effector function of the native sequence Fc region. Preferably, the variant Fc region has at least one amino acid substitution compared to a native sequence Fc region or

to the Fc region of a parent polypeptide, e.g. from about one to about ten amino acid substitutions, and preferably from about one to about five amino acid substitutions in a native sequence Fc region or in the Fc region of the parent polypeptide. The variant Fc region herein will preferably possess at least about 80% sequence identity with a native sequence Fc region and/or with an Fc region of a parent polypeptide, and most preferably at least about 90% sequence identity therewith, more preferably at least about 95% sequence identity therewith.

As used herein "antibody-dependent cell-mediated cytotoxicity" and "ADCC" refer to a cell-mediated reaction in which nonspecific cytotoxic cells that express Fc receptors (FcRs) (e.g. natural killer (NK) cells, neutrophils, and macrophages) recognize bound antibody on a target cell and subsequently cause lysis of the target cell. ADCC activity of a molecule of interest can be assessed using an in vitro ADCC assay, such as that described in U.S. Pat. No. 5,500,362 or 5,821,337. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and NK cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed in vivo, e.g., in a animal model such as that disclosed in Clynes et al., 1998, PNAS (USA), 95:652-656.

As used herein, "Fc receptor" and "FcR" describe a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the FcγRI, FcγRII, and FcγRIII subclasses, including allelic variants and alternatively spliced forms of these receptors. FcγRII receptors include FcγRIIA (an "activating receptor") and FcγRIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. FcRs are reviewed in Ravetch and Kinet, 1991, Ann. Rev. Immunol., 9:457-92; Capel et al., 1994, Immunomethods, 4:25-34; and de Haas et al., 1995, J. Lab. Clin. Med., 126:330-41. "FcR" also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., 1976, J. Immunol., 117:587; and Kim et al., 1994, J. Immunol., 24:249).

"Complement dependent cytotoxicity" and "CDC" refer to the lysing of a target in the presence of complement. The complement activation pathway is initiated by the binding of the first component of the complement system (C1q) to a molecule (e.g. an antibody) complexed with a cognate antigen. To assess complement activation, a CDC assay, e.g. as described in Gazzano-Santoro et al., J. Immunol. Methods, 202:163 (1996), may be performed.

As used herein, the terms "G1" and "antibody G1" are used interchangeably to refer to an antibody produced by the expression vectors having deposit numbers ATCC-PTA-6867 and ATCC-PTA-6866. The amino acid sequence of the heavy chain and light chain variable regions are shown in SEQ ID Nos. 1 and 2. The CDR portions of antibody G1 (including Chothia and Kabat CDRs) are diagrammatically depicted in FIG. 5 of WO2007/054809, the content of which is herein incorporated by reference in its entirety.

The polynucleotides encoding the heavy and light chain variable regions are shown in SEQ ID Nos., 9 and 10. The characterization of antibody G1 is described in the Examples of WO2007/054809, the entire content of which is herein incorporated by reference. G1 is a humanized monoclonal blocking antibody (IgG2) which blocks binding and activity of the neuropeptide CGRP (a and b) and its effect of neurogenic vasodilatation caused by CGRP release. G1 is an IgG2Δa monoclonal anti-CGRP antagonist antibody derived from the murine anti-CGRP antagonist antibody precursor, denoted muMAb7E9 as identified in a screen using spleen cells prepared from a mouse immunized with human and rat CGRP that were fused with murine plasmacytoma cells. G1 was created by grafting the muMAb 7E9 derived CDRs of light and heavy chain into the closest human germ line sequence followed by the introduction of at least 1 mutation into each CDR and 2 framework mutations in V_H. Two mutations were introduced into the Fc domain of G1 to suppress human Fc-receptor activation. G1 and muMab7E9 have been shown to recognise the same epitope.

As used herein, the terms "G2" and "antibody G2" are used interchangeably to refer to an anti-rat CGRP mouse monoclonal antibody as described in Wong H C et al. Hybridoma 12:93-106 (1993). The amino acid sequence of the heavy chain and light chain variable regions are shown in SEQ ID Nos. 19 and 20. The polynucleotides encoding the heavy and light chain variable regions are shown in SEQ ID Nos. 27 and 28. The CDR portions of antibody G2 are provided in SEQ ID Nos. 21 to 26. G2 has been shown to recognise the same epitope as G1.

As used herein, "immunospecific" binding of antibodies refers to the antigen specific binding interaction that occurs between the antigen-combining site of an antibody and the specific antigen recognized by that antibody (i.e., the antibody reacts with the protein in an ELISA or other immunoassay, and does not react detectably with unrelated proteins).

An epitope that "specifically binds", or "preferentially binds" (used interchangeably herein) to an antibody or a polypeptide is a term well understood in the art, and methods to determine such specific or preferential binding are also well known in the art. A molecule is said to exhibit "specific binding" or "preferential binding" if it reacts or associates more frequently, more rapidly, with greater duration and/or with greater affinity with a particular cell or substance than it does with alternative cells or substances. An antibody "specifically binds" or "preferentially binds" to a target if it binds with greater affinity, avidity, more readily, and/or with greater duration than it binds to other substances. It is also understood by reading this definition that, for example, an antibody (or moiety or epitope) that specifically or preferentially binds to a first target may or may not specifically or preferentially bind to a second target. As such, "specific binding" or "preferential binding" does not necessarily require (although it can include) exclusive binding. Generally, but not necessarily, reference to binding means preferential binding.

The terms "polypeptide", "oligopeptide", "peptide" and "protein" are used interchangeably herein to refer to polymers of amino acids of any length. The polymer may be linear or branched, it may comprise modified amino acids, and it may be interrupted by non-amino acids. The terms also encompass an amino acid polymer that has been modified naturally or by intervention; for example, disulfide bond formation, glycosylation, lipidation, acetylation, phosphorylation, or any other manipulation or modification, such as conjugation with a labeling component. Also included within the definition are, for example, polypeptides containing one or more analogs of an amino acid (including, for example, unnatural amino acids, etc.), as well as other modifications known in the art. It is understood that, because the polypeptides of this invention are based upon an antibody, the polypeptides can occur as single chains or associated chains.

"Polynucleotide," or "nucleic acid," as used interchangeably herein, refer to polymers of nucleotides of any length, and include DNA and RNA. The nucleotides can be deoxyribonucleotides, ribonucleotides, modified nucleotides or bases, and/or their analogs, or any substrate that can be incor-

porated into a polymer by DNA or RNA polymerase. A polynucleotide may comprise modified nucleotides, such as methylated nucleotides and their analogs. If present, modification to the nucleotide structure may be imparted before or after assembly of the polymer. The sequence of nucleotides may be interrupted by non-nucleotide components. A polynucleotide may be further modified after polymerization, such as by conjugation with a labeling component. Other types of modifications include, for example, "caps", substitution of one or more of the naturally occurring nucleotides with an analog, internucleotide modifications such as, for example, those with uncharged linkages (e.g., methyl phosphonates, phosphotriesters, phosphoamidates, cabamates, etc.) and with charged linkages (e.g., phosphorothioates, phosphorodithioates, etc.), those containing pendant moieties, such as, for example, proteins (e.g., nucleases, toxins, antibodies, signal peptides, ply-L-lysine, etc.), those with intercalators (e.g., acridine, psoralen, etc.), those containing chelators (e.g., metals, radioactive metals, boron, oxidative metals, etc.), those containing alkylators, those with modified linkages (e.g., alpha anomeric nucleic acids, etc.), as well as unmodified forms of the polynucleotide(s). Further, any of the hydroxyl groups ordinarily present in the sugars may be replaced, for example, by phosphonate groups, phosphate groups, protected by standard protecting groups, or activated to prepare additional linkages to additional nucleotides, or may be conjugated to solid supports. The 5' and 3' terminal OH can be phosphorylated or substituted with amines or organic capping groups moieties of from 1 to 20 carbon atoms. Other hydroxyls may also be derivatized to standard protecting groups. Polynucleotides can also contain analogous forms of ribose or deoxyribose sugars that are generally known in the art, including, for example, 2'-O-methyl-, 2'-O-allyl, 2'-fluoro- or 2'-azido-ribose, carbocyclic sugar analogs, α-anomeric sugars, epimeric sugars such as arabinose, xyloses or lyxoses, pyranose sugars, furanose sugars, sedoheptuloses, acyclic analogs and abasic nucleoside analogs such as methyl riboside. One or more phosphodiester linkages may be replaced by alternative linking groups. These alternative linking groups include, but are not limited to, embodiments wherein phosphate is replaced by P(O)S("thioate"), P(S)S ("dithioate"), "(O)NR_2 ("amidate"), P(O)R, P(O)OR', CO or CH_2 ("formacetal"), in which each R or R' is independently H or substituted or unsubstituted alkyl (1-20 C) optionally containing an ether (—O—) linkage, aryl, alkenyl, cycloalkyl, cycloalkenyl or araldyl. Not all linkages in a polynucleotide need be identical. The preceding description applies to all polynucleotides referred to herein, including RNA and DNA.

A "variable region" of an antibody refers to the variable region of the antibody light chain or the variable region of the antibody heavy chain, either alone or in combination. The variable regions of the heavy and light chain each consist of four framework regions (FR) connected by three complementarity determining regions (CDRs) also known as hypervariable regions. The CDRs in each chain are held together in close proximity by the FRs and, with the CDRs from the other chain, contribute to the formation of the antigen-binding site of antibodies. There are at least two techniques for determining CDRs: (1) an approach based on cross-species sequence variability (i.e., Kabat et al. Sequences of Proteins of Immunological Interest, (5th ed., 1991, National Institutes of Health, Bethesda Md.)); and (2) an approach based on crystallographic studies of antigen-antibody complexes (Chothia et al. (1989) Nature 342:877; Al-Lazikani et al (1997) J. Molec. Biol. 273:927-948)). As used herein, a CDR may refer to CDRs defined by either approach or by a combination of both approaches.

A "constant region" of an antibody refers to the constant region of the antibody light chain or the constant region of the antibody heavy chain, either alone or in combination.

As used herein, an "anti-CGRP antagonist antibody" (interchangeably termed "anti-CGRP antibody") refers to an antibody which is able to bind to CGRP and inhibit CGRP biological activity and/or downstream pathway(s). An anti-CGRP antagonist antibody encompasses antibodies that block, antagonize, suppress or reduce (including significantly) CGRP biological activity. For purpose of the present invention, it will be explicitly understood that the term "anti-CGRP antagonist antibody" encompass all the previously identified terms, titles, and functional states and characteristics whereby the CGRP itself, a CGRP biological activity, or the consequences of the biological activity, are substantially nullified, decreased, or neutralized in any meaningful degree. Examples of anti-CGRP antagonist antibodies are provided herein.

As used herein, "substantially pure" refers to material which is at least 50% pure (i.e., free from contaminants), more preferably at least 90% pure, more preferably at least 95% pure, more preferably at least 98% pure, more preferably at least 99% pure.

A "host cell" includes an individual cell or cell culture that can be or has been a recipient for vector(s) for incorporation of polynucleotide inserts. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in morphology or in genomic DNA complement) to the original parent cell due to natural, accidental, or deliberate mutation. A host cell includes cells transfected in vivo with a polynucleotide(s) of this invention.

As used herein, "treatment" is an approach for obtaining beneficial or desired clinical results. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: improvement or alleviation of any aspect of chronic pain and/or symptom of chronic pain. For purposes of this invention, beneficial or desired clinical results include, but are not limited to, one or more of the following: including lessening severity, alleviation of pain and/or a symptom associated with chronic pain.

An "effective amount" of drug, compound, or pharmaceutical composition is an amount sufficient to effect beneficial or desired results including clinical results such as alleviation or reduction in pain sensation. An effective amount can be administered in one or more administrations. For purposes of this invention, an effective amount of drug, compound, or pharmaceutical composition is an amount sufficient to treat, ameliorate, reduce the intensity of and/or prevent chronic pain or symptom associated with chronic pain. As is understood in the clinical context, an effective amount of a drug, compound, or pharmaceutical composition may or may not be achieved in conjunction with another drug, compound, or pharmaceutical composition. Thus, an "effective amount" may be considered in the context of administering one or more therapeutic agents, and a single agent may be considered to be given in an effective amount if, in conjunction with one or more other agents, a desirable result may be or is achieved.

In one embodiment, "prepared for" herein means the medicament is in the form of a dosage unit or the like suitably packaged and/or marked for use in peripheral administration.

"Reducing incidence" of chronic pain and/or a symptom associated with chronic pain means any of reducing severity (which can include reducing need for and/or amount of (e.g.,

exposure to) other drugs and/or therapies generally used for these conditions), duration, and/or frequency.

"Ameliorating" chronic pain and/or a symptom associated with chronic pain means a lessening or improvement of one or more symptoms of chronic pain and/or symptoms associated with chronic pain as compared to not administering an anti-CGRP antagonist antibody. "Ameliorating" also includes shortening or reduction in duration of a symptom.

"Palliating" chronic pain and/or a symptom associated with chronic pain means lessening the extent of one or more undesirable clinical manifestations of chronic pain in an individual or population of individuals treated with an anti-CGRP antagonist antibody in accordance with the invention.

As used therein, "delaying" the development of chronic pain means to defer, hinder, slow, retard, stabilize, and/or postpone progression of chronic pain and/or a symptom associated with chronic pain. This delay can be of varying lengths of time, depending on the history of the disease and/or individuals being treated. As is evident to one skilled in the art, a sufficient or significant delay can, in effect, encompass prevention, in that the individual does not develop chronic pain. A method that "delays" development of the symptom is a method that reduces probability of developing the symptom in a given time frame and/or reduces extent of the symptoms in a given time frame, when compared to not using the method. Such comparisons are typically based on clinical studies, using a statistically significant number of subjects.

A "biological sample" encompasses a variety of sample types obtained from an individual and can be used in a diagnostic or monitoring assay. The definition encompasses blood and other liquid samples of biological origin, solid tissue samples such as a biopsy specimen or tissue cultures or cells derived therefrom, and the progeny thereof. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as proteins or polynucleotides, or embedding in a semi-solid or solid matrix for sectioning purposes. The term "biological sample" encompasses a clinical sample, and also includes cells in culture, cell supernatants, cell lysates, serum, plasma, biological fluid, and tissue samples.

An "individual" or "subject" is a vertebrate, preferably a mammal, more preferably a human. Mammals include, but are not limited to, farm animals (such as cows), sport animals, pets (such as cats, dogs and horses), primates, mice and rats.

As used herein, "vector" means a construct, which is capable of delivering, and preferably expressing, one or more gene(s) or sequence(s) of interest in a host cell. Examples of vectors include, but are not limited to, viral vectors, naked DNA or RNA expression vectors, plasmid, cosmid or phage vectors, DNA or RNA expression vectors associated with cationic condensing agents, DNA or RNA expression vectors encapsulated in liposomes, and certain eukaryotic cells, such as producer cells.

As used herein, "expression control sequence" means a nucleic acid sequence that directs transcription of a nucleic acid. An expression control sequence can be a promoter, such as a constitutive or an inducible promoter, or an enhancer. The expression control sequence is operably linked to the nucleic acid sequence to be transcribed.

As used herein, "pharmaceutically acceptable carrier" includes any material which, when combined with an active ingredient, allows the ingredient to retain biological activity and is non-reactive with the subject's immune system. Examples include, but are not limited to, any of the standard pharmaceutical carriers such as a phosphate buffered saline solution, water, emulsions such as oil/water emulsion, and various types of wetting agents. Preferred diluents for aerosol or parenteral administration are phosphate buffered saline or normal (0.9%) saline. Compositions comprising such carriers are formulated by well known conventional methods (see, for example, Remington's Pharmaceutical Sciences, 18th edition, A. Gennaro, ed., Mack Publishing Co., Easton, Pa., 1990; and Remington, The Science and Practice of Pharmacy 20th Ed. Mack Publishing, 2000).

The term "peripherally administered" as used herein refers to the route by which the a substance, medicament and/or anti-CGRP antagonist antibody is to be delivered, in particular it means not centrally, not spinally, not intrathecally, not delivered directly into the CNS. The term refers to administration routes other than those immediately forgoing and includes via a route which is oral, sublingual, buccal, topical, rectal, via inhalation, transdermal, subcutaneous, intravenous, intra-arterial, intramuscular, intracardiac, intraosseous, intradermal, intraperitoneal, transmucosal, vaginal, intravitreal, intra-articular, peri-articular, local or epicutaneous.

The term "acts peripherally" as used herein refers to the site of action of a substance, compound, medicament and/or anti-CGRP antagonist antibody said site being within the peripheral nervous system as opposed to the central nervous system, said compound, medicament and/or anti-CGRP antagonist antibody said being limited by inability to cross the barrier to the CNS and brain when peripherally administered. The term "centrally penetrating" refers to the ability of a substance to cross the barrier to the brain or CNS.

The term "K_{off}", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "K_d", as used herein, is intended to refer to the dissociation constant of an antibody-antigen interaction.

The present invention is directed to a medicament for the prevention and/or treatment of chronic pain and/or symptoms of chronic pain and methods for prevention and/or treatment of chronic pain and/or symptoms of chronic pain in an individual.

In a first aspect, the invention provides the use of an anti-CGRP antagonist antibody for the manufacture of a medicament for the prevention and/or treatment of chronic pain and/or symptoms of chronic pain, wherein the medicament is prepared for peripheral administration or wherein the medicament is administered peripherally.

In a second aspect, the invention provides an anti-CGRP antagonist antibody for use in the prevention and/or treatment of chronic pain and/or symptoms of chronic pain wherein the antibody is prepared for peripheral administration or wherein the antibody is administered peripherally.

In third aspect, the invention provides the use of an anti-CGRP antagonist antibody for the manufacture of a medicament for ameliorating, controlling, reducing incidence of, or delaying the development or progression of chronic pain and/or symptoms of chronic pain, wherein the medicament is prepared for peripheral administration or wherein the medicament is administered peripherally.

In a fourth aspect, the invention provides a method of preventing and/or treating chronic pain and/or symptoms of chronic pain in an individual, comprising peripheral administration to the individual of an effective amount of an anti-CGRP antagonist antibody.

In a fifth aspect, the invention provides a method of ameliorating, controlling, reducing incidence of, or delaying the development or progression of chronic pain and/or symptoms of chronic pain in an individual, comprising peripheral administration to the individual of an effective amount of an anti-CGRP antagonist antibody.

According to a preferred embodiment of the present invention the individual is preferably a mammal, for example a companion animal such as a horse, cat or dog or a farm animal such as a sheep, cow or pig. Most preferably the mammal is a human.

According to a preferred embodiment of the present invention the medicament and/or anti-CGRP antagonist antibody is prepared for oral, sublingual, buccal, topical, rectal, inhalation, transdermal, subcutaneous, intravenous, intra-arterial, intramuscular, intracardiac, intraosseous, intradermal, intraperitoneal, transmucosal, vaginal, intravitreal, intra-articular, peri-articular, local or epicutaneous administration.

According to a further preferred embodiment the medicament is prepared for peripheral administration prior to and/or during and/or after the development of chronic pain.

In one embodiment, the anti-CGRP antagonist antibody acts peripherally on administration. In one embodiment, the anti-CGRP antagonist antibody is not administered centrally, spinally or intrathecally.

According to a preferred embodiment of the present invention the chronic pain comprises one or more of chronic nociceptive pain, chronic neuropathic pain, chronic inflammatory pain, fibromyalgia, breakthrough pain and persistent pain. The chronic pain may comprise one or more of hyperalgesia, allodynia, central sensitisation, peripheral sensitisation, disinhibition and augmented facilitation.

According to a further preferred embodiment of the present invention the chronic pain is cancer pain, preferably cancer pain arising from malignancy or from cancer preferably selected from one or more of: adenocarcinoma in glandular tissue, blastoma in embryonic tissue of organs, carcinoma in epithelial tissue, leukemia in tissues that form blood cells, lymphoma in lymphatic tissue, myeloma in bone marrow, sarcoma in connective or supportive tissue, adrenal cancer, AIDS-related lymphoma, anemia, bladder cancer, bone cancer, brain cancer, breast cancer, carcinoid tumours, cervical cancer, chemotherapy, colon cancer, cytopenia, endometrial cancer, esophageal cancer, gastric cancer, head cancer, neck cancer, hepatobiliary cancer, kidney cancer, leukemia, liver cancer, lung cancer, lymphoma, Hodgkin's disease, lymphoma, non-Hodgkin's, nervous system tumours, oral cancer, ovarian cancer, pancreatic cancer, prostate cancer, rectal cancer, skin cancer, stomach cancer, testicular cancer, thyroid cancer, urethral cancer, bone cancer, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells, cancer of bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer, tumours that metastasize to the bone, tumours infiltrating the nerve and hollow viscus, tumours near neural structures. Further preferably the cancer pain comprises visceral pain, preferably visceral pain which arises from pancreatic cancer and/or metastases in the abdomen. Further preferably the cancer pain comprises somatic pain, preferably somatic pain due to one or more of bone cancer, metastasis in the bone, postsurgical pain, sarcomas cancer of the connective tissue, cancer of bone tissue, cancer of blood-forming cells of the bone marrow, multiple myeloma, leukaemia, primary or secondary bone cancer.

According to a preferred embodiment of the present invention the anti-CGRP antagonist antibody binds to CGRP, more preferably binds to CGRP and inhibits the ability of CGRP to bind to the CGRP receptor. Preferably the anti-CGRP antagonist antibody binds to both human and rodent CGRP, preferably human and rat CGRP. More preferably the antibody binds to human CGRP, further preferably the anti-CGRP antagonist antibody binds to human α-CGRP or to human α-CGRP and/or β-CGRP. Most preferably the anti-CGRP antagonist antibody is an antibody that exhibits any one or more of the following functional characteristics: (a) binds to CGRP; (b) blocks CGRP from binding to its receptor(s); (c) blocks or decreases CGRP receptor activation, including cAMP activation; (d) inhibits, blocks, suppresses or reduces CGRP biological activity, including downstream pathways mediated by CGRP signalling, such as receptor binding and/or elicitation of a cellular response to CGRP; (e) prevents, ameliorates, or treats any aspect of chronic pain; (f) increases clearance of CGRP; and (g) inhibits (reduces) CGRP synthesis, production or release.

Antibodies of the invention, including G1 and G2, are known to bind CGRP and remove its biological availability for example in the serum thus preventing CGRP access to the its receptor and downstream cellular responses and biological effects of CGRP such as flare and vasodilation.

In a further preferred embodiment of the invention the anti-CGRP antagonist antibody binds to a fragment of CGRP, more preferably to a fragment of CGRP as well as to the full length CGRP. Preferably, the anti-CGRP antagonist antibody binds to the C-terminal region or fragment of CRGP. The C-terminal region or fragment of CRGP preferably comprises amino acids 19-37 or 25-37 or 29-37 or alternatively 30-37, further alternatively 31-37 of CGRP. In a further embodiment, the C-terminal region or fragment of CRGP preferably comprises amino acids 32-37 most preferably 33 to 37 of CGRP. Preferably the CGRP is either α-CGRP or β-CGRP, further preferably human or rodent, further preferably human or rat, more preferably human, further preferably human α-CGRP or β-CGRP, most preferably human α-CGRP.

In a further preferred embodiment of the invention the anti-CGRP antagonist antibody specifically binds to the amino acid sequence GSKAF (SEQ ID NO: 33). Preferably the sequence GSKAF (SEQ ID NO: 33) of CGRP is the epitope to which the anti-CGRP antagonist antibody binds, preferably at position 33 to 37, most preferably the sequence is GXXXF where X can be any amino acid, preferably at positions 33 to 37 of CGRP, the ends defined by amino acids G33 and F37 of CGRP.

In one embodiment, the present invention provides an anti-CGRP antagonist antibody which specifically binds to an epitope defined by amino acids G33 to F37 of CGRP. The anti-CGRP antagonist antibody may specifically bind to the epitope defined by the amino acid sequence GSKAF (SEQ ID NO: 33). In one embodiment, the present invention provides the use of such an antibody in the uses and methods defined in the various aspects of the present invention.

In one embodiment, the anti-CGRP antagonist antibody inhibits or prevents activation of the CGRP receptor. Preferably the anti-CGRP antibody has an IC50 of between 0.0001 (0.1 nM) to 500 μM. In some preferred embodiments, the IC50 is between 0.0001 μM and, or is at about, any of 250 μM, 100 μM, 50 μM, 10 μM, 1 μM, 500 nM, 250 nM, 100 nM, 50 nM, 20 nM, 15 nM, 10 nM, 5 nM, 1 nM, or 0.5 nM as measured in an in vitro binding assay. In some further preferred embodiments, IC50 is less than any of 500 pM, or 100 pM, or 50 pM, as measured in an in vitro binding assay. In a further more preferred embodiment IC50 is 1.2 nM or 31 nM.

In a further preferred embodiment, the anti-CGRP antagonist antibody used is capable of competing with an antibody herein above described for the binding of CGRP or to a fragment of CGRP, or to a fragment of CGRP as well as the full length CGRP, preferably to the C-terminal region or fragment of CRGP, preferably the C-terminal region or fragment of CRGP comprises amino acids 19-37 or 25-37 or 29-37 or alternatively 30-37, further alternatively 31-37 of CGRP. In a further embodiment, the C-terminal region or

fragment of CRGP preferably comprises amino acids 32-37, most preferably 33 to 37 of CGRP.

In a further preferred embodiment, the anti-CGRP antagonist antibody or antigen binding portion thereof as used in the invention is capable of competing with an anti-CGRP antagonist antibody herein above described, in particular G1 or G2 as herein described, for:

(a) the binding of CGRP or a fragment of CGRP, or a fragment of CGRP as well as the full length CGRP, preferably the C-terminal region or fragment of CRGP, preferably the C-terminal region or fragment of CRGP comprising amino acids 19-37 or 25-37 or 29-37 or alternatively 30-37, further alternatively 31-37, preferably amino acids 32-37, most preferably 33 to 37 of CGRP, preferably the CGRP is alpha or beta, preferably beta, more preferably rodent or human, most preferably human.

(b) the binding of the epitope sequence GSKAF (SEQ ID NO: 33), preferably at amino acid position 33 to 37 of CGRP as defined in (a), more preferably to the sequence GXXXF, where X is any amino acid, preferably GXXXF at amino acid position 33 to 37 of CGRP as defined in (a).

(c) the binding as described in (a) or (b) with substantially the same Kd and/or substantially the same K_{off}.

(d) binding to CGRP and inhibiting/antagonising CGRP biological activity and/or downstream pathway(s), preferably the CGRP is alpha or beta, preferably beta, more preferably rodent or human, most preferably human.

The anti-CGRP antagonist antibody preferably binds to CGRP, region of CGRP or fragment of CGRP with a binding affinity (K_d) of between 0.00001 μM (0.01 nM) to 500 μM. In some preferred embodiments, the binding affinity (Kd) is between 0.00001 μM and, or is at about, any of 250 μM, 100 μM, 50 μM, 10 μM, 1 μM, 500 nM, 250 nM, 100 nM, 50 nM, 20 nM, 15 nM, 10 nM, 5 nM, 1 nM, 0.5 nM, 1 nM, 0.05 nM, or 0.01 nM as measured in an in vitro binding assay. In some further preferred embodiments, binding affinity (Kd) is less than any of 500 pM, or 100 pM, 50 pM, or 10 pM, as measured in an in vitro binding assay. In a further more preferred embodiment binding affinity (Kd) is 0.04 nM or 16 nM.

The anti-CGRP antagonist antibody as used in the present invention may be selected from the group of: monoclonal antibodies, polyclonal antibodies, antibody fragments (e.g., Fab, Fab', F(ab')2, Fv, Fc, ScFv etc.), chimeric antibodies, bispecific antibodies, heteroconjugate antibodies, single chain (ScFv) antibodies, mutants thereof, fusion proteins comprising an antibody portion (e.g., a domain antibody), humanized antibodies, and any other modified configuration of the immunoglobulin molecule that comprises an antigen recognition site of the required specificity, including glycosylation variants of antibodies, amino acid sequence variants of antibodies, and covalently modified antibodies. The anti-CGRP antagonist antibody may be murine, rat, human, or any other origin (including chimeric or humanized antibodies). In some embodiments, the anti-CGRP antagonist antibody may be humanized but is more preferably human. Preferably the anti-CGRP antagonist antibody is isolated, further preferably it is substantially pure. Where the anti-CGRP antagonist antibody is an antibody fragment the fragment preferably retains the functional characteristics of the original antibody i.e. the CGRP binding and/or antagonist activity as described in the functional characteristics above.

Examples of anti-CGRP antagonist antibodies are known in the art. Hence according to a preferred embodiment of the present invention the anti-CGRP antagonist antibody as used in the present invention is preferably an anti-CGRP antibody as generally or specifically disclosed in any of (i) WO2007/054809, (ii) WO2007/076336, (iii) Tan et al., Clin. Sci. (Lond). 89:565-73, 1995, (iv) Sigma (Missouri, US), product number C7113 (clone #4901), (v) Plourde et al., Peptides 14:1225-1229, 1993 or which comprises or consists of:

(a) a fragment of said antibody (e.g., Fab, Fab', F(ab')2, Fv, Fc, ScFv etc.),

(b) a light chain of said antibody,

(c) a heavy chain of said antibody,

(d) one or more variable region(s) from a light chain and/or a heavy chain of said antibody,

(e) one or more CDR(s) (one, two, three, four, five or six CDRs) of said antibody,

(f) CDR H3 from the heavy chain of said antibody,

(g) CDR L3 from the light chain of said antibody,

(h) three CDRs from the light chain of said antibody,

(i) three CDRs from the heavy chain of said antibody,

(j) three CDRs from the light chain and three CDRs from the heavy chain, of said antibody,

(k) any one or more of (a) through (j).

According to a preferred embodiment of the present invention the anti-CGRP antagonist antibody is antibody G2 or antibody G1. According to a most preferred embodiment of the present the anti-CGRP antagonist antibody used is the anti-CGRP antibody G1 as specifically disclosed in the patent application WO2007/054809, or comprising its variants shown in Table 6 of WO2007/054809, also including functionally equivalent antibodies to G1, i.e. comprising conservative substitutions of amino acid residues or one or more deletions or additions of amino acids which do not significantly affect their functional characteristics e.g. CRGP binding or antagonist activity and variants which have enhanced or decreased activity and/or binding. As used herein, the terms "G1" and "antibody G1" are used interchangeably to refer to an antibody produced by expression vectors having deposit numbers of ATCC PTA-6867 and ATCC PTA-6866 as disclosed in application WO2007/054809.

According to a further embodiment of the present invention, the anti-CGRP antagonist antibody comprises or consists of a polypeptide selected from: (a) antibody G1 or its variants shown in Table 6 of WO2007/054809; (b) a fragment or a region of antibody G1 or its variants shown in Table 6 of WO2007/054809; (c) a light chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (d) a heavy chain of antibody G1 or its variants shown in Table 6 of WO2007/054809 (e) one or more variable region(s) from a light chain and/or a heavy chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (f) one or more CDR(s) (one, two, three, four, five or six CDRs) of antibody G1 or its variants shown in Table 6 of WO2007/054809; (g) CDR H3 from the heavy chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (h) CDR L3 from the light chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (i) three CDRs from the light chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (j) three CDRs from the heavy chain of antibody G1 or its variants shown in Table 6 of WO2007/054809; (k) three CDRs from the light chain and/or three CDRs from the heavy chain, of antibody G1 or its variants shown in Table 6 of WO2007/054809; and (i) an antibody comprising any one of (b) through (k). The invention also provides polypeptides comprising any one or more of the above. In some embodiments, the at least one, two, three, four, five, or six CDR(s) are at least about 85%, 86%, 87%, 88%, 89%, 90%, 95%, 96%, 97%, 98%, or 99% identical to at least one, two, three, four, five or six CDRs of G1 or its variants shown in Table 6 of WO2007/054809.

Determination of CDR regions is well within the ability of the skilled person. It is understood that in some embodiments,

CDRs can be a combination of the Kabat and Chothia CDR. In some embodiments, the CDRs are the Kabat CDRs. In other embodiments, the CDRs are the Chothia CDRs.

The anti-CGRP antagonist antibody preferably comprises or consists of a fragment or a region of the antibody G1 (e.g., Fab, Fab', F(ab')2, Fv, Fc, ScFv etc.) or its variants shown in Table 6 of WO2007/054809. Preferably said fragment or region has the functional characteristics of an anti-CGRP antagonist antibody for example CGRP binding activity and/or antagonist activity and comprises or consists one or more of a light chain, heavy chain, fragment containing one or more variable regions from a light chain and/or a heavy chain, or one or more CDRs from a light chain and/or a heavy chain of the antibody G1.

According to a further preferred embodiment of the invention the anti-CGRP antagonist antibody comprises a light chain variable region, LCVR, comprising a peptide with a sequence selected from the group consisting of SEQ ID NOs: 28-32 and/or a heavy chain variable region, HCVR, comprising a peptide with a sequence selected from the group consisting of SEQ ID NOs: 34-38 of patent application WO2007/076336.

Further preferably the anti-CGRP antagonist antibody comprises an LCVR polypeptide of a SEQ ID NO as shown in Table 1 of patent application WO2007/076336 and further comprises a HCVR polypeptide of a SED ID NO as shown in Table 1 of patent application WO2007/076336.

According to a further embodiment of the invention the anti-CGRP antagonist antibody used comprises a light chain CDR (CDRL) selected from the group consisting of SEQ ID NOs: 8-13 and/or a heavy chain CDR (CDRH) selected from the group consisting of SEQ ID NOs: 14-22 of patent application WO2007/076336.

Methods of making and isolating the anti-CGRP antagonist antibodies of application WO2007/076336 and data demonstrating the CGRP binding and antagonist characterisation of the same are described in application WO2007/076336.

Preferably the anti-CGRP antagonist antibody for use in the present invention comprises a VH domain that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97% at least 98%, at least 99% or 100% identical in amino acid sequence to SEQ ID NO: 1 or SEQ ID NO: 19 presented herein.

Preferably the anti-CGRP antagonist antibody comprises a VL domain that is at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97% at least 98%, at least 99% or 100% identical in amino acid sequence to SEQ ID NO: 2 or SEQ ID NO: 20 presented herein.

The anti-CGRP antagonist antibody preferably comprises a VH domain and a VL domain that are at least 85%, at least 86%, at least 87%, at least 88%, at least 89%, at least 90%, at least 91%, at least 92%, at least 93%, at least 94%, at least 95%, at least 96%, at least 97% at least 98%, at least 99% or 100% identical in amino acid sequence to SEQ ID NO: 1 and 2 respectively or SEQ ID NO: 19 and 20 presented herein, respectively.

Preferably the anti-CGRP antagonist antibody comprises a VH domain that is at least 90% identical in amino acid sequence to SEQ ID NO: 1 and a VL domain that is at least 90% identical in amino acid sequence to SEQ ID NO: 2 presented herein.

Alternatively, the anti-CGRP antagonist antibody preferably comprises a VH domain that is at least 90% identical in amino acid sequence to SEQ ID NO: 19 and a VL domain that is at least 90% identical in amino acid sequence to SEQ ID NO: 20 presented herein.

The anti-CGRP antagonist antibody preferably comprises at least one CDR selected from the group consisting of: (a). CDR H1 as set forth in SEQ ID NO: 3 or 21; (b). CDR H2 as set forth in SEQ ID NO: 4 or 22; (c). CDR H3 as set forth in SEQ ID NO: 5 or 23; (d). CDR L1 as set forth in SEQ ID NO: 6 or 24; (e) CDR L2 as set forth in SEQ ID NO: 7 or 25; (f). CDR L3 as set forth in SEQ ID NO: 8 or 26; and (g). variants of CDR L1, CDR L2 and CDR H2 as shown in Table 6 of WO2007/054809.

According to a preferred embodiment of the present invention the anti-CGRP antagonist antibody heavy chain constant region may be from any types of constant region, such as IgG, IgM, IgD, IgA, and IgE; and any isotypes, such as IgGI, IgG2, IgG3, and IgG4.

Further preferably the anti-CGRP antagonist antibody comprises a heavy chain produced by the expression vector with ATCC Accession No. PTA-6867. Further preferably the anti-CGRP antagonist antibody comprises a light chain produced by the expression vector with ATCC Accession No. PTA-6866. Further preferably the anti-CGRP antagonist antibody is produced by the expression vectors with ATCC Accession Nos. PTA-6867 and PTA-6866.

Preferably the anti-CGRP antagonist antibody for use in the present invention is antibody G1 or antibody G2 defined herein.

According to a further embodiment of the invention, the anti-CGRP antagonist antibody comprises a modified constant region as for example described in WO2007/054809. Preferably the modified constant region is immunologically inert, including partially immunologically inert, such that it does not trigger complement mediated lysis, does not stimulate antibody-dependent cell mediated cytotoxicity (ADCC), does not activate microglia. Preferably the modified constant region is reduced in one or more of these activities. Most preferably the constant region is modified as described in Eur. J. Immunol. (1999) 29:2613-2624; PCT Application No. PCT/GB99/01441; and/or UK Patent Application No. 9809951.8. According to a preferred embodiment of the invention the anti-CGRP antagonist antibody comprises a human heavy chain IgG2 constant region comprising the following mutations: A330, P331 to S330, S331 (amino acid numbering with reference to the wildtype IgG2 sequence). Eur. J. Immunol. (1999) 29:2613-2624.

Methods of making and isolating the anti-CGRP antagonist antibodies of application WO2007/054809 and data demonstrating the CGRP binding and antagonist characterisation of the same are described in application WO2007/054809. Sequences of SEQ ID No. 1 to 14 of said application are provided herein as SEQ ID No. 1 to 14, respectively.

According to a further embodiment of the present invention the medicament is prepared for peripheral administration between once to 7 times per week, further preferably between once to four times per month, further preferably between once to six times per 6 month period, further preferably once to twelve times per year. Preferably the medicament is prepared to be peripherally administered in a period selected from: once daily, once every two, three, four, five or six days, weekly, once every two weeks, once every three weeks, monthly, once every two months, once every three months, once every four months, once every five months, once every six months, once every seven months, once every eight months, once every nine months, once every ten months, once every eleven months or yearly. According to preferred embodiments the medicament is prepared to be peripherally

administered via a route selected from one or more of; orally, sublingually, buccally, topically, rectally, via inhalation, transdermally, subcutaneously, intravenously, intra-arterially or intramuscularly, via intracardiac administration, intraosseously, intradermally, intraperitoneally, transmucosally, vaginally, intravitreally, epicutaneously, intra-articularly, peri-articularly or locally.

According to a further embodiment of the present invention the medicament is prepared for peripheral administration with an antibody concentration of between 0.1 to 200 mg/ml; preferably at about, or between 0.1 and about, any one of 0.5, 1, 5, 10, 15 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 mg/ml+/−10% error, most preferably at 50 mg/ml.

According to a further embodiment of the present invention the medicament is prepared for peripheral administration with an antibody concentration of between 0.1 to 200 mg/kg of body weight; preferably at about, or between 0.1 and about, any one of 0.5, 1, 5, 10, 15 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190 or 200 mg/kg of body weight+/−10% error, most preferably at 10 mg/kg.

According to a preferred embodiment of the present invention the anti-CGRP antagonist antibody has a half life in-vivo of more than any one of 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142, 144, 146, 148, 150, 152, 154, 156, 158, 160, 162, 164, 166, 168, 170, 172, 174, 176, 178, 180, 182, 184, 186, 188, 190, 192, 194, 196, 198, 200, 202, 204, 206, 208 or 210 days+/−1 day, further preferably more than any one of 7, 8, 9, 10, 11, or 12 months.

Preferably the anti-CGRP antagonist antibody has a half life in-vivo of more than 6 days.

According to a further preferred embodiment of the present invention, the medicament and/or the anti-CGRP antagonist antibody does not produce effects of central nervous system and/or cognitive impairment. Preferably the medicament and/or the anti-CGRP antagonist antibody does not induce any one ore more of the following: amnesia, confusion, depersonalization, hypesthesia, abnormal thinking, trismus, vertigo, akathisia, apathy, ataxia, circumoral paresthesia, CNS stimulation, emotional lability, euphoria, hallucinations, hostility, hyperesthesia, hyperkinesia, hypotonia, incoordination, libido increase, manic reaction, myoclonus, neuralgia, neuropathy, psychosis, seizure, abnormal speech, stupor, suicidal ideation; dizziness, somnolence, Insomnia, anxiety, tremor, depression or paresthesia. Most preferably the medicament and/or the anti-CGRP antagonist antibody does not induce impairment of motor coordination or attention.

According to a further embodiment of the present invention the medicament and/or the anti-CGRP antagonist antibody does not produce respiratory, renal or gastro-intestinal impairment.

According to a further embodiment of the present invention the medicament and/or the anti-CGRP antagonist antibody does not produce effects of physical and/or psychological dependence. Preferably the medicament and/or the anti-CGRP antagonist antibody does not demonstrate affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors, or CNS stimulant, or produce any sedating or euphoric effect.

In one embodiment, the anti-CGRP antagonist antibody, on administration, ameliorates, controls, reduces incidence of, or delays the development or progression of central pain sensation.

In another embodiment the effect of the anti-CGRP antagonist antibody is equal and/or superior to the effects of NSAIDS and/or opiates in the same models of chronic pain. In one embodiment, the anti-CGRP antagonist antibody is effective in treating refractory pain populations.

According to a further aspect of the present invention there is provided the use or method according to any other aspect of the invention wherein the anti-CGRP antagonist antibody is administered separately, sequentially or simultaneously in combination with one or more further pharmacologically active compounds or agents, preferably compounds or agents useful for treating chronic pain. Preferably the additional agent(s) is/are selected from one or more of:

(i) an opioid analgesic, e.g. morphine, heroin, hydromorphone, oxymorphone, levorphanol, levallorphan, methadone, meperidine, fentanyl, cocaine, codeine, dihydrocodeine, oxycodone, hydrocodone, propoxyphene, nalmefene, nalorphine, naloxone, naltrexone, buprenorphine, butorphanol, nalbuphine or pentazocine;

(ii) a nonsteroidal antiinflammatory drug (NSAID), e.g. aspirin, diclofenac, diflusinal, etodolac, fenbufen, fenoprofen, flufenisal, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, phenylbutazone, piroxicam, sulindac, tolmetin or zomepirac, cyclooxygenase-2 (COX-2) inhibitors, celecoxib; rofecoxib; meloxicam; JTE-522; L-745,337; NS398; or a pharmaceutically acceptable salt thereof;

(iii) a barbiturate sedative, e.g. amobarbital, aprobarbital, butabarbital, butabital, mephobarbital, metharbital, methohexital, pentobarbital, phenobartital, secobarbital, talbutal, theamylal or thiopental or a pharmaceutically acceptable salt thereof;

(iv) a benzodiazepine having a sedative action, e.g. chlordiazepoxide, clorazepate, diazepam, flurazepam, lorazepam, oxazepam, temazepam or triazolam or a pharmaceutically acceptable salt thereof;

(v) an H_1 antagonist having a sedative action, e.g. diphenhydramine, pyrilamine, promethazine, chlorpheniramine or chlorcyclizine or a pharmaceutically acceptable salt thereof;

(vi) a sedative such as glutethimide, meprobamate, methaqualone or dichloralphenazone or a pharmaceutically acceptable salt thereof;

(vii) a skeletal muscle relaxant, e.g. baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, methocarbamol or orphrenadine or a pharmaceutically acceptable salt thereof;

(viii) an NMDA receptor antagonist, e.g. dextromethorphan ((+)-3-hydroxy-N-methylmorphinan) or its metabolite dextrorphan ((+)-3-hydroxy-N-methylmorphinan), ketamine, memantine, pyrroloquinoline quinone or cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid or a pharmaceutically acceptable salt thereof;

(ix) an alpha-adrenergic, e.g. doxazosin, tamsulosin, clonidine or 4-amino-6,7-dimethoxy-2-(5-methanesulfonamido-1,2,3,4-tetrahydroisoquinol-2-yl)-5-(2-pyridyl) quinazoline;

(x) a tricyclic antidepressant, e.g. desipramine, imipramine, amytriptiline or nortriptiline;

(xi) an anticonvulsant, e.g. carbamazepine or valproate;

(xii) a tachykinin (NK) antagonist, particularly an NK-3, NK-2 or NK-1 antagonist, e.g. (αR,9R)-7-[3,5-bis(trifluoromethyl)benzyl]-8,9,10,11-tetrahydro-9-methyl-5-(4-methylphenyl)-7H-[1,4]diazocino[2,1-g][1,7]naphthridine-6-13-dione (TAK-637), 5-[[(2R,3S)-2-[(1R)-1-[3,5-bis

(trifluoromethyl)phenyl]ethoxy-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3H-1,2,4-triazol-3-one (MK-869), lanepitant, dapitant or 3-[[2-methoxy-5-(trifluoromethoxy)phenyl]methylamino]-2-phenyl-piperidine (2S, 3S);

(xiii) a muscarinic antagonist, e.g oxybutin, tolterodine, propiverine, tropsium chloride or darifenacin;

(xiv) a COX-2 inhibitor, e.g. celecoxib, rofecoxib or valdecoxib;

(xv) a non-selective COX inhibitor (preferably with GI protection), e.g. nitroflurbiprofen (HCT-1026);

(xvi) a coal-tar analgesic, in particular paracetamol;

(xvii) a neuroleptic such as droperidol;

(xviii) a vanilloid receptor agonist (e.g. resinferatoxin) or antagonist (e.g. capsazepine);

(xix) a beta-adrenergic such as propranolol;

(xx) a local anaesthetic, such as mexiletine;

(xxi) a corticosteriod, such as dexamethasone;

(xxii) a serotonin receptor agonist or antagonist;

(xxiii) a cholinergic (nicotinic) analgesic;

(xxiv) Tramadol (trade mark);

(xxv) a PDEV inhibitor, such as sildenafil, vardenafil or tadalafil;

(xxvi) an alpha-2-delta ligand such as gabapentin or pregabalin;

(xxvii) a canabinoid; and

(xxviii) an antidepressant, such as amitriptyline (Elavil), trazodone (Desyrel), and imipramine (Tofranil) or anticonvulsants such as phenytoin (Dilantin) or carbamazepine (Tegretol).

According to a further aspect of the present invention there is provided a pharmaceutical composition for the prevention and/or treatment of chronic pain and/or symptoms of chronic pain or for ameliorating, controlling, reducing incidence of, or delaying the development or progression of chronic pain and/or symptoms of chronic pain in an individual, comprising an anti-CGRP antagonist antibody and a pharmaceutically acceptable carrier and/or an excipient, wherein the composition is prepared to be peripherally administered.

According to a further aspect of the present invention there is provided a kit comprising:

(a) a pharmaceutical composition as defined above; and

(b) instructions for the peripheral administration of an effective amount of said pharmaceutical composition to an individual for the prevention and/or treatment of chronic pain and/or symptoms of chronic pain or for ameliorating, controlling, reducing incidence of, or delaying the development or progression of chronic pain and/or symptoms of chronic pain.

The kit may include one or more containers containing an anti-CGRP antagonist antibody or polypeptide described herein and instructions for use in accordance with any of the methods and uses of the invention. The kit may further comprise a description of selecting an individual suitable for treatment based on identifying whether that individual has chronic pain or is at risk of having chronic pain. The instructions for the peripheral administration of the pharmaceutical composition may include information as to dosage, dosing schedule and routes of administration for the intended treatment.

Preferred features of each aspect of the invention apply equally to each other aspect mutatis mutandis.

EXAMPLES

The present invention is now described with reference to the following Examples which are intended to illustrate but not to limit the invention.

The following examples and figures are made with reference to antibody G1, an anti-human CGRP human monoclonal antibody; and to antibody G2, an anti-rat CGRP mouse monoclonal antibody (Wong H C et al. Hybridoma 12:93-106 (1993)).

Example 1

Set Up of the Rodent Cancer Mechanistic Pain Model

Tumour cells used are syngeneic MRMT-1 rat mammary gland carcinoma cells donated from the Novartis Institute (London). The cells are cultured in RPMI 1640 (Gibco) with 10% foetal bovine serum (FCS), 1% L-glutamine 2% penicillin/streptomycin (Gibco). Two brief washes are carried out with 0.1% w/v trypsin to release those cells which adhere to the flask, and then quenched with an equal volume of 10% FCS, followed by centrifugation of the solution for 3 minutes at 1200 rpm. The pellet is washed and resuspended in Hanks medium, and the concentration of cells calculated using a Haemocytometer, with trypan blue staining to determine the number of dead MRMT-1 cells. The final concentration of 3×10^3 cells was then obtained by diluting the solution according to the number of cells seen. The final solution was kept on ice until time of injection.

Male Sprague-Dawley rats weighing close to 170 g at time of surgery were used to generate the cancer model. Anaesthesia was induced in the rats using halothane or isoflurane (1.5-2%) 66% N_2O and 33% O_2, the leg was shaved over the appropriate area and disinfected with chlorhexidine (Animalcare Ltd, UK.). A small incision in order to expose the anterior-medial surface of the distal end of the tibia was made. A hole was bored in the periosteum using a 0.7 mm dental drill, through which a 2 cm polythene tubing was fed 1 cm into the intra-medullar cavity of the tibia. Using a Hamilton syringe the pre-prepared 10 μl of 3×10^3 MRMT-1 cells were injected through the tubing into the cavity. The tubing was then removed and the hole plugged using bone restorative material (IRM, Dentsply USA). The wound was then irrigated with 0.9% saline and closed with a metal clip. The sham animals were operated upon using the same procedure but injected with 10 μl of Hank's solution alone. The animals were placed in a thermoregulated recovery box until such time that they were able to be placed back in their housing cages.

Example 2

Assessment of Rodent Anti-CGRP Antibody G2 in the Cancer Pain Model

Testing behaviour towards mechanical stimuli uses von Frey filaments (North Coast Medical Inc., USA) to the plantar surface of both the ipsilateral and contralateral hindpaw. The rats were placed in a Perspex cubicle with a mesh floor and allowed to acclimatise for 10 minutes. Each von Frey was applied 10 times to each hindpaw alternating between the ipsilateral and contralateral, for duration of 2-3 seconds each time. Von Frey Filaments used have bending forces of 1, 5, 9 and 15 g, and a period of 5 minutes was left between ascending von Frey forces. A nocifensive response (a lift) is defined as a brisk withdrawal of the hindpaw and the number of lifts for each paw at each von Frey are recorded (maximum of 10) and expressed as a percentage response.

An assessment of the efficacy of rodent anti-CGRP antibody G2 in attenuating hypersensitivity to a wide variety of static mechanical, cooling and integrated stimuli was carried

out as well as the background basal pain behaviours in this validated model of cancer induced bone pain. The responses measured are attenuated by standard analgesic treatments such as morphine and gabapentin. All measures were made by the same scientist in a blind fashion-blinded to the identity of the compound/control and to the treatment of the animal.

G2-was given IV at 10 mg/kg at day 9 and rats were tested at 2 hrs and then on days 10, 11, 12 and then 14-18 days post treatment (FIG. **1**).

G2 had marked effect on the behavioural responses to the higher intensity mechanical stimuli. Withdrawal frequencies to von Frey 8 g were reduced two hours after injection and were significantly reduced over that seen in the vehicle treated group on days 11 and 12 (days 2 and 3 after injection, p=0.0164 and 0.0311, respectively). In fact, the G2 treated animals now had pain scores similar to the baseline values. By day 14 (day 5 post-G2 injection) there was no discernible difference between the G2 and vehicle-treated groups. Both groups reached a similar level of hypersensitivity to von Frey 8 g by day 18 after MRMT-1 injection (day 9 post-treatment).

A similar reversal in hypersensitivity to von Frey 15 g was also apparent. A reduction in hypersensitivity to von Frey 15 g from vehicle treated group was evident at 2 hours post-injection with significance seen at 2 and 3 days after drug administration (p=0.02 and 0.03 respectively). The reductions were lost by 6 days after G2 administration and both groups now reached similar maximal withdrawal frequencies by 18 days post MRMT-1 injection (FIG. **2**).

The results indicate that G2 reduces noxious pain experienced in the metastatic bone cancer rat model.

Example 3

Rota Rod Test for Motor Impairment

A further end point tested in the bone cancer pain model was ambulation (by rotarod). The test is to obtain a measurement of locomotor impairment comparing antibody treated with control animals, each subjected to the same test under the same conditions. The rota rod test consists of 4 rotatable drums divided by flanges with a motor-driven drum accelerated (Ugo Basile, Comerio, VA, Italy). For a given trial, a rat is placed on the rotating rod and the rotation speed is accelerated from 4 to 16 rpm in 2 min. The time of maximal performance is typically set at 120 sec. Each animal generally receives three trials per day, at 1 hr intervals, for several consecutive days post surgery. The latency to fall off the rod is represented as mean of the three trials.

No differences were found between the antibody G2 group and the vehicle group in the latency to fall from the rotarod during forced ambulation (FIG. **3**). This suggests that G2 does not impair pathways involved in motor co-ordination, or attention and points to a lack of CNS side-effects produced by the antibody.

Example 4

Binding Assay

A binding assay was performed to measure the IC_{50} of anti-CGRP antibody G1 and G2 in blocking human α-CGRP from binding to the CGRP1-receptor in SK-N-MC cells. Dose response curves were plotted and K_i values were determined using the equation: $K_i=IC_{50}/(1+([ligand]/K_D)$; FIG. **4**, where the equilibrium dissociation constant K_D=8 pM for human α-CGRP to CGRP1-receptor as present in SK-N-MC cells. The reported IC_{50} value (in terms of IgG molecules) was converted to binding sites so that it could be compared with the affinities (K_D) determined by Biacore, using N-biotinylated human and rat α-CGRPs were captured on individual flow cells at low levels (typically 100 response units) to provide the reaction surfaces, while an unmodified flow cell served as a reference channel. G1 was titrated over the chip surface Binding affinities were deduced from the quotient of the kinetic rate constants ($K_D=k_{off}/k_{on}$) see Table 1.

TABLE 1

	G2	Mouse Mab 7E9	G1
KD (nM), α-Hu	17	1.0	0.04
IC50 (nM) α-Hu	37	2.6	1.2
KD (nM) α-Rat	1.0	58	1.2

TABLE 2

N-biotin-CGRP on chip	° C.	k_{on} (1/Ms)	k_{off} (1/s)	$T_{1/2}$ (h)	K_D (nM)
α-human	25	1.85×10^5	7.80×10^{-5}	24.68	0.042
α-human	37	5.87×10^5	3.63×10^{-5}	5.30	0.063
β-human	37	4.51×10^5	6.98×10^{-5}	2.76	0.155
α-rat	25	5.08×10^5	6.18×10^{-5}	3.12	1.22
α-rat	37	1.55×10^5	3.99×10^{-4}	0.48	2.57
β-rat	37	5.16×10^5	7.85×10^{-5}	2.45	0.152

Binding affinity of G1 for human α and β CGRP was equivalent (Kd=0.155 and 0.152 nM respectively). Binding affinity of G2 for rat α and β CGRP was equivalent (16 and 17 nM, respectively). Additionally G1 binding affinity is 40-fold more potent in human than rat for α-CGRP (Kd=0.042 and 1.22 nM, respectively) and equi-potent in human and rat for β-CGRP (Kd=0.155 and 0.152 nM, respectively). Antibody G1 also demonstrated good cross species selectivity and binds rat α-CGRP with the same affinity as antibody G2 (around 1.2 nM) Table 2.

G1 binds human and cynomolgus monkey α- and β-CGRP with high affinity (K_D=63 and 155 μM, respectively). G1 displays species selectivity for human/cyno CGRP and binds α- and β-CGRP from other species e.g. rat with lower affinity (K_D=2.57 nM and 152 μM, respectively).

Example 5

Half Life of Anti-CGRP In-Vivo

Serum measurements of anti-CGRP in rat, FIG. **5**, indicate that the half life is of the order of 7 days. The antibody is peripherally restricted having a molecular weight of around 150,000, FIGS. **5***a*, **5***b*, i.e. it does not cross into the central nervous system or cross the blood brain barrier.

Example 6

Selectivity of Anti-CGRP Antibody

We determined the specificity of antibody G1 to human or rat CGRP by using the Biacore chip to "probe" the free concentration of a premixed complex of mAb+peptide. As expected when we pre-incubated antibody G1 with human or rat CGRP the response was fully blocked. In contrast pre-incubating G1, with an excess of amylin, calcitonin or adrenomedullin was comparable to the control response (G1 plus buffer) demonstrating that G1 did not form a complex with these peptides (FIG. **7**).

Example 7

Identification of Antibody G1 Binding Epitope

Interaction analysis was conducted at 25° C. on a Biacore 3000™ system equipped with streptavidin-coated (SA) sensor chips (Biacore AB, Uppsala, Sweden) using a standard Biacore running buffer (HBS-P). First we confirmed that an N-biotinylated 25-37 human α-CGRP fragment bound with the same affinity to antibody G1, as full-length N-biotinylated human α-CGRP. Each amino acid between position 27-37 was then mutated individually to alanine and expressed the fold loss in affinity compared to the wild-type fragment. N-biotinylated fragments were captured on individual flow cells at low levels (typically 100 response units) to provide the reaction surfaces, while an unmodified flow cell served as a reference channel. Purified Fab fragments of antibody G1 were generated. Fab fragments were titrated over the chip using 1 μM as the top concentration of a two-fold dilution series. Association and dissociation phases were monitored at 100 μl/min for 1 minute and 5 minutes respectively. Surfaces were regenerated with a mixture of 35% ethanol+25 mM NaOH+0.5M NaCl.

The alanine scan results show that antibody G1 binds to the C-terminal region of human α-CGRP, particularly residues 25 to 37, and shows specific binding to a region (i.e. loss of affinity is markedly increased when the specific binding region is mutated) which can be defined as the epitope and which lies within the last 5 C-terminal amino acids, i.e. from G33A to F37A. Most profound changes in affinity are caused through the G33A and F37A mutation (FIG. **6**). C-terminal Phe is important for selectivity of antibody G1 for CGRP vs related peptides and gene family members (FIG. **8**).

Thus, in one embodiment, the present invention provides an anti-CGRP antagonist antibody which specifically binds to an epitope defined by amino acids G33 to F37 of CGRP. The anti-CGRP antagonist antibody may specifically bind to the epitope defined by the amino acid sequence GSKAF (SEQ ID NO: 33), more specifically to the epitope of CGRP is defined as GXXXF where X can be any amino acid, the G33 and F37 being the most important residues of the epitope for defining high affinity binding of the anti-CGRP antagonist antibody.

Example 8

Analysis of Indicators of Physical or Psychological Dependence

Neither antibody G1 nor antibody G2 demonstrate CNS penetration. Additionally long term observation of animals (rats) dosed with either antibody to levels used in the previous examples did not reveal adverse CNS events such as sedation or stimulation/euphoric behaviour in comparison to control animals. These observations indicate an absence of dependency risk for the antibodies and hence a significantly improved safety of the antibodies over current opiates used in current pain therapies.

Example 9

Analysis of Indicators of Gastro-Intestinal Adverse Effects

A 1 month in-vivo rat study with antibody G2 and 1 week comparative study with antibody G1 demonstrated that no adverse gastro intestinal effects were observed on behaviour, food intake, stool production or histopathology in comparison to control animals. These observations indicate an absence of gastrointestinal risk for the antibodies and hence a significantly improved safety of the antibodies over current NSAIDs used in current pain therapies.

Example 10

G1 and G2 as Anti-CGRP Antagonist Antibodies

A known consequence of CGRP biological activity is the generation neurogenic flare when delivered in vivo. G1 and G2 are demonstrated to be anti-CGRP antagonist antibodies in that they prevent the development of neurogenic flare in vivo.

Using a neurogenic skin flare rat model the efficacy of G1 was tested for its ability to block CGRP effect in vivo. The saphenous nerve in the rat is electrically stimulated causing CGRP release from nerve endings and leading to vasodilation, the resulting changes in blood flow can be measured using laser Dopler methods.

Changes in blood flow parameters were expressed as the area under the curve (AUC, change in arbitrary Doppler flux units multiplied by time). CGRP receptor antagonist $CGRP_{8-37}$ (400 nmol/kg, i.v.) was used as a positive control to validate the specificity of the model (data not shown). To determine the effect of G1 prior to dosing for each animal, the baseline blood flow response to stimulation was established with two saphenous nerve stimulations each 30 minutes apart. Rats were treated with G1 after the blood flow response of the second stimulation had returned to baseline levels (approximately 10 minutes post stimulation) and an additional four stimulations at 30 minute intervals were performed.

Results (FIG. **9**) demonstrated that in vehicle treated animals no significant change in blood flow response was but rats treated with G1 showed a significant decrease in blood flow response starting at 90 and 120 minutes post dose for 10 mg/kg and 1 mg/kg, respectively. Similar activity was achieved using D2. Additionally in further neurogenic flare and vasodilatation model tests G1 showed marked effect at 7 days post IV dosing (predicted ED_{50}=6 ug/ml in saphenous nerve stimulation model). The conclusions form the tests done is that G1 and G2 demonstrate anti-CGRP antagonist activity.

Similar CGRP function-blocking ability for the antibodies is also shown in the publication, Zeller J, et. al. Br J Pharmacol. 2008 December; 155(7):1093-103. Epub 2008 Sep. 8.

The following materials have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, Va. 20110-2209, USA (ATCC):

Material	Antibody No.	ATCC Accession No.	Date of Deposit
pDb.CGRP.hKGI	G1 heavy chain	PTA-6867	Jul. 15, 2005
pEb.CGRP.hFcGl	G1 light chain	PTA-6866	Jul. 15, 2005

Vector pEb.CGRP.hKGI is a polynucleotide encoding the G1 light chain variable region and the light chain kappa constant region; and vector pDb.CGRP.hFcG1 is a polynucleotide encoding the G1 heavy chain variable region and the heavy chain IgG2 constant region containing the following mutations: A330P331 to S330S331 (amino acid numbering with reference to the wildtype IgG2 sequences; see Eur. J. Immunol. (1999) 29:2613-2624).

Below are given antibody sequences useful for practicing the present invention.

Antibody sequences
Antibody G1 heavy chain variable region amino acid sequence
(SEQ ID NO: 1)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWISWVRQAPGKGLEWVAEIRSESDA

SATHYAEAVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCLAYFDYGLAIQNYWGQG

TLVTVSS

Antibody G1 light chain variable region amino acid sequence
(SEQ ID NO: 2)
EIVLTQSPATLSLSPGERATLSCKASKRVTTYVSWYQQKPGQAPRLLIYGASNRYLGIP

ARFSGSGSGTDFTLTISSLEPEDFAVYYCSQSYNYPYTFGQGTKLEIK

Antibody G1 CDR H1 (extended CDR)
(SEQ ID NO: 3)
GFTFSNYWIS

Antibody G1 CDR H2 (extended CDR)
(SEQ ID NO: 4)
EIRSESDASATHYAEAVKG

Antibody G1 CDR H3
(SEQ ID NO: 5)
YFDYGLAIQNY

Antibody G1 CDR L1
(SEQ ID NO: 6)
KASKRVTTYVS

Antibody G1 CDR L2
(SEQ ID NO: 7)
GASNRYL

Antibody G1 CDR L3
(SEQ ID NO: 8)
SQSYNYPYT

Antibody G1 heavy chain variable region nucleotide sequence
(SEQ ID NO: 9)
GAAGTTCAGCTGGTTGAATCCGGTGGTGGTCTGGTTCAGCCAGGTGGTTCCCTGC

GTCTGTCCTGCGCTGCTTCCGGTTTCACCTTCTCCAACTACTGGATCTCCTGGGTT

CGTCAGGCTCCTGGTAAAGGTCTGGAATGGGTTGCTGAAATCCGTTCCGAATCCGA

CGCGTCCGCTACCCATTACGCTGAAGCTGTTAAAGGTCGTTTCACCATCTCCCGTG

ACAACGCTAAGAACTCCCTGTACCTGCAGATGAACTCCCTGCGTGCTGAAGACACC

GCTGTTTACTACTGCCTGGCTTACTTTGACTACGGTCTGGCTATCCAGAACTACTGG

GGTCAGGGTACCCTGGTTACCGTTTCCTCC

Antibody G1 light chain variable region nucleotide sequence
(SEQ ID NO: 10)
GAAATCGTTCTGACCCAGTCCCCGGCTACCCTGTCCCTGTCCCCAGGTGAACGTGCT

ACCCTGTCCTGCAAAGCTTCCAAACGGGTTACCACCTACGTTTCCTGGTACCAGCAGA

AACCCGGTCAGGCTCCTCGTCTGCTGATCTACGGTGCTTCCAACCGTTACCTCGGTAT

CCCAGCTCGTTTCTCCGGTTCCGGTTCCGGTACCGACTTCACCCTGACCATCTCCTCC

CTGGAACCCGAAGACTTCGCTGTTTACTACTGCAGTCAGTCCTACAACTACCCCTACA

CCTTCGGTCAGGGTACCAAACTGGAAATCAAA

Antibody G1 heavy chain full antibody amino acid sequence
(including modified IgG2 as described herein)
(SEQ ID NO: 11)
EVQLVESGGGLVQPGGSLRLSCAASGFTFSNYWISWVRQAPGKGLEWVAEIRSESDA

SATHYAEAVKGRFTISRDNAKNSLYLQMNSLRAEDTAVYYCLAYFDYGLAIQNYWGQG

TLVTVSSASTKGPSVFPLAPCSRSTSESTAALGCLVKDYFPEPVTVSWNSGALTSGVH

-continued

TFPAVLQSSGLYSLSSVVTVPSSNFGTQTYTCNVDHKPSNTKVDKTVERKCCVECPPC

PAPPVAGPSVFLFPPKPKDTLMISRTPEVTCVVVDVSHEDPEVQFNWYVDGVEVHNAK

TKPREEQFNSTFRVVSVLTVVHQDWLNGKEYKCKVSNKGLPSSIEKTISKTKGQPREP

QVYTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTTPPMLDSDGSF

FLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Antibody G1 light chain full antibody amino acid sequence
(SEQ ID NO: 12)

EIVLTQSPATLSLSPGERATLSCKASKRVTTYVSWYQQKPGQAPRLLIYGASNRYLGIP

ARFSGSGSGTDFTLTISSLEPEDFAVYYCSQSYNYPYTFGQGTKLEIKRTVAAPSVFIF

PPSDEQLKSGTASVVCLLNNFYPREAKVQWKVDNALQSGNSQESVTEQDSKDSTYSL

SSTLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRGEC

Antibody G1 heavy chain full antibody nucleotide sequence
(including modified IgG2 as described herein)
(SEQ ID NO: 13)

GAAGTTCAGCTGGTTGAATCCGGTGGTGGTCTGGTTCAGCCAGGTGGTTCCCTGC

GTCTGTCCTGCGCTGCTTCCGGTTTCACCTTCTCCAACTACTGGATCTCCTGGGTT

CGTCAGGCTCCTGGTAAAGGTCTGGAATGGGTTGCTGAAATCCGTTCCGAATCCGA

CGCGTCCGCTACCCATTACGCTGAAGCTGTTAAAGGTCGTTTCACCATCTCCCGTG

ACAACGCTAAGAACTCCCTGTACCTGCAGATGAACTCCCTGCGTGCTGAAGACACC

GCTGTTTACTACTGCCTGGCTTACTTTGACTACGGTCTGGCTATCCAGAACTACTG

GGGTCAGGGTACCCTGGTTACCGTTTCCTCCGCCTCCACCAAGGGCCCATCTGTC

TTCCCACTGGCCCCATGCTCCCGCAGCACCTCCGAGAGCACAGCCGCCCTGGGCT

GCCTGGTCAAGGACTACTTCCCAGAACCTGTGACCGTGTCCTGGAACTCTGGCGC

TCTGACCAGCGGCGTGCACACCTTCCCAGCTGTCCTGCAGTCCTCAGGTCTCTACT

CCCTCAGCAGCGTGGTGACCGTGCCATCCAGCAACTTCGGCACCCAGACCTACAC

CTGCAACGTAGATCACAAGCCAAGCAACACCAAGGTCGACAAGACCGTGGAGAGA

AAGTGTTGTGTGGAGTGTCCACCTTGTCCAGCCCCTCCAGTGGCCGGACCATCCG

TGTTCCTGTTCCCTCCAAAGCCAAAGGACACCCTGATGATCTCCAGAACCCCAGAG

GTGACCTGTGTGGTGGTGGACGTGTCCCACGAGGACCCAGAGGTGCAGTTCAACT

GGTATGTGGACGGAGTGGAGGTGCACAACGCCAAGACCAAGCCAAGAGAGGAGC

AGTTCAACTCCACCTTCAGAGTGGTGAGCGTGCTGACCGTGGTGCACCAGGACTG

GCTGAACGGAAAGGAGTATAAGTGTAAGGTGTCCAACAAGGGACTGCCATCCAGC

ATCGAGAAGACCATCTCCAAGACCAAGGGACAGCCAAGAGAGCCACAGGTGTATA

CCCTGCCCCCATCCAGAGAGGAGATGACCAAGAACCAGGTGTCCCTGACCTGTCT

GGTGAAGGGATTCTATCCATCCGACATCGCCGTGGAGTGGGAGTCCAACGGACAG

CCAGAGAACAACTATAAGACCACCCCTCCAATGCTGGACTCCGACGGATCCTTCTT

CCTGTATTCCAAGCTGACCGTGGACAAGTCCAGATGGCAGCAGGGAAACGTGTTC

TCTTGTTCCGTGATGCACGAGGCCCTGCACAACCACTATACCCAGAAGAGCCTGTC

CCTGTCTCCAGGAAAGTAA

Antibody G1 light chain full antibody nucleotide sequence
(SEQ ID NO: 14)

GAAATCGTTCTGACCCAGTCCCCGGCTACCCTGTCCCTGTCCCCAGGTGAACGTG

CTACCCTGTCCTGCAAAGCTTCCAAACGGGTTACCACCTACGTTTCCTGGTACCAG

CAGAAACCCGGTCAGGCTCCTCGTCTGCTGATCTACGGTGCTTCCAACCGTTACCT

-continued

CGGTATCCCAGCTCGTTTCTCCGGTTCCGGTTCCGGTACCGACTTCACCCTGACCA

TCTCCTCCCTGGAACCCGAAGACTTCGCTGTTTACTACTGCAGTCAGTCCTACAAC

TACCCCTACACCTTCGGTCAGGGTACCAAACTGGAAATCAAACGCACTGTGGCTGC

ACCATCTGTCTTCATCTTCCCTCCATCTGATGAGCAGTTGAAATCCGGAACTGCCT

CTGTTGTGTGCCTGCTGAATAACTTCTATCCGCGCGAGGCCAAAGTACAGTGGAAG

GTGGATAACGCCCTCCAATCCGGTAACTCCCAGGAGAGTGTCACAGAGCAGGACA

GCAAGGACAGCACCTACAGCCTCAGCAGCACCCTGACCCTGAGCAAAGCAGACTA

CGAGAAACACAAAGTCTACGCCTGCGAAGTCACCCATCAGGGCCTGAGTTCTCCA

GTCACAAAGAGCTTCAACCGCGGTGAGTGCTAA

Amino acid sequence comparison of human and rat CGRP (human α-CGRP (SEQ ID
NO: 15); human β-CGRP (SEQ ID NO: 16); rat α-CGRP (SEQ ID NO: 17); and
rat β-CGRP (SEQ ID NO: 18)):

(SEQ ID NO: 15)

NH_2-ACDTATCVTHRLAGLLSRSGGVVKNNFVPTNVGSKAF-$CONH_2$

(SEQ ID NO: 16)

NH_2-ACNTATCVTHRLAGLLSRSGGMVKSNFVPTNVGSKAF-$CONH_2$

(SEQ ID NO: 17)

NH_2-SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNVGSEAF-$CONH_2$

(SEQ ID NO: 18)

NH_2-SCNTATCVTHRLAGLLSRSGGVVKDNFVPTNVGSKAF-$CONH_2$

Antibody G2 heavy chain variable region amino acid sequence

(SEQ ID NO: 19)

EVQLQQSGPELVKPGASVKMSCKASGYTFTSSVMHWVKQKPGQGLEWIGYINPYNDG

TKYNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCAKGGNDGYWGQGTTLTVS

S

Antibody G2 light chain variable region amino acid sequence

(SEQ ID NO: 20)

EIVLTQSPTTMAASPGEKITITCSASSSISSIYLHWYQQKPGFSPKVLIYRASNLASGVPA

RFSGSGSGTSYSLTIGTMEAEDVATYYCQQGSTIPFTFGSGTKLEIK

Antibody G2 CDR H1 (extended CDR)

(SEQ ID NO: 21)

SSVMH

Antibody G2 CDR H2 (extended CDR)

(SEQ ID NO: 22)

YINPYNDGTKYNEKFKG

Antibody G2 CDR H3

(SEQ ID NO: 23)

GGNDGY

Antibody G2 CDR L1

(SEQ ID NO: 24)

SASSSISSIYLH

Antibody G2 CDR L2

(SEQ ID NO: 25)

RASNLAS

Antibody G2 CDR L3

(SEQ ID NO: 26)

QQGSTIPFT

Antibody G2 heavy chain variable region nucleotide sequence

(SEQ ID NO: 27)

GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCAGTGAAG

ATGTCCTGCAAGGCTTCTGGATACACATTCACTAGCTCTGTTATGCACTGGGTGAAGC

AGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATTAATCCTTACAATGATGGTAC

-continued

TAAGTACAATGAGAAGTTCAAAGGCAAGGCCACACTGACTTCAGACAAATCCTCCAGC

ACAGCCTACATGGAACTCAGCAGCCTGACCTCTGAGGACTCTGCGGTCTATTACTGTG

CAAAAGGGGGTAACGATGGCTACTGGGGCCAAGGCACTACTCTCACAGTCTCCTCA

Antibody G2 light chain variable region nucleotide sequence
(SEQ ID NO: 28)

GAAATTGTGCTCACCCAGTCTCCAACCACCATGGCTGCATCTCCCGGGGAGAAGATCA

CTATCACCTGTAGTGCCAGCTCAAGTATAAGTTCCATTTACTTGCATTGGTATCAGCAG

AAGCCAGGATTCTCCCCTAAAGTCTTGATTTATAGGGCATCCAATCTGGCTTCTGGAGT

CCCAGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCACAATTGGCACC

ATGGAGGCTGAAGATGTTGCCACTTACTACTGCCAGCAGGGTAGTACTATACCATTCA

CGTTCGGCTCGGGGACAAAGTTGGAAATAAAA

Antibody G2 heavy chain full antibody amino acid sequence
(not including Fc domain)
(SEQ ID NO: 29)

EVQLQQSGPELVKPGASVKMSCKASGYTFTSSVMHWVKQKPGQGLEWIGYINPYNDGTK

YNEKFKGKATLTSDKSSSTAYMELSSLTSEDSAVYYCAKGGNDGYWGQGTTLTVSSAKTT

PPSVYPLAPGSAAQTNSMVTLGCLVKGYFPEPVTVTWNSGSLSSGVHTFPAVLQSDLYTL

SSSVTVPSSTWPSETVTCNVAHPASSTKVDKKIVPRD

Antibody G2 light chain full antibody amino acid sequence
(SEQ ID NO: 30)

EIVLTQSPTTMAASPGEKITITCSASSSISSIYLHWYQQKPGFSPKVLIYRASNLASGVPARF

SGSGSGTSYSLTIGTMEAEDVATYYCQQGSTIPFTFGSGTKLEIKRADAAPTVSIFPPSSEQ

LTSGGASVVCFLNNFYPRDINVKWKIDGSERQNGVLNSWTDQDSKDSTYSMSSTLTLTKD

EYERHNSYTCEATHKTSTSPIVKSFNRNEC

Antibody G2 heavy chain full antibody nucleotide sequence
(not including Fc domain)
(SEQ ID NO: 31)

GAGGTCCAGCTGCAGCAGTCTGGACCTGAGCTGGTAAAGCCTGGGGCTTCAGTGAAG

ATGTCCTGCAAGGCTTCTGGATACACATTCACTAGCTCTGTTATGCACTGGGTGAAGC

AGAAGCCTGGGCAGGGCCTTGAGTGGATTGGATATATTAATCCTTACAATGATGGTAC

TAAGTACAATGAGAAGTTCAAAGGCAAGGCCACACTGACTTCAGACAAATCCTCCAGC

ACAGCCTACATGGAACTCAGCAGCCTGACCTCTGAGGACTCTGCGGTCTATTACTGTG

CAAAAGGGGGTAACGATGGCTACTGGGGCCAAGGCACTACTCTCACAGTCTCCTCAG

CCAAAACGACACCCCCATCTGTCTATCCACTGGCCCCTGGATCTGCTGCCCAAACTAA

CTCCATGGTGACCCTGGGATGCCTGGTCAAGGGCTATTTCCCTGAGCCAGTGACAGT

GACCTGGAACTCTGGATCCCTGTCCAGCGGTGTGCACACCTTCCCAGCTGTCCTGCA

GTCTGACCTCTACACTCTGAGCAGCTCAGTGACTGTCCCCTCCAGCACCTGGCCCAG

CGAGACCGTCACCTGCAACGTTGCCCACCCGGCCAGCAGCACCAAGGTGGACAAGAA

AATTGTGCCCAGGGAT

Antibody G2 light chain full antibody nucleotide sequence
(SEQ ID NO: 32)

GAAATTGTGCTCACCCAGTCTCCAACCACCATGGCTGCATCTCCCGGGGAGAAGA

TCACTATCACCTGTAGTGCCAGCTCAAGTATAAGTTCCATTTACTTGCATTGGTATC

AGCAGAAGCCAGGATTCTCCCCTAAAGTCTTGATTTATAGGGCATCCAATCTGGCT

TCTGGAGTCCCAGCTCGCTTCAGTGGCAGTGGGTCTGGGACCTCTTACTCTCTCA

CAATTGGCACCATGGAGGCTGAAGATGTTGCCACTTACTACTGCCAGCAGGGTAG

TACTATACCATTCACGTTCGGCTCGGGGACAAAGTTGGAAATAAAACGGGCTGATG

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CTGCACCAACTGTATCCATCTTCCCACCATCCAGTGAGCAGTTAACATCTGGAGGT

GCCTCAGTCGTGTGCTTCTTGAACAACTTCTACCCCAGAGACATCAATGTCAAGTG

GAAGATTGATGGCAGTGAACGACAAAATGGTGTCCTGAACAGTTGGACTGATCAG

GACAGCAAAGACAGCACCTACAGCATGAGCAGCACCCTCACATTGACCAAGGACG

AGTATGAACGACATAACAGCTATACCTGTGAGGCCACTCACAAGACATCAACTTCA

CCCATCGTCAAGAGCTTCAACAGGAATGAGTGTTAA

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 35

<210> SEQ ID NO 1
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G1 heavy chain variable region

<400> SEQUENCE: 1

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Glu Ile Arg Ser Glu Ser Asp Ala Ser Ala Thr His Tyr Ala Glu
50 55 60

Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
65 70 75 80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
85 90 95

Tyr Cys Leu Ala Tyr Phe Asp Tyr Gly Leu Ala Ile Gln Asn Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 2
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G1 light chain variable region

<400> SEQUENCE: 2

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Lys Arg Val Thr Thr Tyr
20 25 30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Asn Arg Tyr Leu Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

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Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Ser Tyr Asn Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 3
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G1 CDR H1

<400> SEQUENCE: 3

Gly Phe Thr Phe Ser Asn Tyr Trp Ile Ser
1 5 10

<210> SEQ ID NO 4
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G1 CDR H2

<400> SEQUENCE: 4

Glu Ile Arg Ser Glu Ser Asp Ala Ser Ala Thr His Tyr Ala Glu Ala
1 5 10 15

Val Lys Gly

<210> SEQ ID NO 5
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G1 CDR H3

<400> SEQUENCE: 5

Tyr Phe Asp Tyr Gly Leu Ala Ile Gln Asn Tyr
1 5 10

<210> SEQ ID NO 6
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G1 CDR L1

<400> SEQUENCE: 6

Lys Ala Ser Lys Arg Val Thr Thr Tyr Val Ser
1 5 10

<210> SEQ ID NO 7
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G1 CDR L2

<400> SEQUENCE: 7

Gly Ala Ser Asn Arg Tyr Leu
1 5

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<210> SEQ ID NO 8
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G1 CDR L3

<400> SEQUENCE: 8

Ser Gln Ser Tyr Asn Tyr Pro Tyr Thr
1 5

<210> SEQ ID NO 9
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G1 heavy chain variable region

<400> SEQUENCE: 9

gaagttcagc tggttgaatc cggtggtggt ctggttcagc caggtggttc cctgcgtctg 60

tcctgcgctg cttccggttt caccttctcc aactactgga tctcctgggt tcgtcaggct 120

cctggtaaag gtctggaatg ggttgctgaa atccgttccg aatccgacgc gtccgctacc 180

cattacgctg aagctgttaa aggtcgtttc accatctccc gtgacaacgc taagaactcc 240

ctgtacctgc agatgaactc cctgcgtgct gaagacaccg ctgtttacta ctgcctggct 300

tactttgact acggtctggc tatccagaac tactggggtc agggtaccct ggttaccgtt 360

tcctcc 366

<210> SEQ ID NO 10
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G1 light chain variable region

<400> SEQUENCE: 10

gaaatcgttc tgacccagtc cccggctacc ctgtccctgt ccccaggtga acgtgctacc 60

ctgtcctgca aagcttccaa acgggttacc acctacgttt cctggtacca gcagaaaccc 120

ggtcaggctc ctcgtctgct gatctacggt gcttccaacc gttacctcgg tatcccagct 180

cgtttctccg gttccggttc cggtaccgac ttcaccctga ccatctcctc cctggaaccc 240

gaagacttcg ctgtttacta ctgcagtcag tcctacaact acccctacac cttcggtcag 300

ggtaccaaac tggaaatcaa a 321

<210> SEQ ID NO 11
<211> LENGTH: 448
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G1 heavy chain

<400> SEQUENCE: 11

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asn Tyr
20 25 30

Trp Ile Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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        35                  40                  45

Ala Glu Ile Arg Ser Glu Ser Asp Ala Ser Ala Thr His Tyr Ala Glu
    50                  55                  60

Ala Val Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser
65                  70                  75                  80

Leu Tyr Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr
                85                  90                  95

Tyr Cys Leu Ala Tyr Phe Asp Tyr Gly Leu Ala Ile Gln Asn Tyr Trp
            100                 105                 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro
        115                 120                 125

Ser Val Phe Pro Leu Ala Pro Cys Ser Arg Ser Thr Ser Glu Ser Thr
    130                 135                 140

Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr
145                 150                 155                 160

Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro
                165                 170                 175

Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr
            180                 185                 190

Val Pro Ser Ser Asn Phe Gly Thr Gln Thr Tyr Thr Cys Asn Val Asp
        195                 200                 205

His Lys Pro Ser Asn Thr Lys Val Asp Lys Thr Val Glu Arg Lys Cys
    210                 215                 220

Cys Val Glu Cys Pro Pro Cys Pro Ala Pro Pro Val Ala Gly Pro Ser
225                 230                 235                 240

Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser Arg
                245                 250                 255

Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp Pro
            260                 265                 270

Glu Val Gln Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn Ala
        275                 280                 285

Lys Thr Lys Pro Arg Glu Glu Gln Phe Asn Ser Thr Phe Arg Val Val
    290                 295                 300

Ser Val Leu Thr Val Val His Gln Asp Trp Leu Asn Gly Lys Glu Tyr
305                 310                 315                 320

Lys Cys Lys Val Ser Asn Lys Gly Leu Pro Ser Ser Ile Glu Lys Thr
                325                 330                 335

Ile Ser Lys Thr Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu
            340                 345                 350

Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr Cys
        355                 360                 365

Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu Ser
    370                 375                 380

Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Met Leu Asp
385                 390                 395                 400

Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser
                405                 410                 415

Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu Ala
            420                 425                 430

Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
        435                 440                 445
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<210> SEQ ID NO 12

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<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G1 light chain

<400> SEQUENCE: 12

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Lys Ala Ser Lys Arg Val Thr Thr Tyr
20 25 30

Val Ser Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Asn Arg Tyr Leu Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Ser Gln Ser Tyr Asn Tyr Pro Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
195 200 205

Phe Asn Arg Gly Glu Cys
210

<210> SEQ ID NO 13
<211> LENGTH: 1347
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G1 heavy chain

<400> SEQUENCE: 13

gaagttcagc tggttgaatc cggtggtggt ctggttcagc caggtggttc cctgcgtctg 60

tcctgcgctg cttccggttt caccttctcc aactactgga tctcctgggt tcgtcaggct 120

cctggtaaag gtctggaatg ggttgctgaa atccgttccg aatccgacgc gtccgctacc 180

cattacgctg aagctgttaa aggtcgtttc accatctccc gtgacaacgc taagaactcc 240

ctgtacctgc agatgaactc cctgcgtgct gaagacaccg ctgtttacta ctgcctggct 300

tactttgact acggtctggc tatccagaac tactggggtc agggtaccct ggttaccgtt 360

tcctccgcct ccaccaaggg cccatctgtc ttcccactgg ccccatgctc ccgcagcacc 420

tccgagagca cagccgccct gggctgcctg gtcaaggact acttcccaga acctgtgacc 480

gtgtcctgga actctggcgc tctgaccagc ggcgtgcaca ccttcccagc tgtcctgcag 540

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tcctcaggtc tctactccct cagcagcgtg gtgaccgtgc catccagcaa cttcggcacc 600

cagacctaca cctgcaacgt agatcacaag ccaagcaaca ccaaggtcga caagaccgtg 660

gagagaaagt gttgtgtgga gtgtccacct tgtccagccc ctccagtggc cggaccatcc 720

gtgttcctgt tccctccaaa gccaaaggac accctgatga tctccagaac cccagaggtg 780

acctgtgtgg tggtggacgt gtcccacgag gacccagagg tgcagttcaa ctggtatgtg 840

gacggagtgg aggtgcacaa cgccaagacc aagccaagag aggagcagtt caactccacc 900

ttcagagtgg tgagcgtgct gaccgtggtg caccaggact ggctgaacgg aaaggagtat 960

aagtgtaagg tgtccaacaa gggactgcca tccagcatcg agaagaccat ctccaagacc 1020

aagggacagc caagagagcc acaggtgtat accctgcccc catccagaga ggagatgacc 1080

aagaaccagg tgtccctgac ctgtctggtg aagggattct atccatccga catcgccgtg 1140

gagtgggagt ccaacggaca gccagagaac aactataaga ccaccctcc aatgctggac 1200

tccgacggat ccttcttcct gtattccaag ctgaccgtgg acaagtccag atggcagcag 1260

ggaaacgtgt tctcttgttc cgtgatgcac gaggccctgc acaaccacta tacccagaag 1320

agcctgtccc tgtctccagg aaagtaa 1347

<210> SEQ ID NO 14
<211> LENGTH: 645
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G1 light chain

<400> SEQUENCE: 14

gaaatcgttc tgacccagtc cccggctacc ctgtccctgt ccccaggtga acgtgctacc 60

ctgtcctgca aagcttccaa acgggttacc acctacgttt cctggtacca gcagaaaccc 120

ggtcaggctc ctcgtctgct gatctacggt gcttccaacc gttacctcgg tatcccagct 180

cgtttctccg gttccggttc cggtaccgac ttcaccctga ccatctcctc cctggaaccc 240

gaagacttcg ctgtttacta ctgcagtcag tcctacaact acccctacac cttcggtcag 300

ggtaccaaac tggaaatcaa acgcactgtg gctgcaccat ctgtcttcat cttccctcca 360

tctgatgagc agttgaaatc cggaactgcc tctgttgtgt gcctgctgaa taacttctat 420

ccgcgcgagg ccaaagtaca gtggaaggtg gataacgccc tccaatccgg taactcccag 480

gagagtgtca cagagcagga cagcaaggac agcacctaca gcctcagcag caccctgacc 540

ctgagcaaag cagactacga gaaacacaaa gtctacgcct gcgaagtcac ccatcagggc 600

ctgagttctc cagtcacaaa gagcttcaac cgcggtgagt gctaa 645

<210> SEQ ID NO 15
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide, Alpha-CGRP

<400> SEQUENCE: 15

Ala Cys Asp Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asn Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe

35

<210> SEQ ID NO 16
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide, Beta-CGRP

<400> SEQUENCE: 16

Ala Cys Asn Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Met Val Lys Ser Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> SEQ ID NO 17
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide, Alpha-CGRP

<400> SEQUENCE: 17

Ser Cys Asn Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asp Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Glu Ala Phe
35

<210> SEQ ID NO 18
<211> LENGTH: 37
<212> TYPE: PRT
<213> ORGANISM: Rattus norvegicus
<220> FEATURE:
<223> OTHER INFORMATION: Polypeptide, Beta-CGRP

<400> SEQUENCE: 18

Ser Cys Asn Thr Ala Thr Cys Val Thr His Arg Leu Ala Gly Leu Leu
1 5 10 15

Ser Arg Ser Gly Gly Val Val Lys Asp Asn Phe Val Pro Thr Asn Val
20 25 30

Gly Ser Lys Ala Phe
35

<210> SEQ ID NO 19
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic
polypeptide, Antibody G2 heavy chain variable region

<400> SEQUENCE: 19

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
20 25 30

Val Met His Trp Val Lys Gln Lys Pro Gly Gln Gly Leu Glu Trp Ile
35 40 45

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Gly Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe
50 55 60

Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Gly Gly Asn Asp Gly Tyr Trp Gly Gln Gly Thr Thr Leu Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 20
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G2 light chain variable region

<400> SEQUENCE: 20

Glu Ile Val Leu Thr Gln Ser Pro Thr Thr Met Ala Ala Ser Pro Gly
1 5 10 15

Glu Lys Ile Thr Ile Thr Cys Ser Ala Ser Ser Ser Ile Ser Ser Ile
20 25 30

Tyr Leu His Trp Tyr Gln Gln Lys Pro Gly Phe Ser Pro Lys Val Leu
35 40 45

Ile Tyr Arg Ala Ser Asn Leu Ala Ser Gly Val Pro Ala Arg Phe Ser
50 55 60

Gly Ser Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Gly Thr Met Glu
65 70 75 80

Ala Glu Asp Val Ala Thr Tyr Tyr Cys Gln Gln Gly Ser Thr Ile Pro
85 90 95

Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 21
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR H1

<400> SEQUENCE: 21

Ser Ser Val Met His
1 5

<210> SEQ ID NO 22
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR H2

<400> SEQUENCE: 22

Tyr Ile Asn Pro Tyr Asn Asp Gly Thr Lys Tyr Asn Glu Lys Phe Lys
1 5 10 15

Gly

<210> SEQ ID NO 23

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<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR H3

<400> SEQUENCE: 23

Gly Gly Asn Asp Gly Tyr
1 5

<210> SEQ ID NO 24
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR L1

<400> SEQUENCE: 24

Ser Ala Ser Ser Ser Ile Ser Ser Ile Tyr Leu His
1 5 10

<210> SEQ ID NO 25
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR L2

<400> SEQUENCE: 25

Arg Ala Ser Asn Leu Ala Ser
1 5

<210> SEQ ID NO 26
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic peptide, Antibody G2 CDR L3

<400> SEQUENCE: 26

Gln Gln Gly Ser Thr Ile Pro Phe Thr
1 5

<210> SEQ ID NO 27
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G2 heavy chain variable region

<400> SEQUENCE: 27

gaggtccagc tgcagcagtc tggacctgag ctggtaaagc ctggggcttc agtgaagatg 60

tcctgcaagg cttctggata cacattcact agctctgtta tgcactgggt gaagcagaag 120

cctgggcagg gccttgagtg gattggatat attaatcctt acaatgatgg tactaagtac 180

aatgagaagt tcaaaggcaa ggccacactg acttcagaca aatcctccag cacagcctac 240

atggaactca gcagcctgac ctctgaggac tctgcggtct attactgtgc aaaaggggt 300

aacgatggct actggggcca aggcactact ctcacagtct cctca 345

<210> SEQ ID NO 28

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<211> LENGTH: 324
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polynucleotide, Antibody G2 light chain variable region

<400> SEQUENCE: 28

gaaattgtgc tcacccagtc tccaaccacc atggctgcat ctcccgggga gaagatcact 60

atcacctgta gtgccagctc aagtataagt tccatttact tgcattggta tcagcagaag 120

ccaggattct cccctaaagt cttgatttat agggcatcca atctggcttc tggagtccca 180

gctcgcttca gtggcagtgg gtctgggacc tcttactctc tcacaattgg caccatggag 240

gctgaagatg ttgccactta ctactgccag cagggtagta ctataccatt cacgttcggc 300

tcggggacaa agttggaaat aaaa 324

<210> SEQ ID NO 29
<211> LENGTH: 216
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: Synthetic polypeptide, Antibody G2 heavy chain

<400> SEQUENCE: 29

Glu Val Gln Leu Gln Gln Ser Gly Pro Glu Leu Val Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Met Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Ser
20 25 30

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35 40 45

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Lys Gly Lys Ala Thr Leu Thr Ser Asp Lys Ser Ser Ser Thr Ala Tyr
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Met Glu Leu Ser Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
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Val Ser Ser Ala Lys Thr Thr Pro Pro Ser Val Tyr Pro Leu Ala Pro
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145 150 155 160

Leu Ser Ser Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Asp Leu
165 170 175

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Phe Thr Phe Gly Ser Gly Thr Lys Leu Glu Ile Lys Arg Ala Asp Ala
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Ala Pro Thr Val Ser Ile Phe Pro Pro Ser Ser Glu Gln Leu Thr Ser
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Gly Gly Ala Ser Val Val Cys Phe Leu Asn Asn Phe Tyr Pro Arg Asp
130 135 140

Ile Asn Val Lys Trp Lys Ile Asp Gly Ser Glu Arg Gln Asn Gly Val
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Leu Asn Ser Trp Thr Asp Gln Asp Ser Lys Asp Ser Thr Tyr Ser Met
165 170 175

Ser Ser Thr Leu Thr Leu Thr Lys Asp Glu Tyr Glu Arg His Asn Ser
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atggaactca gcagcctgac ctctgaggac tctgcggtct attactgtgc aaaaggggct 300

aacgatggct actggggcca aggcactact ctcacagtct cctcagccaa aacgacaccc 360

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agctcagtga ctgtcccctc cagcacctgg cccagcgaga ccgtcacctg caacgttgcc 600

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ccaggattct cccctaaagt cttgatttat agggcatcca atctggcttc tggagtccca 180

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gctgaagatg ttgccactta ctactgccag cagggtagta ctataccatt cacgttcggc 300

tcggggacaa agttggaaat aaaacgggct gatgctgcac caactgtatc catcttccca 360

ccatccagtg agcagttaac atctggaggt gcctcagtcg tgtgcttctt gaacaacttc 420

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            20                  25                  30

Gly Ser Glu Ala Phe
        35
```

The invention claimed is:

1. A method for reducing incidence of or treating allodynia in an individual, comprising administering to the individual an effective amount of an anti-CGRP antagonist antibody, wherein the anti-CGRP antagonist antibody is a monoclonal antibody.

2. The method of claim **1**, wherein the anti-CGRP antagonist antibody is peripherally administered.

3. The method of claim **1**, wherein the anti-CGRP antagonist antibody is administered orally, sublingually, via inhalation, transdermally, subcutaneously, intravenously, intra-arterially, intra-articularly, peri-articularly, or intramuscularly.

4. The method of claim **3**, wherein the anti-CGRP antagonist antibody is administered subcutaneously or intravenously.

5. The method of claim **1**, wherein the anti-CGRP antagonist antibody acts peripherally on administration.

6. The method of claim **1**, wherein the anti-CGRP antagonist antibody blocks CGRP from binding to its receptor.

7. The method of claim **1**, wherein the anti-CGRP antagonist antibody blocks or decreases CGRP receptor activation.

8. The method of claim **1**, wherein the anti-CGRP antagonist antibody increases clearance of CGRP.

9. The method of claim **1**, wherein the anti-CGRP antagonist antibody inhibits CGRP synthesis, production or release.

10. The method of claim **1**, wherein the anti-CGRP antagonist antibody is a human antibody.

11. The method of claim **1**, wherein the anti-CGRP antagonist antibody is a humanized antibody.

12. The method of claim **1**, wherein the anti-CGRP antagonist antibody binds CGRP with a Kd of 50 nM or less as measured in an in vitro binding assay.

13. The method according to claim **1**, wherein the anti-CGRP antagonist antibody has a half-life in-vivo of at least 7 days.

14. The method of claim **1**, wherein the anti-CGRP antagonist antibody binds a C-terminal fragment having amino acids 25-37 of CGRP or a C-terminal epitope within amino acids 25-37 of CGRP.

15. The method of claim **1**, wherein the anti-CGRP antagonist antibody comprises: (a) CDR H1 as set forth in SEQ ID NO: 3 or 21; (b) CDR H2 as set forth in SEQ ID NO: 4 or SEQ ID NO: 22; (c) CDR H3 as set forth in SEQ ID NO: 5 or 23; (d) CDR L1 as set forth in SEQ ID NO: 6 or SEQ ID NO: 24; (e) CDR L2 as set forth in SEQ ID NO: 7 or SEQ ID NO: 25; and (f) CDR L3 as set forth in SEQ ID NO: 8 or 26.

16. The method of claim **1**, wherein the anti-CGRP antagonist antibody comprises a V_H domain that comprises the amino acid sequence to SEQ ID NO: 1 and a V_L domain that comprises the amino acid sequence to SEQ ID NO: 2.

17. The method of claim **1**, wherein the anti-CGRP antagonist antibody comprises a heavy chain produced by the expression vector with ATCC Accession No. PTA-6867.

18. The method of claim **1**, wherein the anti-CGRP antagonist antibody comprises a light chain produced by the expression vector with ATCC Accession No. PTA-6866.

19. The method of claim **1**, wherein the individual is a human.

20. The method of claim **1**, wherein the anti-CGRP antagonist antibody is formulated with a pharmaceutically acceptable excipient.

* * * * *

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 September 2010 (10.09.2010)

PCT

(10) International Publication Number
WO 2010/102244 A1

(51) International Patent Classification:
C07K 16/28 (2006.01) *A61K 39/00* (2006.01)
A61K 39/395 (2006.01)

(21) International Application Number:
PCT/US2010/026413

(22) International Filing Date:
5 March 2010 (05.03.2010)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/158,285 6 March 2009 (06.03.2009) US
61/168,130 9 April 2009 (09.04.2009) US

(71) Applicant *(for all designated States except US)*: **KALOBIOS PHARMACEUTICALS, INC.** [US/US]; 260 E. Grand Avenue, South San Francisco, California 94080 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **BEBBINGTON, Christopher, R.** [GB/US]; 260 E. Grand Avenue, South San Francisco, California 94080 (US). **YARRANTON, Geoffrey, T.** [GB/US]; 260 E. Grand Avenue, South San Francisco, California 94080 (US). **PALATH, Varghese** [US/US]; 260 E. Grand Avenue, South San Francisco, California 94080 (US).

(74) Agents: **LOCKYER, Jean M.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, 8th Floor, San Francisco, California 94111-3834 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

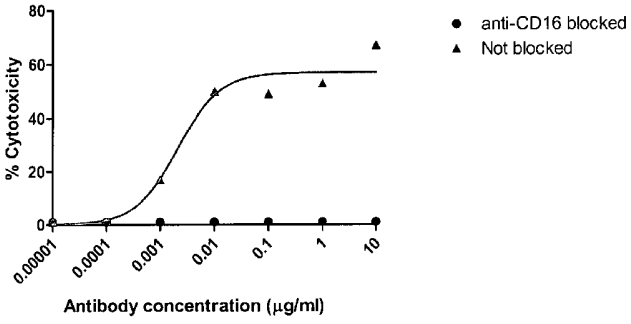
Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: TREATMENT OF LEUKEMIAS AND CHRONIC MYELOPROLIFERATIVE DISEASES WITH ANTIBODIES TO EPHA3

Figure 2



(57) **Abstract**: The invention provides methods and compositions comprising anti-EphA3 antibodies for the treatment of myeloproliferative disorders.

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Treatment of Leukemias and Chronic Myeloproliferative Diseases with Antibodies to EphA3

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. provisional application no. 61/158,285, filed March 6, 2009 and U.S. provisional application no. 61/168,130 filed April 9, 2009. Each application is herein incorporated by reference.

BACKGROUND OF THE INVENTION

[0002] Eph receptor tyrosine kinases (Ephs) belong to a large group of receptor tyrosine kinases (RTKs), kinases that phosphorylate proteins on tyrosine residues. Ephs and their membrane bound ephrin ligands (ephrins) control cell positioning and tissue organization (Poliakov, *et al.*, *Dev Cell* 7:465-80, 2004). In contrast to other receptor tyrosine kinases, Eph receptor activation does not only require ligand binding and dimerization but also involves preformed ligand oligomers. Thus, tyrosine phosphorylation of Eph receptors requires presentation of ephrin ligands in their clustered or membrane-attached forms (Davis *et al.*, *Science* 266:816-819, 1994). Functional and biochemical Eph responses occur at higher ligand oligomerization states (Stein *et al.*, *Genes Dev* 12:667-678, 1998).

[0003] Among other patterning functions, various Ephs and ephrins have been shown to play a role in vascular development. The de-regulated re-emergence of some ephrins and their receptors in adults also has been observed to contribute to tumor invasion, metastasis and neo-angiogenesis. For example, dominant-negative, soluble EphA2 or A3 proteins exhibit effects on ephrin-induced endothelial cell function *in vitro*, and tumor angiogenesis and progression *in vivo* (Nakamoto,. *et al.*, *Microsc Res Tech* 59:58-67, 2002; Brantley-Sieders, *et al.*, *Curr Pharm Des* 10:3431-42, 2004; Brantley, *et al. Oncogene* 21:7011-26, 2002; Cheng, *et al. Neoplasia* 5:445-56, 2003; and Dobrzanski, *et al. Cancer Res* 64:910-9, 2004). Furthermore, Eph family members have been found to be over-expressed on tumor cells from a wide variety of human solid tumors (Brantley-Sieders, *et al.*, *Curr Pharm Des* 10:3431-42, 2004; Marme, *Ann Hematol* 81 Suppl 2:S66, 2002; and Booth, *et al.*, *Nat Med* 8:1360-1, 2002).

[0004] Epha3 has also been reported to be activated and overexpressed on $CD34^+$ cells in chronic myeloid leukemia (CML) patients in the accelerated phase and blast crisis stage

(Cilloni *et al.*, American Society of Hematology, Abstract 1092, 2008 (available online November 14, 2008)). Cilloni *et al.* reported that when primary CML cells or EphA3-transfected normal cells were incubated with a specific monoclonal antibody that they referred to as a blocking antibody, the antibody induced a significant reduction of proliferation in primary cells and transfected cells, reduced colony growth and induced changes to the adhesion properties. The antibody did not induce any significant changes in normal control cells or cells from CML patient in the chronic stage.

[0005] There have been no reports that EphA3 is a therapeutic target in other myeloproliferative disorder.

BRIEF SUMMARY OF THE INVENTION

[0006] The invention is based, in part, on the discovery that neoplastic myeloid cells, including neoplastic myeloid stem cells, in the bone marrow and peripheral blood samples obtained from a patient that has chronic myeloid leukemia (CML), acute myeloid leukemia (AML), chronic myelomonocytic leukemia (CMML), juvenile myelomonocytic leukemia (JMML), myelodysplastic syndrome (MDS), polycythemia vera (PV), essential thrombocythemia (ET), or idiopathic myelofibrosis (IM), express EphA3 protein on the cell surface and that such cells can be killed using an activating anti-EphA3 antibody or an antibody that induces ADCC.

[0007] In one aspect, the invention provides a method of killing AML cells, MDS cells, CMML cells, JMML cells, CML cells, PV cells, ET cells, or IM cells, the method comprising contacting the cells with an anti-EphA3 antibody . In one aspect, the invention provides a method of treating a patient that has AML, CCML, JMML, MDS, CML, PV, ET or IM, the method comprising administering an anti-EphA antibody to the patient. In some embodiments, the anti-EphA3 antibody dimerizes EphA3. In some embodiments, the anti-EphA3 antibody activates EphA3 and kills the target cells by apoptosis. In some embodiments, the anti-EphA3 antibody kills the target cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC). In some embodiments, the invention provides a method of killing myeloproliferative disorder cells that express EphA3 on the surface, the method comprising contacting the cells with an anti-EphA3 antibody, wherein the anti-EphA3 antibody (i) activates EphA3 and (ii) induces antibody-dependent cell-mediated cytotoxicity (ADCC). In some embodiments, the invention provides a method of treating a patient that

has a myeloproliferative disorder and has myeloproliferative disorder cells the express EphA3 on the cell surface, the method comprising administering a therapeutically effective amount of an anti-EphA3 antibody to the patient, wherein the anti-EphA3 antibody (i) activates EphA3 and (ii) induces ADCC. In some embodiments, the invention provides a method of killing myeloproliferative disorder cells that express EphA3 on the surface, the method comprising contacting the cells with an anti-EphA3 antibody that activates EphA3 or induces ADCC, wherein the myeloproliferative disorder cells are acute myeloid leukemia (AML) cells or myelodysplastic syndrome (MDS) cells. In some embodiments, the invention provides a method of treating a patient that has a myeloproliferative disorder and has myeloproliferative disorder cells the express EphA3 on the cell surface, the method comprising administering a therapeutically effective amount of an anti-EphA3 antibody to the patient, wherein the anti-EphA3 antibody activates EphA3 or induces ADCC, wherein the myeloproliferative disorder is AML or MDS.

[0008] In some embodiments, the anti-EphA3 antibody for use in the methods of the invention is a recombinant or chimeric antibody. In some embodiments, the anti-EphA3 antibody is a human antibody. The anti-EphA3 antibody may be a polyclonal antibody or a monoclonal antibody. In some embodiments, the anti-EphA3 antibody is a multivalent antibody that comprises a Fab, a Fab', or an Fv. In some embodiments, the antibody is a $F(ab')_2$. In some embodiments, the anti-EphA3 antibody competes for EphA3 binding with mAb IIIA4. In some embodiments, the antibody binds to the same epitope as mAB IIIA4. In typical embodiments, the antibody does not block ephrin ligand binding, *e.g.,* ephrinA5 binding, to EphA3. In some embodiments the anti-EphA3 antibody comprises the V_H and V_L regions of mAb IIIA4. In some, embodiments, the anti EphA3 antibody comprises the V_H and V_L region CDR1, CDR2 and CDR3 of mAb IIIA4. In some embodiments, the antibody comprises the V_H region CDR3 and V_L region CDR3 of mAb IIIA4. In some embodiments, the antibody induces ADCC. Thus, in some embodiments the antibody has an active isotype, *e.g.,* the antibody has a human heavy chain constant region that is a gamma-1 or gamma-3 region. In some embodiments, the antibody does not induce ADCC, *e.g.,* the antibody has a human heavy chain constant region that is a gamma-2 or gamma-4 region.

[0009] In the context of this invention, "an anti-EphA3 antibody that activates EphA3 or induces ADCC" refers to an antibody that (i) activates EphA3 (ii) induces ADCC, or (iii) activates and induces ADCC.

[0010] In some embodiments of the invention, a myeloproliferative disorder patient is treated with an anti-EphA3 antibody as described herein and also receives treatment with another therapeutic agent for the disease. Thus, in some embodiments, the method comprises administering one or more additional therapeutic agents. For example, when the myeloproliferative disorder is CML, additional therapeutic agents include imatinib mesylate, nilotinib, dasatinib, or another chemotherapeutic agent. When the myeloproliferative disorder is AML, the additional therapeutic agents may be cytosine arabinoside alone or in combination with daunorubicin.

[0011] Normal myeloid blast cells and stem cells do not express EphA3 on the cell surface. Thus, in additional aspects, the invention provides a method of identifying a patient having a myeloproliferative disorder that is a candidate for treatment with an anti-EphA3 antibody, wherein the method comprises detecting EphA3 expression by myeloid blast cells and/or stem cells from the patient.

[0012] In some embodiments, the invention provides a method of determining that an AML patient or MDS patient is a candidate for treatment with an anti-EphA3 antibody, the method comprising: providing a sample from the patient, where the sample comprises myeloproliferative disorder cells; and detecting expression of EphA3 on the myeloproliferative disorder cells. In some embodiments, the invention provides a method of determining that a CMPD patient is a candidate for treatment with an anti-EphA3 antibody, the method comprising: providing a sample comprising neoplastic stem cells from the patient; and detecting expression of EphA3 by the neoplastic stem cells. In some embodiments, the invention provides a method of monitoring the efficacy of treatment of a patient having a myeloproliferative disorder with EphA3+ myeloproliferative cells, wherein the myeloproliferative disorder is AML or MDS, the method comprising: obtaining a sample comprising myeloproliferative disorder stem cells and/or blast cells from the patient following a therapeutic treatment for the myeloproliferative disorder; and detecting expression of EphA3 on the myeloproliferative disorder stem cells and/or blast cells. Ins some embodiments, the invention provides a method of monitoring the efficacy of treatment of a CMPD patient that has neoplastic myeloproliferative disorder stem cells that express EphA3, the method comprising: obtaining a sample comprising the neoplastic stem cells from the patient following a therapeutic treatment for the CMPD; and detecting expression of EphA3 on the stem cells.

[0013] EphA3 expression can be detected using commonly known techniques. Thus, in some embodiments detecting expression of EphA3 comprises detecting protein expression on the cell surface, *e.g.*, using flow cytometry. In some embodiments, the step of detecting expression of EphA3 comprises detecting EphA3 RNA levels, *e.g.*, using an amplification reaction such as RT-PCR.

[0014] The invention further provides a pharmaceutical composition comprising an anti-EphA3 antibody as described herein for use in treating a patient that has a myeloproliferative disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] Figure 1 provides data showing binding of an engineered human anti-EphA3 antibody to leukemic stem cells. AML primary bone marrow cells were stained with: engineered human anti-EphA3 antibody or IgG1 control and FITC-conjugated anti-human IgG; PE-conjugated anti-CD34; PEcy5-conjugated anti-CD38; and APC-conjugated anti-CD123 antibodies for flow cytometry analysis (50, 000 events per sample). A) isotype control gating for CD34 analysis. (B) Sample stained with anti-EphA3 and anti-CD34. (C) Sample stained for CD34 and CD38 (R2 represents CD34+ CD38- cells). (D) Identification of EphA3 and CD123 expression on CD34+ CD38- cells (R2 gate).

[0016] Figure 2 provides data showing induction of CD16-mediated ADCC activity by an engineered human anti-EphA3 antibody. Peripheral blood mononuclear cells from a patient suffering from Essential Thrombocythemia were used as the target. PBMC effector cells from a normal individual were added at an effector: target ratio of 200:1 in the presence of anti-EphA3 antibody at the concentrations shown. ADCC activity was analyzed in the presence of anti-CD16 antibody to inhibit Fc-mediated effector function (circles) or in the absence of CD16-blocking antibody (triangles) by measuring LDH release after 16 hours.

[0017] Figure 3 provides data showing enhanced ADCC activity shown by an engineered human anti-EphA3 antibody (IgG1k) deficient in α 1,6 fucose. LK63 target cells were incubated with fucosylated anti-EphA3 antibody (hatched bars) or antibody deficient in α1,6 fucose produced from kifunensine-treated cells (solid bars) at the concentrations shown. PBMC effector cells were added at an effector: target ratio of 100:1 for 16 hours and ADCC activity was determined by measuring LDH release.

[0018] Figure 4 provides data showing apoptosis activity of a human engineered antibody. Bone marrow cells (98% EphA3$^+$ by flow cytometry) from a CML patient were incubated in 96-well microtiter wells ($2x10^5$ cells per well) with human engineered anti-EphA3 antibody or IgG1 control antibody at the concentrations shown for 24 hours. Cells were then stained with Annexin V-FITC and propidium iodide and analyzed by flow cytometry. Percent cells undergoing apoptosis (Annexin V-positive) are shown.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0019] The term "myeloproliferative disorders" as used herein refers to certain chronic myeloproliferative diseases classified as chronic myeloid proliferative disorders (CMPDs); acute myeloid leukemia (AML); myeloid dysplastic syndrome (MDS); chronic myelomonocytic leukemia (CMML); and juvenile myelomonocytic leukemia (JMML). In the context of this invention, a "myeloproliferative disorder" thus refers to chronic myeloid leukemia (CML); polycythemia vera (PV); essential thrombocythemia (ET); idiopathic myelofibrosis (IM), which is also referred to as primary myelofibrosis; AML; MDS; CMML; and JMML, The term "JMML" encompasses all diagnoses referred to as Juvenile Chronic Myeloid Leukemia (JCML), Chronic Myelomonocytic Leukemia of Infancy, and Infantile Monosomy 7 Syndrome. Myeloproliferative disorders can be diagnosed using known criteria, *e.g.,* the World Health Organization (WHO) criteria, the French-American-British (FAB) classification system, the International Prognostic Scoring System (IPSS), and the like. In the 2008 WHO classification, CMPDs are referred to as myeloproliferative neoplasms (MPNs). Myeloproliferative disorders are often characterized by the presence of particular mutations. For example, CML is characterized by the presence of BCR-ABL. PV, ET, and IM are "non-BCR-ABL" (also referred to herein as "BCR-ABL minus" or "BCR-ABL negative") CMPDs, as these disorders do not have BCR-ABL. However, BCR-ABL negative disorders are often characterized by the presence of JAK2 mutations, which are rare in CML.

[0020] The term "myeloid stem cells" or "stem cells" as used herein are hematopoietic stem cells that are characterized as CD34$^+$, CD123$^+$, and CD38$^-$.

[0021] The term "myeloproliferative disorder cells" refers to neoplastic myeloid cells that are characteristic of a myeloproliferative disorder. The term encompasses myeloid cells that may not yet be considered to be malignant, *e.g.,* such as the myeloid cells that are

characteristic of myelodysplastic syndrome, as well as malignant cells, such as malignant acute leukemia cells. The term encompasses both blast cells and stem cells.

[0022] The terms "cancer cell" or "tumor cell" are used interchangeably to refer to a neoplastic cell. The term includes cells that are benign as well as malignant. Neoplastic transformation is associated with phenotypic changes of the tumor cell relative to the cell type from which it is derived. The changes can include loss of contact inhibition, morphological changes, and aberrant growth. (see, Freshney, *Culture of Animal Cells a Manual of Basic Technique* (3rd edition, 1994).

[0023] "Inhibiting growth of a cancer" in the context of the invention refers to slowing growth and/or reducing the cancer cell burden of a patient that has a myeloproliferative disorder. "Inhibiting growth of a cancer" thus includes killing cancer cells.

[0024] As used herein "EphA3" refers to the Eph receptor A3. This receptor has also been referred to as "Human embryo kinase", "hek", "eph-like tyrosine kinase 1", "etk1" or "tyro4". EphA3 belongs to the ephrin receptor subfamily of the protein-tyrosine kinase family. EPH and EPH-related receptors have been implicated in mediating developmental events. Receptors in the EPH subfamily typically have a single kinase domain and an extracellular region containing a Cys-rich domain and 2 fibronectin type III repeats. The ephrin receptors are divided into 2 groups based on the similarity of their extracellular domain sequences and their affinities for binding ephrin-A and ephrin-B ligands. EphA3 binds ephrin-A ligands. EphA3 nucleic acid and protein sequences are known. An exemplary human EphA3 amino acid sequence is available under accession number (EAW68857).

[0025] For the purposes of the present invention, "activation" of EphA3 causes phosphorylation of EphA3 and apoptosis. An antibody that activates EphA3 or "an activating antibody" causes phosphorylation of EphA3 and apoptosis and is therefore considered to be an agonist in the context of this invention. EphA3 can be activated by dimerization, which leads to apoptosis. In some embodiments, an antibody that activates EphA3 competes with mAb IIIA4 for binding to EphA3. Typically, an "activating" antibody binds to the ligand binding domain (amino acids 29-202 of EphA3) wherein amino acid residues 131, 132, and 136 are important for binding. In some embodiments, the activating antibody binds to a site encompassing the residues 131, 132, and 136 within the ligand binding domain of human EphA3 protein.

[0026] In the present invention, "EphA3 antibody" or "anti-EphA3 antibody" are used interchangeably to refer to an antibody that specifically binds to EphA3. In some embodiments, the antibody can dimerize EphA3. The term encompasses antibodies that bind to EphA3 in the presence of ephrin ligand (*e.g.,* ephrin-A5) binding, as well as antibodies that bind to the ligand binding site.

[0027] An "EphA3 antibody that binds to EphA3 in the presence of binding of an ephrin ligand" refers to an antibody that does not significantly prevent binding of an ephrin ligand, such as ephrin-A5, to EphA3. The presence of such an antibody in a binding reaction comprising EphA3 and an ephrin ligand, *e.g.,* ephrin-A5, reduces ephrin ligand binding to EphA3 by less than about 30%, typically less than 20% or 10%.

[0028] The term "mAb IIIA4" refers to monoclonal antibody IIIA4 that was originally raised against LK63 human acute pre-B leukemia cells to affinity isolate EphA3 (Boyd, *et al. J Biol Chem* 267:3262-3267, 1992). mAb IIIA4 binds to the native EphA3 globular ephrin-binding domain (*e.g.,* Smith, *et al., J. Biol. Chem* 279:9522-9531, 2004). It is deposited in the European Collection of Animal Cell Cultures under accession no. 91061920 (*see, e.g.,* EP patent no. EP0590030).

[0029] An "antibody having an active isotype" as used herein refers to an antibody that has a human Fc region that binds to an Fc receptor present on immune effector cells. "Active isotypes" include IgG1, IgG3, IgM, IgA, and IgE. The term encompasses antibodies that have a human Fc region that comprises modifications, such as mutations or changes to the sugar composition and/or level of glycosylation, that modulate Fc effector function.

[0030] An "Fc region" refers to the constant region of an antibody excluding the first constant region immunoglobulin domain. Thus, Fc refers to the last two constant region immunoglobulin domains of IgA, IgD, and IgG, and the last three constant region immunoglobulin domains of IgE and IgM, and the flexible hinge N-terminal to these domains. For IgA and IgM Fc may include the J chain. For IgG, Fc comprises immunoglobulin domains Cγ2 and Cγ3 and the hinge between Cγ1 and Cγ. It is understood in the art that the boundaries of the Fc region may vary, however, the human IgG heavy chain Fc region is usually defined to comprise residues C226 or P230 to its carboxyl-terminus, using the numbering is according to the EU index as in Kabat et al. (1991, NIH Publication 91-3242, National Technical Information Service, Springfield, Va.). The term "Fc region" may refer to this region in isolation or this region in the context of an antibody or antibody

fragment. "Fc region " includes naturally occurring allelic variants of the Fc region as well as modifications that modulate effector function. Fc regions also include variants that don't result in alterations to biological function. For example, one or more amino acids can be deleted from the N-terminus or C-terminus of the Fc region of an immunoglobulin without substantial loss of biological function. Such variants can be selected according to general rules known in the art so as to have minimal effect on activity (see, *e.g.*, Bowie, *et al.*, *Science* 247:306-1310, 1990).

[0031] As used herein, an "antibody" refers to a protein functionally defined as a binding protein and structurally defined as comprising an amino acid sequence that is recognized by one of skill as being derived from the framework region of an immunoglobulin encoding gene of an animal producing antibodies. An antibody can consist of one or more polypeptides substantially encoded by immunoglobulin genes or fragments of immunoglobulin genes. The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD and IgE, respectively.

[0032] A typical immunoglobulin (antibody) structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (V_L) and variable heavy chain (V_H) refer to these light and heavy chains respectively.

[0033] The term "antibody" as used herein includes antibody fragments that retain binding specificity. For example, there are a number of well characterized antibody fragments. Thus, for example, pepsin digests an antibody C-terminal to the disulfide linkages in the hinge region to produce F(ab)'2, a dimer of Fab which itself is a light chain joined to VH-CH1 by a disulfide bond. The F(ab)'2 may be reduced under mild conditions to break the disulfide linkage in the hinge region thereby converting the (Fab')2 dimer into an Fab' monomer. The Fab' monomer is essentially an Fab with part of the hinge region (see, Fundamental Immunology, W.E. Paul, ed., Raven Press, N.Y. (1993), for a more detailed description of other antibody fragments). While various antibody fragments are defined in terms of the

digestion of an intact antibody, one of skill will appreciate that fragments can be synthesized de novo either chemically or by utilizing recombinant DNA methodology. Thus, the term antibody, as used herein also includes antibody fragments either produced by the modification of whole antibodies or synthesized using recombinant DNA methodologies.

[0034] Antibodies include V_H-V_L dimers, including single chain antibodies (antibodies that exist as a single polypeptide chain), such as single chain Fv antibodies (sFv or scFv) in which a variable heavy and a variable light region are joined together (directly or through a peptide linker) to form a continuous polypeptide. The single chain Fv antibody is a covalently linked V_H-V_L which may be expressed from a nucleic acid including V_H- and V_L- encoding sequences either joined directly or joined by a peptide-encoding linker (*e.g.,* Huston, *et al. Proc. Nat. Acad. Sci. USA*, 85:5879-5883, 1988). While the V_H and V_L are connected to each as a single polypeptide chain, the V_H and V_L domains associate non-covalently. Alternatively, the antibody can be another fragment. Other fragments can also be generated, *e.g.,* using recombinant techniques, as soluble proteins or as fragments obtained from display methods. Antibodies can also include diantibodies and miniantibodies. Antibodies of the invention also include heavy chain dimers, such as antibodies from camelids. For the purposes of this inventor, antibodies are employed in a form that can activate EphA3 present on the surface of myeloproliferative cells or that can kill myeloproliferative cells by ADCC. Thus, in some embodiments an antibody is dimeric. In other embodiments, the antibody may be in a monomeric form that has an active isotype. In some embodiments the antibody is in a multivalent form, *e.g.,* a trivalent or tetravalent form, that can cross-link EphA3.

[0035] As used herein, "V-region" refers to an antibody variable region domain comprising the segments of Framework 1, CDR1, Framework 2, CDR2, and Framework3, including CDR3 and Framework 4, which segments are added to the V-segment as a consequence of rearrangement of the heavy chain and light chain V-region genes during B-cell differentiation.

[0036] As used herein, "complementarity-determining region (CDR)" refers to the three hypervariable regions in each chain that interrupt the four "framework" regions established by the light and heavy chain variable regions. The CDRs are primarily responsible for binding to an epitope of an antigen. The CDRs of each chain are typically referred to as CDR1, CDR2, and CDR3, numbered sequentially starting from the N-terminus, and are also typically identified by the chain in which the particular CDR is located. Thus, a V_H CDR3 is

located in the variable domain of the heavy chain of the antibody in which it is found, whereas a V_L CDR1 is the CDR1 from the variable domain of the light chain of the antibody in which it is found.

[0037] The sequences of the framework regions of different light or heavy chains are relatively conserved within a species. The framework region of an antibody, that is the combined framework regions of the constituent light and heavy chains, serves to position and align the CDRs in three dimensional space.

[0038] The amino acid sequences of the CDRs and framework regions can be determined using various well known definitions in the art, *e.g.,* Kabat, Chothia, international ImMunoGeneTics database (IMGT), and AbM (*see, e.g.,* Johnson *et al., supra*; Chothia & Lesk, 1987, Canonical structures for the hypervariable regions of immunoglobulins. *J. Mol. Biol.* 196, 901-917; Chothia C. et al., 1989, Conformations of immunoglobulin hypervariable regions. Nature 342, 877-883; Chothia C. et al., 1992, structural repertoire of the human VH segments J. Mol. Biol. 227, 799-817; Al-Lazikani *et al., J.Mol.Biol* 1997, 273(4)). Definitions of antigen combining sites are also described in the following: Ruiz et al., IMGT, the international ImMunoGeneTics database. *Nucleic Acids Res.*, 28, 219–221 (2000); and Lefranc,M.-P. IMGT, the international ImMunoGeneTics database. *Nucleic Acids Res.* Jan 1;29(1):207-9 (2001); MacCallum *et al*, Antibody-antigen interactions: Contact analysis and binding site topography, *J. Mol. Biol.*, 262 (5), 732-745 (1996); and Martin *et al*, *Proc. Natl Acad. Sci.* USA, 86, 9268–9272 (1989); Martin, *et al*, *Methods Enzymol.*, 203, 121–153, (1991); Pedersen *et al*, *Immunomethods*, 1, 126, (1992); and Rees *et al*, In Sternberg M.J.E. (ed.), Protein Structure Prediction. Oxford University Press, Oxford, 141–172 1996).

[0039] "Epitope" or "antigenic determinant" refers to a site on an antigen to which an antibody binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation. Methods of determining spatial conformation of epitopes include, for example, x-ray crystallography and 2-dimensional nuclear magnetic resonance. See, e.g., Epitope Mapping Protocols in Methods in Molecular Biology, Vol. 66, Glenn E. Morris, Ed (1996).

[0040] As used herein, "chimeric antibody" refers to an immunoglobulin molecule in which (a) the constant region, or a portion thereof, is altered, replaced or exchanged so that the antigen binding site (variable region) is linked to a constant region of a different or altered class, effector function and/or species, or an entirely different molecule which confers new properties to the chimeric antibody, e.g., an enzyme, toxin, hormone, growth factor, drug, etc.; or (b) the variable region, or a portion thereof, is altered, replaced or exchanged with a variable region, or portion thereof, having a different or altered antigen specificity; or with corresponding sequences from another species or from another antibody class or subclass.

[0041] As used herein, "humanized antibody" refers to an immunoglobulin molecule in CDRs from a donor antibody are grafted onto human framework sequences. Humanized antibodies may also comprise residues of donor origin in the framework sequences. The humanized antibody can also comprise at least a portion of a human immunoglobulin constant region. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. Humanization can be performed using methods known in the art (*e.g.,* Jones *et al., Nature* 321:522-525; 1986; Riechmann *et al., Nature* 332:323-327, 1988; Verhoeyen *et al., Science* 239:1534-1536, 1988); Presta, *Curr. Op. Struct. Biol.* 2:593-596, 1992; U.S. Patent No. 4,816,567), including techniques such as "superhumanizing" antibodies (Tan et *al., J. Immunol.* 169: 1119, 2002) and "resurfacing" (*e.g.,* Staelens *et al., Mol. Immunol.* 43: 1243, 2006; and Roguska *et al., Proc. Natl. Acad. Sci USA* 91: 969, 1994).

[0042] A "HUMANEERED™" antibody in the context of this invention refers to an engineered human antibody having a binding specificity of a reference antibody. An engineered human antibody for use in this invention has an immunoglobulin molecule that contains minimal sequence derived from a donor immunoglobulin. In some embodiments, the engineered human antibody may retain only the minimal essential binding specificity determinant from the CDR3 regions of a reference antibody. Typically, an engineered human antibody is engineered by joining a DNA sequence encoding a binding specificity determinant (BSD) from the CDR3 region of the heavy chain of the reference antibody to human V_H segment sequence and a light chain CDR3 BSD from the reference antibody to a human V_L segment sequence. A "BSD" refers to a CDR3-FR4 region, or a portion of this region that mediates binding specificity. A binding specificity determinant therefore can be a CDR3-FR4, a CDR3, a minimal essential binding specificity determinant of a CDR3 (which refers to any region smaller than the CDR3 that confers binding specificity when present in

the V region of an antibody), the D segment (with regard to a heavy chain region), or other regions of CDR3- FR4 that confer the binding specificity of a reference antibody. Methods for engineering human antibodies are provided in US patent application publication no. 20050255552 and US patent application publication no. 20060134098.

[0043] The term "human antibody" as used herein refers to an antibody that is substantially human, i.e., has FR regions, and often CDR regions, from a human immune system. Accordingly, the term includes humanized and HUMANEERED™ antibodies as well as antibodies isolated from mice reconstituted with a human immune system and antibodies isolated from display libraries.

[0044] A "hypofucosylated" antibody preparation refers to an antibody preparation in which the average content of α1,6-fucose is less than 50% of that found in naturally occurring IgG antibody preparations. As understood in the art, "hypofucosylated" is used in reference to a population of antibodies.

[0045] An "afucosylated" antibody lacks α1,6-fucose attached to the CH2 domain of the IgG heavy chain.

[0046] The term "heterologous" when used with reference to portions of a nucleic acid indicates that the nucleic acid comprises two or more subsequences that are not normally found in the same relationship to each other in nature. For instance, the nucleic acid is typically recombinantly produced, having two or more sequences, e.g., from unrelated genes arranged to make a new functional nucleic acid. Similarly, a heterologous protein will often refer to two or more subsequences that are not found in the same relationship to each other in nature.

[0047] The term "recombinant" when used with reference, *e.g.,* to a cell, or nucleic acid, protein, or vector, indicates that the cell, nucleic acid, protein or vector, has been modified by the introduction of a heterologous nucleic acid or protein or the alteration of a native nucleic acid or protein, or that the cell is derived from a cell so modified. Thus, *e.g.,* recombinant cells express genes that are not found within the native (non-recombinant) form of the cell or express native genes that are otherwise abnormally expressed, under expressed or not expressed at all. By the term "recombinant nucleic acid" herein is meant nucleic acid, originally formed in vitro, in general, by the manipulation of nucleic acid, *e.g.*, using polymerases and endonucleases, in a form not normally found in nature. In this manner,

operably linkage of different sequences is achieved. Thus an isolated nucleic acid, in a linear form, or an expression vector formed in vitro by ligating DNA molecules that are not normally joined, are both considered recombinant for the purposes of this invention. It is understood that once a recombinant nucleic acid is made and reintroduced into a host cell or organism, it will replicate non-recombinantly, i.e., using the in vivo cellular machinery of the host cell rather than in vitro manipulations; however, such nucleic acids, once produced recombinantly, although subsequently replicated non-recombinantly, are still considered recombinant for the purposes of the invention. Similarly, a "recombinant protein" is a protein made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid as depicted above.

[0048] The phrase "specifically (or selectively) binds" to an antibody or "specifically (or selectively) immunoreactive with," when referring to a protein or peptide, refers to a binding reaction where the antibody binds to the protein of interest. In the context of this invention, the antibody typically binds to EphA3 with an affinity that is at least 100-fold better than its affinity for other antigens.

[0049] The term "equilibrium dissociation constant (K_D) refers to the dissociation rate constant (k_d, $time^{-1}$) divided by the association rate constant (k_a, $time^{-1}$, M^{-1}). Equilibrium dissociation constants can be measured using any known method in the art. The antibodies of the present invention are high affinity antibodies. Such antibodies have an affinity better than 500 nM, and often better than 50 nM or 10 nM. Thus, in some embodiments, the antibodies of the invention have an affinity in the range of 500 nM to 100 pM, or in the range of 50 or 25 nM to 100 pM, or in the range of 50 or 25 nM to 50 pM, or in the range of 50 nM or 25 nM to 1 pM.

[0050] As used herein, "cancer therapeutic agent" refers to an agent that when administered to a patient suffering from cancer, in a therapeutically effective dose, will cure, or at least partially arrest the symptoms of the disease and complications associated with the disease.

[0051] The terms "identical" or percent "identity," in the context of two or more polypeptide (or nucleic acid) sequences, refer to two or more sequences or subsequences that are the same or have a specified percentage of amino acid residues (or nucleotides) that are the same (i.e., about 60% identity, preferably 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or higher identity over a specified region, when compared and aligned for maximum correspondence over a comparison window or designated region)

as measured using a BLAST or BLAST 2.0 sequence comparison algorithms with default parameters described below, or by manual alignment and visual inspection (*see, e.g.*, NCBI web site). Such sequences are then said to be "substantially identical." "Substantially identical" sequences also includes sequences that have deletions and/or additions, as well as those that have substitutions, as well as naturally occurring, *e.g.,* polymorphic or allelic variants, and man-made variants. As described below, the preferred algorithms can account for gaps and the like. Preferably, protein sequence identity exists over a region that is at least about 25 amino acids in length, or more preferably over a region that is 50-100 amino acids = in length, or over the length of a protein.

[0052] A "comparison window", as used herein, includes reference to a segment of one of the number of contiguous positions selected from the group consisting typically of from 20 to 600, usually about 50 to about 200, more usually about 100 to about 150 in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned. Methods of alignment of sequences for comparison are well-known in the art. Optimal alignment of sequences for comparison can be conducted, *e.g.*, by the local homology algorithm of Smith & Waterman, *Adv. Appl. Math.* 2:482 (1981), by the homology alignment algorithm of Needleman & Wunsch, *J. Mol. Biol.* 48:443 (1970), by the search for similarity method of Pearson & Lipman, *Proc. Nat'l. Acad. Sci. USA* 85:2444 (1988), by computerized implementations of these algorithms (GAP, BESTFIT, FASTA, and TFASTA in the Wisconsin Genetics Software Package, Genetics Computer Group, 575 Science Dr., Madison, WI), or by manual alignment and visual inspection (see, e.g., Current Protocols in Molecular Biology (Ausubel et al., eds. 1995 supplement)).

[0053] Preferred examples of algorithms that are suitable for determining percent sequence identity and sequence similarity include the BLAST and BLAST 2.0 algorithms, which are described in Altschul *et al., Nuc. Acids Res.* 25:3389-3402 (1977) and Altschul *et al., J. Mol. Biol.* 215:403-410 (1990). BLAST and BLAST 2.0 are used, with the parameters described herein, to determine percent sequence identity for the nucleic acids and proteins of the invention. The BLASTN program (for nucleotide sequences) uses as defaults a wordlength (W) of 11, an expectation (E) of 10, M=5, N=-4 and a comparison of both strands. For amino acid sequences, the BLASTP program uses as defaults a wordlength of 3, and expectation (E) of 10, and the BLOSUM62 scoring matrix (see Henikoff & Henikoff, *Proc. Natl. Acad. Sci. USA* 89:10915 (1989)) alignments (B) of 50, expectation (E) of 10, M=5, N=-4, and a comparison of both strands.

[0054] An indication that two polypeptides are substantially identical is that the first polypeptide is immunologically cross reactive with the antibodies raised against the second polypeptide. Thus, a polypeptide is typically substantially identical to a second polypeptide, *e.g.*, where the two peptides differ only by conservative substitutions.

[0055] The terms "isolated," "purified," or "biologically pure" refer to material that is substantially or essentially free from components that normally accompany it as found in its native state. Purity and homogeneity are typically determined using analytical chemistry techniques such as polyacrylamide gel electrophoresis or high performance liquid chromatography. A protein that is the predominant species present in a preparation is substantially purified. The term "purified" in some embodiments denotes that a protein gives rise to essentially one band in an electrophoretic gel. Preferably, it means that the protein is at least 85% pure, more preferably at least 95% pure, and most preferably at least 99% pure.

[0056] The terms "polypeptide," "peptide" and "protein" are used interchangeably herein to refer to a polymer of amino acid residues. The terms apply to amino acid polymers in which one or more amino acid residue is an artificial chemical mimetic of a corresponding naturally occurring amino acid, as well as to naturally occurring amino acid polymers, those containing modified residues, and non-naturally occurring amino acid polymer.

[0057] The term "amino acid" refers to naturally occurring and synthetic amino acids, as well as amino acid analogs and amino acid mimetics that function similarly to the naturally occurring amino acids. Naturally occurring amino acids are those encoded by the genetic code, as well as those amino acids that are later modified, e.g., hydroxyproline, γ-carboxyglutamate, and O-phosphoserine. Amino acid analogs refers to compounds that have the same basic chemical structure as a naturally occurring amino acid, e.g., an α carbon that is bound to a hydrogen, a carboxyl group, an amino group, and an R group, e.g., homoserine, norleucine, methionine sulfoxide, methionine methyl sulfonium. Such analogs may have modified R groups (e.g., norleucine) or modified peptide backbones, but retain the same basic chemical structure as a naturally occurring amino acid. Amino acid mimetics refers to chemical compounds that have a structure that is different from the general chemical structure of an amino acid, but that functions similarly to a naturally occurring amino acid.

[0058] Amino acids may be referred to herein by either their commonly known three letter symbols or by the one-letter symbols recommended by the IUPAC-IUB Biochemical

Nomenclature Commission. Nucleotides, likewise, may be referred to by their commonly accepted single-letter codes.

[0059] "Conservatively modified variants" applies to both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical or associated, e.g., naturally contiguous, sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode most proteins. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to another of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are "silent variations," which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes silent variations of the nucleic acid. One of skill will recognize that in certain contexts each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine, and TGG, which is ordinarily the only codon for tryptophan) can be modified to yield a functionally identical molecule. Accordingly, often silent variations of a nucleic acid which encodes a polypeptide is implicit in a described sequence with respect to the expression product, but not with respect to actual probe sequences.

[0060] As to amino acid sequences, one of skill will recognize that individual substitutions, deletions or additions to a nucleic acid, peptide, polypeptide, or protein sequence which alters, adds or deletes a single amino acid or a small percentage of amino acids in the encoded sequence is a "conservatively modified variant" where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art. Such conservatively modified variants are in addition to and do not exclude polymorphic variants, interspecies homologs, and alleles of the invention. Typically conservative substitutions for one another: 1) Alanine (A), Glycine (G); 2) Aspartic acid (D), Glutamic acid (E); 3) Asparagine (N), Glutamine (Q); 4) Arginine (R), Lysine (K); 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W); 7) Serine (S), Threonine (T); and 8) Cysteine (C), Methionine (M) (see, e.g., Creighton, Proteins (1984)).

[0061] The term "a" or "an" is generally intended to mean "one or more" unless otherwise indicated.

Introduction

[0062] The invention is based, in part, on the discovery that EphA3-expressing neoplastic blast and/or neoplastic stem cells in patients that have a myeloproliferative disorder can be killed by contacting the EphA3-expressing myeloproliferative disorder cells with an activating antibody and/or an antibody that induces ADCC. Accordingly, in one aspect, the invention provides methods of treating a CML, PV, ET, IM, AML, MDS, CMML, or JMML patient, comprising administering an activating anti-EphA3 antibody to the patient. In some embodiments, the methods of the invention comprise administering an anti-EphA3 antibody that induces ADCC to a CML, PV, ET, IM, AML, MDS, CMML, or JMML patient. In some embodiments, an anti-EphA3 antibody that is administered to a CML, PV, ET, IM, AML, MDS, CMML, or JMML patient (i) is an activating anti-EphA3 antibody and (ii) induces ADCC.

[0063] In some embodiments, an anti-EphA3 antibody for use in this invention does not block binding of EphA3 to ephrin, *e.g.,* ephrin-A5. In some embodiments, the antibody dimerizes EphA3. In some embodiments, the antibody cross-links EphA3. In some embodiments, the antibody competes with Mab IIIA4 for binding to EphA3, *e.g.,* such an antibody may bind to the same epitope as Mab IIIA4. In some embodiments, the antibody has an active isotype where the heavy chain constant domain can bind to Fc receptor present on immune effector cells, leading to ADCC.

Anti EphA3 antibodies

[0064] The anti-EphA3 antibodies of the invention can be raised against EphA3 proteins, or fragments, or produced recombinantly. Any number of techniques can be used to determine antibody binding specificity. *See, e.g.*, Harlow & Lane, Antibodies, A Laboratory Manual (1988) for a description of immunoassay formats and conditions that can be used to determine specific immunoreactivity of an antibody

[0065] In some embodiments, the anti-EphA3 antibody is a polyclonal antibody. Methods of preparing polyclonal antibodies are known to the skilled artisan (e.g., Harlow & Lane, Antibodies, A Laboratory manual (1988); Methods in Immunology). Polyclonal antibodies can be raised in a mammal by one or more injections of an immunizing agent and, if desired, an adjuvant. The immunizing agent includes a EphA3 receptor protein, or fragment thereof.

[0066] In some embodiments, the anti-EphA3 antibody is a monoclonal antibody. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler & Milstein, *Nature* 256:495 (1975). In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized *in vitro*.

[0067] Human monoclonal antibodies can be produced using various techniques known in the art, including phage display libraries (Hoogenboom & Winter, *J. Mol. Biol.* 227:381 (1991); Marks *et al., J. Mol. Biol.* 222:581 (1991)). The techniques of Cole *et al.* and Boerner *et al.* are also available for the preparation of human monoclonal antibodies (Cole *et al.*, Monoclonal Antibodies and Cancer Therapy, p. 77 (1985) and Boerner *et al., J. Immunol.* 147(1):86-95 (1991)). Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, *e.g.*, mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, *e.g.*, in U.S. Patent Nos. 5,545,807; 5,545,806; 5,569,825; 5,625,126; 5,633,425; 5,661,016, and in the following scientific publications: Marks *et al., Bio/Technology* 10:779-783 (1992); Lonberg *et al., Nature* 368:856-859 (1994); Morrison, *Nature* 368:812-13 (1994); Fishwild *et al., Nature Biotechnology* 14:845-51 (1996); Neuberger, *Nature Biotechnology* 14:826 (1996); Lonberg & Huszar, *Intern. Rev. Immunol.* 13:65-93 (1995).

[0068] In some embodiments the anti-EphA3 antibodies are chimeric or humanized monoclonal antibodies. As noted *supra*, humanized forms of antibodies are chimeric immunoglobulins in which a CDR of a human antibody is replaced by a CDR of a non-human species such as mouse, rat or rabbit having the desired specificity, affinity and capacity.

[0069] An antibody that is employed in the invention can be in numerous formats. In some embodiments, the antibody can include an Fc region, *e.g.*, a human Fc region. For example, such antibodies include IgG antibodies that bind EphA3 and that have an active isotype. In some embodiments, the antibody can be an active fragment (*e.g.*, it can dimerize EphA3) or can comprise a derivative of an antibody such as an Fab, Fab', $F(ab')_2$, Fv, scFv, or a single domain antibody ("dAb"). For example, in some embodiments, the antibody may be a

$F(ab')_2$. Other exemplary embodiments of antibodies that can be employed in the invention include activating nanobodies or activating camellid antibodies. Such antibodies may additionally be recombinantly engineered by methods well known to persons of skill in the art. As noted above, such antibodies can be produced using known techniques. As appreciated by one of skill in the art, in some embodiments when an antibody is in a format that can be monovalent, *e.g.,* an Fv or Fab format, the antibody may be employed as a multivalent antibody, such as a trivalent or tetravalent antibody. Methods of generating multivalent antibodies are known (*see, e.g.,* King *et al., Cancer Res.* 54:6176-6185, 1994).

[0070] In many embodiments, an antibody for use in the invention has an Fc constant region that has an effector function, *e.g.,* binds to an Fc receptor present on immune effector cells. Exemplary "effector functions" include C1q binding; complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (*e.g.*, B cell receptor), and the like. Such effector functions generally require the Fc region to be combined with a binding domain (*e.g.* an antibody variable domain) and can be assessed using known assays (see, *e.g.,* the references cited hereinbelow.)

[0071] Anti-EphA3 antibodies that have an active isotype and are bound to Fc-receptors on effector cells, such as macrophages, monocytes, neutrophils and NK cells, can induce cell death by ADCC.

[0072] The Fc region can be from a naturally occurring IgG1, or other active isotypes, including IgG3, IgM, IgA, and IgE. "Active isotypes" include antibodies where the Fc region comprises modifications to increase binding to the Fc receptor or otherwise improve the potency of the antibody. Such an Fc constant region may comprise modifications, such as mutations, changes to the level of glycosylation and the like, that increase binding to the Fc receptor. There are many methods of modifying Fc regions that are known in the art. For example, U.S. Patent Application Publication No. 20060039904 describes variants of Fc receptors that have enhanced effector function, including modified binding affinity to one or more Fc ligands (e.g., FcγR, C1q). Additionally, such Fc variants have altered antibody-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) activity. Other Fc variants include those disclosed by Ghetie et *al., Nat Biotech.* 15:637-40, 1997; Duncan *et al, Nature* 332:563-564, 1988; Lund *et al., J. Immunol* 147:2657-2662, 1991; Lund *et al, Mol Immunol* 29:53-59, 1992; Alegre *et al,*

Transplantation 57:1537-1543, 1994; Hutchins *et al., Proc Natl. Acad Sci USA* 92:11980-11984, 1995; Jefferis *et al, Immunol Lett.* 44:111-117, 1995; Lund *et al., FASEB J* 9:115-119, 1995; Jefferis *et al, Immunol Lett* 54:101-104, 1996; Lund *et al, J Immunol* 157:4963-4969, 1996; Armour *et al., Eur J Immunol* 29:2613-2624, 1999; Idusogie *et al, J Immunol* 164:4178-4184, 200; Reddy *et al, J Immunol* 164:1925-1933, 2000; Xu *et al., Cell Immunol* 200:16-26, 2000; Idusogie *et al, J Immunol* 166:2571-2575, 2001; Shields *et al., J Biol Chem* 276:6591-6604, 2001; Jefferis *et al, Immunol Lett* 82:57-65. 2002; Presta *et al., Biochem Soc Trans* 30:487-490, 2002; Lazar *et al., Proc. Natl. Acad. Sci. USA* 103:4005-4010, 2006; U.S. Pat. Nos. 5,624,821; 5,885,573; 5,677,425; 6,165,745; 6,277,375; 5,869,046; 6,121,022; 5,624,821; 5,648,260; 6,194,551; 6,737,056; 6,821,505; 6,277,375; 7,335,742; and 7,317,091; and PCT Publications WO 94/2935; WO 99/58572; WO 00/42072; WO 02/060919, and WO 04/029207,

[0073] In some embodiments, the glycosylation of Fc regions may be modified. for example, a modification may be aglycosylation, for example, by altering one or more sites of glycosylation within the antibody sequence. Such an approach is described in further detail in U.S. Pat. Nos. 5,714,350 and 6,350,861. An Fc region can also be made that has an altered type of glycosylation, such as a hypofucosylated Fc variant having reduced amounts of fucosyl residues or an Fc variant having increased bisecting GlcNAc structures. Such carbohydrate modifications can be accomplished by, for example, expressing the antibody in a host cell with altered glycosylation machinery. Cells with altered glycosylation machinery, including yeast and plants, have been described in the art and can be used as host cells in which to express recombinant antibodies of the invention to thereby produce an antibody with altered glycosylation. Techniques for modifying glycosylation include those disclosed *e.g.,* in Umana *et al, Nat. Biotechnol* 17:176-180, 1999; Davies, *et al., Biotechnol. Bioeng.* 74:288-294, 2001; Shields *et al, J Biol Chem* 277:26733-26740, 2002; Shinkawa *et al., J Biol Chem* 278:3466-3473, 2003; Niwa *et al. Clinc. Cancer Res.* 1-:6248-6255, 2004; Presta *et al., Biochem Soc Trans* 30:487-490, 2002; Kanda *et al, Glycobiology* 17:104-118, 2006; U.S. Pat. Nos. 6,602,684; 6,946,292; and 7,214,775; U.S. Patent Application Publication Nos. 20070248600; 20070178551; 20080060092; 20060253928; PCT publications WO 00/61739; WO 01/292246; WO 02/311140; and WO 02/30954; and Potillegent™ technology (Biowa, Inc. Princeton, N.J.); and GlycoMAb™. glycosylation engineering technology (GLYCART biotechnology AG, Zurich, Switzerland). In a hypofucosylated antibody preparation,

typically at least 50 to 70% of the antibody molecule, often at least 80% of the molecules, or at least 90% of the molecules, lack fucose.

[0074] In some embodiments of the invention, the antibody is additionally engineered to reduce immunogenicity, *e.g.,* so that the antibody is suitable for repeat administration. Methods for generating antibodies with reduced immunogenicity include humanization and humaneering procedures and modification techniques such as de-immunization, in which an antibody is further engineered, *e.g.,* in one or more framework regions, to remove T cell epitopes.

[0075] In some embodiments, the antibody is a HUMANEERED™ antibody. A HUMANEERED™ antibody is an engineered human antibody having a binding specificity of a reference antibody, obtained by joining a DNA sequence encoding a binding specificity determinant (BSD) from the CDR3 region of the heavy chain of the reference antibody to human V_H segment sequence and a light chain CDR3 BSD from the reference antibody to a human V_L segment sequence. Methods for generating such antibodies are provided in US patent application publication no. 20050255552 and US patent application publication no. 20060134098.

[0076] An antibody can further be de-immunized to remove one or more predicted T-cell epitopes from the V-region of an antibody. Such procedures are described, for example, in WO 00/34317.

[0077] In some embodiments, the variable region is comprised of human V-gene sequences. For example, a variable region sequence can have at least 80% identity, or at least 85% or at least 90% identity, or higher, to human germ-line V-gene sequences.

[0078] An antibody used in the invention can include a human constant region. The constant region of the light chain may be a human kappa or lambda constant region. The heavy chain constant region is often a gamma chain constant region, for example, a gamma-1 or gamma-3 constant region.

[0079] In some embodiments, *e.g.,* where the antibody is a fragment, the antibody can be conjugated to another molecule, *e.g.,* to provide an extended half-life *in vivo* such as a polyethylene glycol (pegylation) or serum albumin. Examples of PEGylation of antibody fragments are provided in Knight *et al., Platelets* 15:409, 2004 (for abciximab); Pedley *et al.,*

Br. J. Cancer 70:1126, 1994 (for an anti-CEA antibody); and Chapman *et al., Nature Biotech.* 17:780, 1999.

Antibody Specificity

[0080] An antibody for use in the invention activates EphA3 and/or kills EphA3$^+$ cells by ADCC. An example of an antibody suitable for use with the present invention is an antibody that has the binding specificity of mAb IIIA4. The monoclonal antibody mAb IIIA4 binds to the native EphA3 globular ephrin-binding domain (Smith *et al., J. Biol. Chem.* 279:9522-9531, 2004; and Vearing *et al., Cancer Res.* 65:6745-6754, 2005). High affinity mAb IIIA4 binding to the EphA3 surface has little effect on the overall affinity of ephrin-A5 interactions with EphA3.

[0081] In some embodiments, a monoclonal antibody that competes with mAb IIIA4 for binding to EphA3, or that binds the same epitope as mAb IIIA4, is used. Any of a number of competitive binding assays can be used to measure competition between two antibodies for binding to the same antigen. For example, a sandwich ELISA assay can be used for this purpose. In an exemplary assay, ELISA is carried out by using a capture antibody to coat the surface of a well. A subsaturating concentration of tagged-antigen is then added to the capture surface. This protein will be bound to the antibody through a specific antibody:antigen interaction. After washing, a second antibody that is linked to a detectable moiety is added to the ELISA. If this antibody binds to the same site on the antigen as the capture antibody, or interferes with binding to that site, it will be unable to bind to the target protein as that site will no longer be available for binding. If however this second antibody recognizes a different site on the antigen it will be able to bind. Binding can be detected by quantifying the amount of detectable label that is bound. The background is defined by using a single antibody as both capture and detection antibody, whereas the maximal signal can be established by capturing with an antigen specific antibody and detecting with an antibody to the tag on the antigen. By using the background and maximal signals as references, antibodies can be assessed in a pair-wise manner to determine specificity. The ability of a particular antibody to recognize the same epitope as another antibody is typically determined by such competition assays.

[0082] A first antibody is considered to competitively inhibit binding of a second antibody, if binding of the second antibody to the antigen is reduced by at least 30%, usually at least

about 40%, 50%, 60% or 75%, and often by at least about 90%, in the presence of the first antibody using any of the assays described above.

[0083] In some embodiments, the antibody binds to the same epitope as mAb IIIA4. The epitope for IIIA4 and human engineered derivatives resides in the N-terminal globular ligand binding domain of EphA3 (amino acids 29-202 in the partial human EphA3 sequence below):

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  1 MDCQLSILLL LSCSVLDSFG ELIPQPSNEV NLLDSKTIQG ELGWISYPSH GWEEISGVDE
 61 HYTPIRTYQV CNVMDHSQNN WLRTNWVPRN SAQKIYVELK FTLRDCNSIP LVLGTCKETF
121 NLYYMESDDD HGVKFREHQF TKIDTIAADE SFTQMDLGDR ILKLNTEIRE VGPVNKKGFY
181 LAFQDVGACV ALVSVRVYFK KC
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[0084] The IIIA4 antibody binds adjacent to but does not interfere substantially with binding of EphrinA5 to the receptor. The epitope for antibody IIIA4 has been further characterized by Smith *et al., J. Biol. Chem.* 279: 9522, 2004 using site-directed mutagenesis. In this analysis, mutation of Glycine at position 132 to Glutamic acid (G132E) abolishes binding to IIIA4. Mutation of Valine 133 to Glutamic acid (V133E) reduces binding of EphA3 to IIIA4 antibody approximately 100-fold. It has subsequently been observed by the inventors that Arginine 136 is also part of the epitope. This residue is changed to Leucine in the sequence of the highly conserved EphA3 protein in the rat (R136L). Rat EphA3 does not bind IIIA4 or a human engineered derivative of IIIA4. Thus, G132, V133 and R136 (bolded and underlined in the sequence above) are important amino acids within the IIIA4 epitope.

Binding Affinity

[0085] In some embodiments, the antibodies suitable for use with the present invention have a high affinity binding for human EphA3. For the purposes of this invention, high affinity binding between an antibody and an antigen exists if the dissociation constant (K_D) of the antibody is < about 10 nM, for example, about 5 nM, or about 2 nM, or about 1 nM, or less. A variety of methods can be used to determine the binding affinity of an antibody for its target antigen such as surface plasmon resonance assays, saturation assays, or immunoassays such as ELISA or RIA, as are well known to persons of skill in the art. An exemplary method for determining binding affinity is by surface plasmon resonance analysis on a BIAcore™ 2000 instrument (Biacore AB, Freiburg, Germany) using CM5 sensor chips, as described by Krinner *et al.*, (2007) *Mol. Immunol.* Feb;44(5):916-25. (Epub 2006 May 11)).

[0086] The anti-EphA3 antibody can bind to any region of EphA3. In some embodiments, the anti-EphA3 antibody activates EphA3. Often, the antibody dimerizes EphA3. In some embodiments, the antibody clusters EphA3. In some embodiments, an anti-EphA3 antibody can also be employed that has an active isotype, such as an IgG1, IgG3, IgM, IgA, or IgE, and is cytotoxic to myeloproliferative disorder cells via ADCC. Antibodies for use in the invention can also be multivalent including forms of monomers that are cross-linked or otherwise multimerized to form multivalent antibodies.

[0087] In some embodiments, an antibody employed in the invention does not compete with an EphA3 ligand for binding to EphA3, whereas in other embodiments an EphA3 antibody for use in the invention can compete for binding of an EphA3 ligand such as an ephrin, *e.g.,* ephrin-A5, to EphA3. Antibodies that compete with a ligand for binding to EphA3, can be identified using techniques as described above, where an ephrin ligand such as ephrin-A5, is used instead of another antibody for a competition analysis.

[0088] In exemplary embodiments, the anti-EphA3 antibody comprises the V_L and V_H regions of mAb IIIA4. In other embodiments, the anti-EphA3 antibody comprises CDRs 1, 2 and 3 of mAb IIIA4. In some embodiments, the anti-EphA3 antibody comprises CDR3 of mAb IIIA4. Table 1 provides CDR sequences (defined according to Kabat numbering) of antibodies that bind to the same epitope as mAb IIIA4. Affinity for EphA3 antigen was determined by ELISA. An antibody of the invention may thus also have heavy chain and/or lights chain CDRs set forth in Table 1.

Table 1

antibody	CDRH1	CDRH2	CDRH3	AFFINITY (nM)
IIIA4	SYWIN	DIYPGSGNTNYDEKFKR	SGYYEDFDS	2.5
FA3AM-H12A	TYWIS	DIYPGSGNTNYDEKFQG	SGYYEEFDS	3.2
K3D	TYWIS	DIYPGSGNTNYDEKFEG	SGYYEEFDS	25

antibody	CDRL1	CDRL2	CDRL3	AFFINITY (nM)
IIIA4	RASQEISGYLG	AASTLDS	VQYANYPYT	2.5
FA3AM-H12A	RASQGIISYLA	AASSLQS	VQYANYPYT	3.2
K3D	RASQGIISYLA	AASSLQS	VQYMNYPYT	25

[0089] Antibodies as described herein for use in the invention can be identified using known assays for the characteristic of interest. Thus, antibodies can be identified by screening for the ability to activate EphA3 (*e.g.,* using n apoptosis assay as described in the

examples), the ability to induce ADCC (*e.g.*, using an ADCC assay as described in the examples), and for binding specificity and affinity using assays described above.

Non-Antibody EphA3 binding agents

[0090] Other proteins that bind to EphA3 and dimerize or activate EphA3 receptor may also be administered to a patient that has a leukemia or CMPD. Such proteins include a soluble Ephrin A5-Fc protein.

[0091] Other EphA3 binding agents include scaffolded proteins that bind EphA3. Thus, the EphA3 binding agent can be an "antibody mimetic" that targets and binds to the antigen in a manner similar to antibodies. When an antibody mimetic is used, the form of the mimetic is such that it dimerizes EphA3. For example, the antibody mimetic may be used in a dimeric or multivalent format.

[0092] Certain antibody mimetics use non-immunoglobulin protein scaffolds as alternative protein frameworks for the variable regions of antibodies. For example, Ku *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 92:6552-6556, 1995) discloses an alternative to antibodies based on cytochrome b562 in which two of the loops of cytochrome b562 were randomized and selected for binding against bovine serum albumin. The individual mutants were found to bind selectively with BSA similarly with anti-BSA antibodies.

[0093] U.S. Patent Nos. 6,818,418 and 7,115,396 disclose an antibody mimic featuring a fibronectin or fibronectin-like protein scaffold and at least one variable loop. Known as Adnectins, these fibronectin-based antibody mimics exhibit many of the same characteristics of natural or engineered antibodies, including high affinity and specificity for any targeted ligand. The structure of these fibronectin-based antibody mimics is similar to the structure of the variable region of the IgG heavy chain. Therefore, these mimics display antigen binding properties similar in nature and affinity to those of native antibodies. Further, these fibronectin-based antibody mimics exhibit certain benefits over antibodies and antibody fragments. For example, these antibody mimics do not rely on disulfide bonds for native fold stability, and are, therefore, stable under conditions which would normally break down antibodies. In addition, since the structure of these fibronectin-based antibody mimics is similar to that of the IgG heavy chain, the process for loop randomization and shuffling may be employed in vitro that is similar to the process of affinity maturation of antibodies *in vivo*.

[0094] Beste *et al.* (*Proc. Natl. Acad. Sci. U.S.A.* 96:1898-1903, 1999) disclose an antibody mimic based on a lipocalin scaffold (Anticalin®). Lipocalins are composed of a β-barrel with four hypervariable loops at the terminus of the protein. The loops were subjected to random mutagenesis and selected for binding with, for example, fluorescein. Three variants exhibited specific binding with fluorescein, with one variant showing binding similar to that of an anti-fluorescein antibody. Further analysis revealed that all of the randomized positions are variable, indicating that Anticalin® would be suitable to be used as an alternative to antibodies. Thus, Anticalins® are small, single chain peptides, typically between 160 and 180 residues, which provides several advantages over antibodies, including decreased cost of production, increased stability in storage and decreased immunological reaction.

[0095] U.S. Patent No. 5,770,380 discloses a synthetic antibody mimetic using the rigid, non-peptide organic scaffold of calixarene, attached with multiple variable peptide loops used as binding sites. The peptide loops all project from the same side geometrically from the calixarene, with respect to each other. Because of this geometric confirmation, all of the loops are available for binding, increasing the binding affinity to a ligand. However, in comparison to other antibody mimics, the calixarene-based antibody mimic does not consist exclusively of a peptide, and therefore it is less vulnerable to attack by protease enzymes. Neither does the scaffold consist purely of a peptide, DNA or RNA, meaning this antibody mimic is relatively stable in extreme environmental conditions and has a long life span. Further, since the calixarene-based antibody mimic is relatively small, it is less likely to produce an immunogenic response.

[0096] Murali *et al.* (*Cell Mol Biol* 49:209-216, 2003) describe a methodology for reducing antibodies into smaller peptidomimetics, they term "antibody like binding peptidomimetics" (ABiP) which may also be useful as an alternative to antibodies.

[0097] WO 00/60070 discloses a polypeptide chain having CTL4A-like β-sandwich architecture. The peptide scaffold has from 6 to 9 β-strands, wherein two or more of the polypeptide β-loops constitute binding domains for other molecules, such as antigen binding fragments. The basic design of the scaffold is of human origin, thus reducing the risk of inducing an immune response. The β-sandwich scaffold may have improved stability and pharmacokinetic properties *in vivo* when compared to standard antibodies as the molecule contains a second, non-immunoglobulin disulphide bridge. As antigen binding domains can

be located at opposite ends of a single peptide chain, the β-sandwich also facilitates design of bispecific monomeric molecules.

[0098] In addition to non-immunoglobulin protein frameworks, antibody properties have also been mimicked in compounds comprising RNA molecules and unnatural oligomers (*e.g.*, protease inhibitors, benzodiazepines, purine derivatives and beta-turn mimics). Accordingly, non-antibody EphA3 binding agents can also include such compounds.

[0099] In some embodiments, the EphA3 binding agents employed in the invention competed with mAb IIIA4 for binding to EphA3. Such agents can be identified using known assays, such as the exemplary competition assays described herein.

Identification of patients who are candidate for treatment with anti-EphA3

[0100] The invention also provides methods of determining whether a patient having a myeloproliferative disorder is a candidate for treatment with an anti-EphA3 antibody. The methods comprise detecting the expression of EphA3 on myeloproliferative disorder cells from the patient. In some embodiments, expression of EphA3 is detected on blast cells. In some embodiments, EphA3 expression is detected on stem cells. In some embodiments, EphA3 expression is detected on both blast and stem cells.

[0101] In some embodiments, a blood sample, *e.g.,* a serum or plasma sample, from a myeloproliferative disorder patient can be evaluated for elevated levels (*e.g.,* in comparison to a normal patient that does not have a myeloproliferative disorder) of soluble EphA3 to determine if the patient is a candidate for treatment with an anti-EphA3 antibody. In some embodiments, levels of soluble EphA3 can be determined in a patient to monitor the efficacy of treatment with an anti-EphA3 antibody. Soluble EphA3 can be detected using known immunoassays, *e.g.,* an ELISA.

[0102] EphA3 expression can be detected using methods well known in the art. Often, an immunological assay can be used to detect levels of EphA3 protein. Immunological assays include ELISA, fluorescent-activated cell sorting, and the like. Alternatively EphA3 expression can be detected by detecting the level of mRNA encoding EphA3. Often, a nucleic acid amplification method, *e.g.,* an RT-PCR is employed to quantify the amount of RNA.

[0103] A sample comprising myeloproliferative disorder cells is obtained from the patient for evaluating EphA3 expression. The sample is often a peripheral blood sample, but other suitable samples, *e.g.,* a bone marrow sample, may also be analyzed.

[0104] A patient is considered to be a candidate for treatment with an anti-EphA3 antibody if blast cells, stem cells, or both that are present in the sample comprising myeloproliferative disorder cells express EphA3. Accordingly, "an $EphA3^+$ patient" as used here is a patient that shows EphA3 expression on myeloproliferative disorder cells relative to cells from normal controls, *e.g.,* patients who do not have a hematopoietic disorder.

Treatment of myeloproliferative disorders

[0105] In one aspect, the methods of the present invention comprise administering an anti-EphA3 agent, typically an anti-EphA3 antibody, to a patient that has AML, CML, PV, ET, IM, MDS, CMML, or JMML and has neoplastic myeloproliferative disorder cells that express EphA3 on the cell surface. In some embodiments, an anti-EphA3 agent, such as an antibody, is administered to a patient that neoplastic myeloid stem cells (characterized as $CD34^+$, $CD123^+$ and $CD38^-$) that express EphA3 A patient, such as an AML patient, that is treated with the anti-EphA3 agent, *e.g.,* an anti-EphA3, in accordance with the invention may therefore have both hematopoietic stem cells and blast cells that express EphA3. Other patients that are treated using methods and compositions described herein may express EphA3 only on blast cells. Still other patients may express EphA3 only on stem cells. In some embodiments, a patient treated with the anti-EphA3 antibody is an AML or MDS patient having myeloproliferative disorder blast cells that expresses EphA3 on the surface.

[0106] Leukemic and myeloproliferative disorder stem cells can be identified by commonly used techniques such as immunophenotyping using flow cytometry, or by *in vitro* cell culture techniques or *in vivo* transplantation experiments.

[0107] Stem cells are multipotent progenitor cells that may be further defined functionally as cells with self-renewing capacity (*see, e.g.,* Reya *et al., Nature* 414:105-111, 2001, and references cited therein). This may be demonstrated, for example, in long-term culture initiating cell (LTC-IC) assays in which cells are cultured on irradiated bone-marrow stromal feeder cells. In this assay, the presence of stem cells is revealed by the ability to serially transfer colonies for extended periods (e.g.,at least 5 weeks e.g. Guan and Hogge (2000) Leukemia 14: 2135). Serial transfer assays may also be carried out by culturing stem cell-

derived colonies in methyl cellulose in the presence of growth factors, such as a combination of stem cell factor (SCF), interleukin-3 (IL3), granulocyte macrophage colony stimulating factor (GM-CSF) and erythropoietin (EPO).

[0108] *In vivo* transplantation to identify stem cells is carried out by passaging by serial transfer in mice with defective immune systems (SCID/NOD mice; van Rhenen *et al.*, *Clin. Cancer. Res.* 11: 6520-6527, 2005).

[0109] In flow cytometry analysis, leukemic or chronic myeloproliferative disorder (CMPD) stem cells are typically present in the CD34-positive, CD38-negative cell compartment (although approximately 10% of AML cases are CD34-negative). Leukemic or CMPD stem cells can be identified in the CD38-negative cell compartment as CD123-positive cells (Jordan *et al., Leukemia* 14: 1777-1784, 2000) although other markers may also be used to identify stem cells including the presence of CD117, CD45RA or CD133.

[0110] Blast cells are unipotent cells that are able to participate in granulopoiesis. Blast cells are larger cells than normal human mononuclear and polymorphonuclear blood cells and can be identified by microscopy from blood smears or by flow cytometry analysis on the basis of high forward scatter (FSC) and side scatter (SSC) compared with monocytes and granulocytes.

[0111] The anti-EphA3 composition can be formulated for use in a variety of drug delivery systems. One or more physiologically acceptable excipients or carriers can also be included in the compositions for proper formulation. Suitable formulations for use in the present invention are found in *Remington: The Science and Practice of Pharmacy*, 21st Edition, Philadelphia, PA. Lippincott Williams & Wilkins, 2005. For a brief review of methods for drug delivery, see, Langer, *Science* s249: 1527-1533 (1990).

[0112] The anti-EphA3 antibody for use in the methods of the invention is provided in a solution suitable for injection into the patient such as a sterile isotonic aqueous solution for injection. The anti-EphA3 antibody is dissolved or suspended at a suitable concentration in an acceptable carrier. In some embodiments the carrier is aqueous, *e.g.*, water, saline, phosphate buffered saline, and the like. The compositions may contain auxiliary pharmaceutical substances as required to approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, and the like.

[0113] The pharmaceutical compositions of the invention are administered to a patient that has a myeloproliferative disorder in an amount sufficient to at least partially arrest the disease or symptoms of the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." A therapeutically effective dose is determined by monitoring a patient's response to therapy. Typical benchmarks indicative of a therapeutically effective dose are known in the art, depending on the disease. For example, therapeutic efficacy may be indicated by the decrease of the number of abnormal myeloid cells that are characteristic of the particular myeloid proliferation disorder in the blood or bone marrow.

[0114] The dose of the anti-EphA3 antibody is chosen in order to provide effective therapy for the patient and is in the range of about 0.1 mg/kg body weight to about 25 mg/kg body weight or in the range about 1 mg to about 2 g per patient. The dose is often in the range of about 0.5 mg/kg or about 1 mg/kg to about 10 mg/kg, or approximately about 50 mg to about 1000 mg / patient. In some embodiments, the antibody is administered in an amount less than about 0.1mg/kg body weight, *e.g.,* in an amount of about 20 mg/patient or less. The dose may be repeated at an appropriate frequency which may be in the range once per day to once every three months, depending on the pharmacokinetics of the antibody (e.g. half-life of the antibody in the circulation) and the pharmacodynamic response (e.g. the duration of the therapeutic effect of the antibody). In some embodiments where the antibody or modified antibody fragment has an *in vivo* half-life of between about 7 and about 25 days and antibody dosing is repeated between once per week and once every 3 months. In other embodiments, the antibody is administered approximately once per month.

[0115] Amounts that are administered that are effective will depend upon the severity of the disease and the general state of the patient's health, including other factors such as age, weight, gender, administration route, etc. Single or multiple administrations of the anti EphA3 antibody may be administered depending on the dosage and frequency as required and tolerated by the patient. In any event, the methods provide a sufficient quantity of the anti EphA3 antibody to effectively treat the myeloproliferative disorder.

[0116] An anti-EphA3 antibody or anti-EphA3 agonist binding agent, *e.g.,* that induces dimerization or activates EphA3, can be used in combination with one or more additional therapeutic agents to treat the myeloproliferative disorder. Therapeutic agents that can be administered in conjunction with anti-EphA3 binding agents include compounds such as

MYLOTARG® (gemtuzumab ozogamicin for injection); a tyrosine kinase inhibitor such as imatinib mesylate (GLEEVEC®), nilotinib (TASIGNA®), and dasatinib (SPRYCEL®); interferon-α, and various chemotherapeutic agents.

[0117] In some embodiments, an anti-EphA3 activating antibody an be used in combination with one or more additional therapeutic agents to treat a patient that has chronic myeloid leukemia where leukemic stem cells from the patient express EphA3. Such therapeutic agents include various chemotherapeutic agents and imatinib mesylate (GLEEVEC®).

[0118] In some embodiments, an anti-EphA3 antibody, *e.g.,* an activating antibody, can be used in combination with one or more additional agents to treat acute myeloid leukemia. Such agents include cytosine arabinoside alone and in combination with daunorubicin.

[0119] In some embodiments, an anti-EphA3 activating antibody can be used in combination with one or more additional therapeutic agents to treat a patient that has a BCR-ABL negative CMPD. Such inhibitors include JAK2 inhibitors, which are known in the art and undergoing clinical evaluation.

[0120] Patients can receive one or more of these additional therapeutic agents as concomitant therapy. Alternatively, patients may be treated sequentially with additional therapeutic agents.

[0121] In some embodiments, an anti-EphA3 activating antibody is administered to a patient that has undergone a bone marrow transplant.

[0122] In some embodiments, an anti-EphA3 antibody, or other activating Epha3 binding agent, is administered by injection or infusion through any suitable route including but not limited to intravenous, subcutaneous, intramuscular, intranasal, or intraperitoneal routes. In some embodiments, the anti EphA3 antibody is diluted in a physiological saline solution for injection prior to administration to the patient. The antibody is administered, for example, by intravenous infusion over a period of between 15 minutes and 2 hours.

[0123] The following examples are provided by way of illustration only and not by way of limitation. Those of skill in the art will readily recognize a variety of non-critical parameters that could be changed or modified to yield essentially similar results.

EXAMPLES

Example 1. Identification of CMPDs and leukemias that express EphA3 on the surface

[0124] Flow cytometry was used to evaluate the expression of EphA3 on the surface of tumor cells from patients diagnosed with a myeloproliferative disorder. Cells isolated from peripheral blood (buffy coat cell preparations; peripheral blood mononuclear cells (PBMC)) or bone marrow aspirates were suspended at 1 x 10^6 cells/ 0.1ml in flow cytometry buffer (PBS, 2 mM EDTA, 2 % fetal bovine serum, 0.05% sodium azide) with 1 μg normal IgG to block Fc-receptor binding (rat IgG; US Biological or anti-FcR antibodies). Anti-EphA3 antibody or negative control human IgG1 was added at 5 μg/ml and incubated on ice for 20 min. Cells were washed by dilution in flow cytometry buffer and centrifugation at 1000 rpm for 5 min. The cell pellet was resuspended in FITC-conjugated goat $F(ab)'_2$ anti-human IgG antibody (Caltag) diluted in flow cytometry buffer (1:20) and incubated on ice for 20 min. Cells were washed once by centrifugation and resuspended in flow cytometry buffer containing propidium iodide (Sigma) diluted 1:1000. Viable cells which exclude propidium iodide were analyzed by flow cytometry to identify EphA3-expressing cells in comparison with cells stained with negative control antibody.

[0125] Table 2 shows that EphA3 is detectable on the cell surface in a proportion of acute and chronic myeloid leukemias and in myeloproliferative disorders including idiopathic myelofibrosis and essential thrombocythemia peripheral blood mononuclear cells.

Table 2. Summary of Flow Cytometry screen of bone marrow and peripheral blood (PBMC) samples for surface EphA3 detected by flow cytometry

Tumor type	Number of samples tested	EphA3 positive samples*	Samples positive for EphA3 (%)
AML	41	26	63
CML	10	5	50
MDS	16	7	44
IM (PBMC)	1	1	
ET (PBMC)	1	1	
PV (PBMC)	2	1	

*Sample defined as positive if at least 5% of cells show higher immunofluorescence than the fluorescence intensity in samples stained with isotype control antibody

[0126] Leukemic stem cells in AML were also evaluated for surface EphA3 expression. Bone marrow-derived cells from an AML patient were stained with antibodies to CD34, CD38 and CD123 to identify the leukemic stem cell population (characterized as CD34-positive, CD123-positive and CD38-negative). PE-conjugated anti-CD34; PEcy5-conjugated anti-CD38; and APC-conjugated anti-CD123 antibodies were used for flow cytometry analysis (50, 000 events per sample). Binding of human engineered antibody specific for EphA3 to CD34, CD38-gated cells is shown in Figure 1. All of the CD123-positive (CD34-positive and CD38-negative) leukemic stem cells were positive for EphA3 expression.

[0127] EphA3 was not detectable on normal hematopoietic CD34-positive stem cells (data not shown). Further, antibody to EphA3 did not interfere with normal hematopoiesis in *in vitro* colony formation assays.

Example 2. Evaluation of the ability of an anti-EphA3 antibody to induce apoptosis of myeloproliferative disorder cells

[0128] This example demonstrates that an anti-EphA3 antibody induced apoptosis in myeloproliferative disorder cells.

[0129] An engineered human activating antibody that binds to EphA3 was evaluated for the ability to induce apoptosis *in vitro* in primary cells isolated from patients or individuals suffering from myeloproliferative disorders. Cells were seeded at 2.5 x 10^5 cells/ well in 96-well "U"-bottom plates in 0.1 ml culture medium (RPMI 1640 with 10% fetal bovine serum). Anti-EphA3 antibody or human IgG1 isotype control antibody was added to final concentrations between 10 μg/ml and 1 ng/ml and the plates were incubated at 37°C and 5% carbon dioxide in a tissue-culture incubator for 24 hours. As a positive control for apoptosis induction, separate cell samples were incubated with camptothecin (10 μM; Calbiochem). At the end of the incubation, cells were harvested and washed by centrifugation at 1000 rpm for 5 min followed by incubation in 0.1 ml of 1x Annexin V binding buffer (BD Pharmingen , Cat # 556547, component no.51-66121E) containing 5 μl FITC-conjugated Annexin V (BD Pharmingen, component no. 51-65874X) and 5 μl Propidium Iodide (component no.51-66211E) for 15 minutes at room temperature in the dark. Four hundred μl of 1X binding buffer was added to each tube and annexin V-staining apoptotic cells were identified by flow cytometry. Figure 4 provides data showing apoptosis activity of a human engineered antibody.

[0130] The results shown in Table 3 demonstrate that the antibody induced apoptosis in several samples at levels comparable to camptothecin. In samples in which only a small proportion of the cells express EphA3, the anti-EphA3 antibody induced apoptosis in a similar small proportion of the cells, indicating that the induction of apoptosis is specific for EphA3-positive cells.

Table 3. Induction of apoptosis by an engineered human activating antibody that binds to EphA3. (PB, peripheral blood; BM, bone marrow).

Sample	Disease	$EphA3^+$ cells (%)	Anti-EphA3-mediated apoptosis (% cell death)	Camptothecin-mediated apoptosis (% cell death)
PB-1	ET	27	64	78
PB-2	PV	6	1.8	73.2
BM, 06	AML	65	85.5	59.8
BM, 07	AML	80	46.7	47.8

Example 3. Evaluation of the ability of an anti-EphA3 antibody to induce ADCC in myeloproliferative disorder cells

Preparation of anti-EphA3 antibody deficient in α 1,6-fucose

[0131] CHO cells expressing a recombinant engineered human anti-EphA3 antibody (IgG1k) were cultured in CHO-SFM II medium (Invitrogen) containing 2 μg/ml kifunensine to generate antibody with a modified glycosylation pattern defective in α 1,6–fucose as described (Zhou *et al., Biotechnol. Bioeng.* 99:652-665, 2008). Antibody purified by Protein A affinity chromatography showed significant reduction in the level of α 1,6–fucose determined by binding of *Lens culinaris* Lectin (Sigma) on protein blots with less than 10% antibody molecules containing this sugar moiety.

ADCC assay

[0132] Human PBMC effector cells were isolated from buffy coat samples by Ficoll-hypaque density separation according to standard techniques. Primary mononuclear cells from bone marrow or peripheral blood from patients with leukemia or myeloproliferative disorders were used as target cells in ADCC assays. Tumor target cells were incubated for 16 hours with human effector cells at an effector: target ratio of 100:1 or 200:1 for PBMC. Lactate dehydrogenase (LDH) released from dead cells was determined by CytoTox 96 assay

(Promega). In this assay, incubation of target cells with antibody in the absence of effector cells showed no detectable cytotoxicity.

[0133] Results of a representative ADCC assay in which killing of human essential thrombocythemia cells was induced by an anti-EphA3 antibody (IgG1k) in the presence of PBMC effector cells are shown in Figure 2. The antibody showed potent ADCC activity in this assay. Inclusion of an antibody to CD16 abrogates the cytotoxic activity of the anti-EphA3 antibody, indicating that ADCC is mediated by the CD16 receptor (FcRIII). Anti-CD16 antibody (BD Pharmingen) was added at a concentration of 5 μg/ml.

[0134] The antibody preparation deficient in α 1,6 fucose was evaluated in comparison with fucosylated antibody in ADCC assays. In the assay shown in Figure 3, a pre-B cell leukemia derived cell line LK63 was used as the target. The antibody deficient in α 1,6 fucose was significantly more potent than the fucosylated antibody in this assay. ADCC activity was detected with low levels of defucosylated antibody (0.1 ng/ml), a concentration at which fucosylated antibody showed no detectable ADCC activity.

[0135] The engineered human anti-EphA3 antibody also shows potent ADCC activity against primary human tumor cells from bone marrow samples from AML patients and shows ADCC activity against EphA3-positive cells in the peripheral blood of polycythemia vera patients as shown in Table 4.

Table 4. ADCC activity of an engineered human anti-EphA3 antibody against cells from patients with leukemia or myeloproliferative disease. (PB, peripheral blood; BM, bone marrow).

Sample	Disease	$EphA3^+$ cells (%)	Anti-EphA3-mediated ADCC (% cytotoxicity at 16 h)
PB-1	ET	27	70
PB-2	PV	6	8
BM, 06	AML	65	85.5
BM, 07	AML	80	46.7
BM, 157260	AML	65	70

[0136] Table 5 summarizes data on the cell phenotype of EphA3-expressing cells from a larger panel of primary samples from bone marrow aspirates from AML and myelodysplastic syndrome patients and shows the proportion of cells in each sample killed by anti-EphA3 antibody either by direct induction of apoptosis or by effector-cell mediated ADCC activity. In these samples, in each case in which $CD123^{+}$ $CD34^{+}$ $CD38^{-}$ leukemic stem cells (LSC) could be identified, 100% of these LSC were also positive for EphA3 expression. In the majority of samples, there is good correlation between the percent of cells killed either by ADCC or apoptosis mediated by an engineered human anti-EphA3 antibody and the proportion of cells detected as positive for EphA3 by flow cytometry, indicating specificity of the antibody for EphA3-expressing cells.

Table 5 Summary of expression of EphA3 on malignant blast and leukemic stem cells: A human engineered antibody kills EphA3+ cells by two independent mechanisms.

	Flow Cytometry Analysis on Bone Marrow Samples					Anti-EphA3 activity	
		CD34+ Bone marrow		Leukemic Stem Cells (CD34+CD38-CD123+)			
Patient Sample	EphA3+ (% of total cells)	CD34+ (% of total cells)	EphA3+ (% of CD34+ cells)	LSC (% of total cells)	EphA3+ (% of LSC)	% Total Cells Killed by ADCC	% Total Cells Killed by Apoptosis
AML1	0	0	0	0	N/A	0	0
AML2	51	59	98	0	N/A	86	86
AML3	83	81	100	N/D	N/A	47	50
AML4	88	40	100	25	100	95	79
AML5	55	90	64	0	N/A	72	79
AML6	21	20	100	12	99	20	22
AML7	16	77	12	10	100	20	15
AML8	24	0	0	0	N/A	22	20
AML9	31	16	36	0	N/A	40	45
AML10	41	43	92	0	N/A	50	48
AML11	55	56	99	0	N/A	65	75
AML12	14	27	22	0	N/A	20	15
MDS 1	15	17	22	1	100	25	20
MDS 2	9	28	35	3	100	20	19

5

[0137] All publications, patent applications, accession numbers, and other references cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference.

WHAT IS CLAIMED IS:

1. A method of killing myeloproliferative disorder cells that express EphA3 on the cell surface, the method comprising contacting the cells with an anti-EphA3 antibody, wherein the anti-EphA3 antibody (i) activates EphA3 and (ii) induces antibody-dependent cell-mediated cytotoxicity (ADCC).

2. A method of treating a patient that has a myeloproliferative disorder and has myeloproliferative disorder cells that express EphA3 on the cell surface, the method comprising administering a therapeutically effective amount of an anti-EphA3 antibody to the patient, wherein the anti-EphA3 antibody (i) activates EphA3 and (ii) induces ADCC.

3. The method of claim 1 or claim 2, wherein the myeloproliferative disorder cells are chronic myeloproliferative disorder (CMPD) cells.

4. The method of claim 3, wherein the CMPD cells are BCR-ABL negative CMPD cells.

5. The method of claim 3, wherein the CMPD cells are CML cells.

6. The method of claim 5, further comprising administering at least one additional therapeutic agent, wherein the at least one additional therapeutic agent is a chemotherapeutic agent.

7. The method of claim 6, wherein the chemotherapeutic agent is imatinib mesylate, nilotinib, or dasatinib.

8. The method of any one of the preceding claims, wherein the antibody comprises a human heavy chain gamma-1 or gamma-3 constant region.

9. The method of any one of the preceding claims, wherein the antibody is hypofucosylated.

10. The method of any one of the preceding claims, wherein the anti-EphA3 antibody competes with mab IIIA4 for binding to EphA3.

11. The method of any one of any one of the preceding claims, wherein the anti EphA3 antibody is a recombinant or chimeric antibody.

12. The method of any one of the preceding claims, wherein the anti EphA3 antibody is a human antibody.

13. The method of any one of claims 1 to 12, wherein the anti EphA3 antibody is a monoclonal antibody.

14. The method of any one of claims 1 to 12, wherein the anti EphA3 antibody is a polyclonal antibody.

15. The method of any one of the preceding claims, wherein the antibody comprises the V_H region CDR3 and V_L region CDR3 of mAb IIIA4.

16. The method of claim 15, wherein the anti EphA3 antibody comprises V_H and V_L region CDR1, CDR2 and CDR3 of mAb IIIA4.

17. A method of killing myeloproliferative disorder cells that express EphA3 on the surface, the method comprising contacting the cells with an anti-EphA3 antibody that activates EphA3 or induces ADCC, wherein the myeloproliferative disorder cells are acute myeloid leukemia (AML) cells or myelodysplastic syndrome (MDS) cells.

18. A method of treating a patient that has a myeloproliferative disorder and has myeloproliferative disorder cells the express EphA3 on the cell surface, the method comprising administering a therapeutically effective amount of an anti-EphA3 antibody to the patient, wherein the anti-EphA3 antibody activates EphA3 or induces ADCC, wherein the myeloproliferative disorder is AML or MDS.

19. The method of claim 17 or claim 18, wherein the myeloproliferative disorder cells are AML cells.

20. The method of claim 19, further comprising administering at least one additional therapeutic agent, wherein the at least one additional therapeutic agent is cytosine arabinoside alone or in combination with daunorubicin.

21. The method of claim 17 or claim 18, wherein the antibody activates EphA3.

22. The method of any one of claims 17 to 20, wherein the antibody comprises a human heavy chain constant region.

23. The method of any one of claims 17 to 38, wherein the anti-EphA3 antibody competes for EphA3 binding with mAb IIIA4.

24. The method of any one of the preceding claims, wherein the antibody is a $(Fab')_2$.

25. The method of any one of claims 17 to 23, wherein the anti EphA3 antibody is a recombinant or chimeric antibody.

26. The method of any one of claims 17 to 25, wherein the anti EphA3 antibody is a human antibody.

27. The method of any one of claims 17 to 26, wherein the anti EphA3 antibody is a polyclonal antibody.

28. The method of any one of claims 17 to 26, wherein the anti EphA3 antibody is a monoclonal antibody.

29. The method of any one of claims 17 to 28, wherein the anti EphA3 antibody is a multivalent antibody that comprises a Fab, a Fab', or an Fv.

30. The method of any one of claims 17 to 29, wherein the anti EphA3 antibody comprises the V_H and V_L regions of mAb IIIA4.

31. The method of any one of claims 17 to 29, wherein the anti EphA3 antibody comprises the V_H and V_L region CDR1, CDR2 and CDR3 of mAb IIIA4.

32. The method of any one of claims 17 to 29, wherein the antibody comprises the V_H region CDR3 and V_L region CDR3 of mAb IIIA4.

33. The method of any one of claims 17 to 32, wherein the anti-EphA3 antibody induces ADCC.

34. The method of claim 33, wherein the antibody blocks binding of ephrinA5 ligand to EphA3.

35. The method of claim 33, wherein the antibody is hypofucosylated.

36. The method of claim 33, wherein the antibody has a human gamma-1 or gamma-3 constant region.

37. The method of claim 33, wherein the antibody blocks binding of ephrinA5 ligand to EphA3.

38. The method of any one of claims 22 to 32, wherein the human heavy chain constant region is a gamma-2 or gamma-4 region.

39. A method of determining that an AML patient or MDS patient is a candidate for treatment with an anti-EphA3 antibody, the method comprising:

providing a sample from the patient, where the sample comprises myeloproliferative disorder cells; and

detecting expression of EphA3 on the myeloproliferative disorder cells.

40. The method of claim 39, wherein EphA3 is detected on blast cells,

41. The method of claim 39, wherein EphA3 is detected on stem cells.

42. The method of claim 39, wherein EphA3 is detected on both blast and stem cells.

43. The method of claim 39, wherein the step of detecting expression of EphA3 comprises detecting protein expression on the cell surface.

44. The method of claim 39, wherein the step of detecting expression of EphA3 comprises detecting EphA3 RNA levels.

45. The method of claim 44, wherein detecting EphA3 RNA levels comprises performing an amplification reaction.

46. The method of claim 45, wherein the amplification reaction comprises RT-PCR.

47. A method of determining that a CMPD patient is a candidate for treatment with an anti-EphA3 antibody, the method comprising:

providing a sample comprising neoplastic stem cells from the patient; and

detecting expression of EphA3 by the neoplastic stem cells.

48. A method of monitoring the efficacy of treatment of a patient having a myeloproliferative disorder with $EphA3^+$ myeloproliferative cells, wherein the myeloproliferative disorder is AML or MDS, the method comprising:

obtaining a sample comprising myeloproliferative disorder stem cells and/or blast cells from the patient following a therapeutic treatment for the myeloproliferative disorder; and

detecting expression of EphA3 on the myeloproliferative disorder stem cells and/or blast cells.

49. A method of monitoring the efficacy of treatment of a CMPD patient that has neoplastic myeloproliferative disorder stem cells that express EphA3, the method comprising:

obtaining a sample comprising the neoplastic stem cells from the patient following a therapeutic treatment for the CMPD; and

detecting expression of EphA3 on the stem cells.

Figure 1

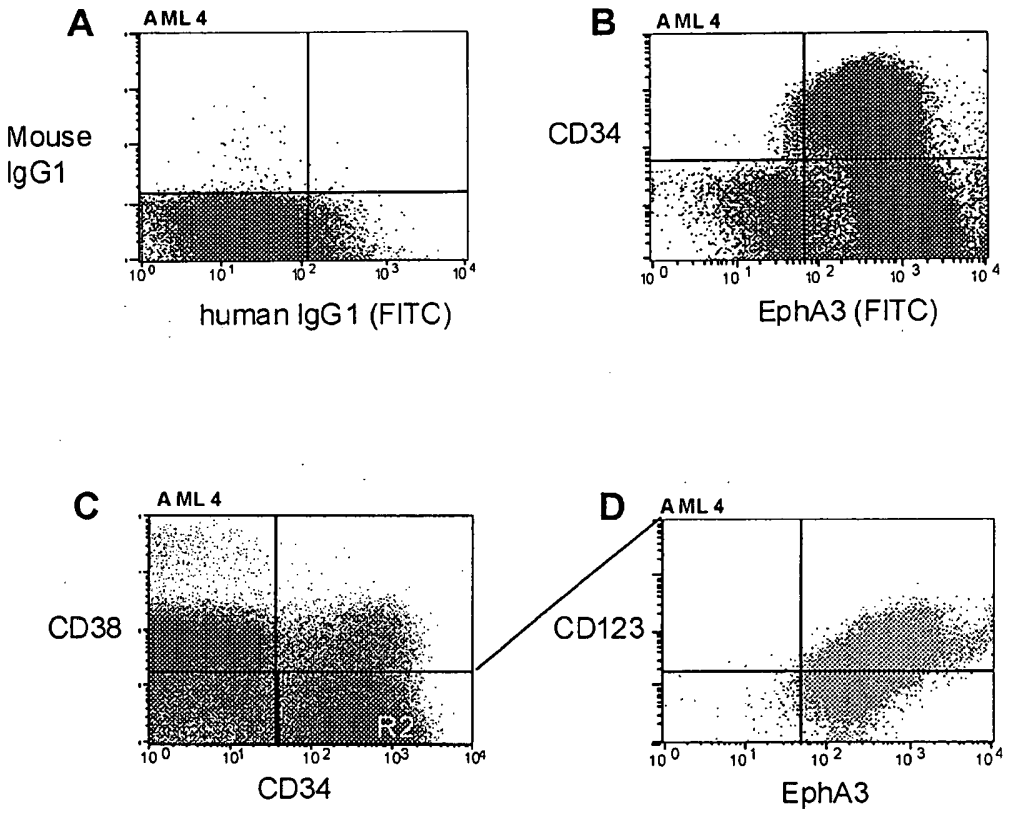
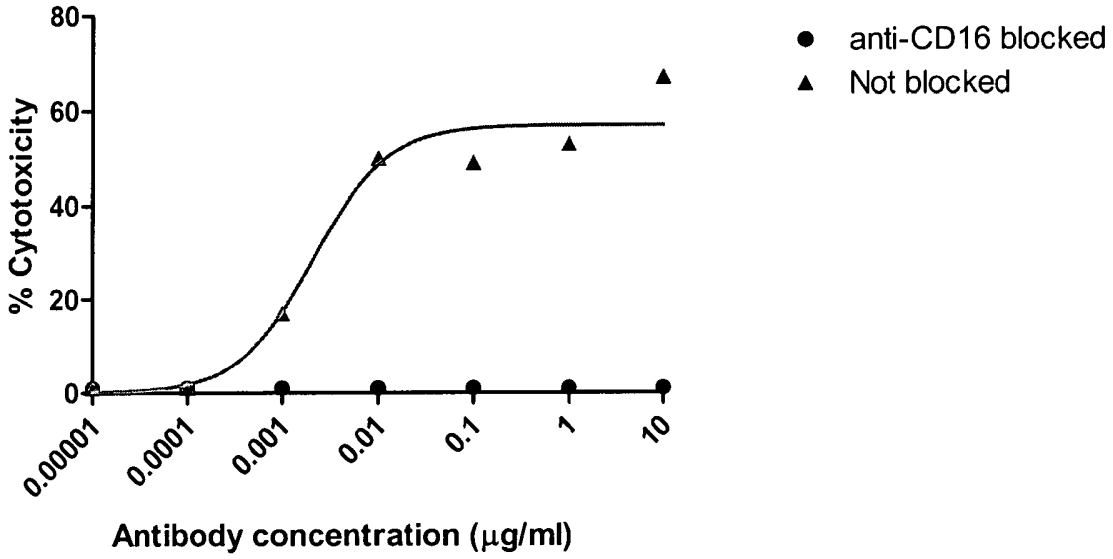

A
AML 4
Mouse IgG1
human IgG1 (FITC)
B
AML 4
CD34
EphA3 (FITC)
C
AML 4
CD38
CD34
R2
D
AML 4
CD123
EphA3

Figure 2


80
60
40
20
0
% Cytotoxicity
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0.0001
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0.01
0.1
1
10
Antibody concentration (μg/ml)
anti-CD16 blocked
Not blocked

Figure 3

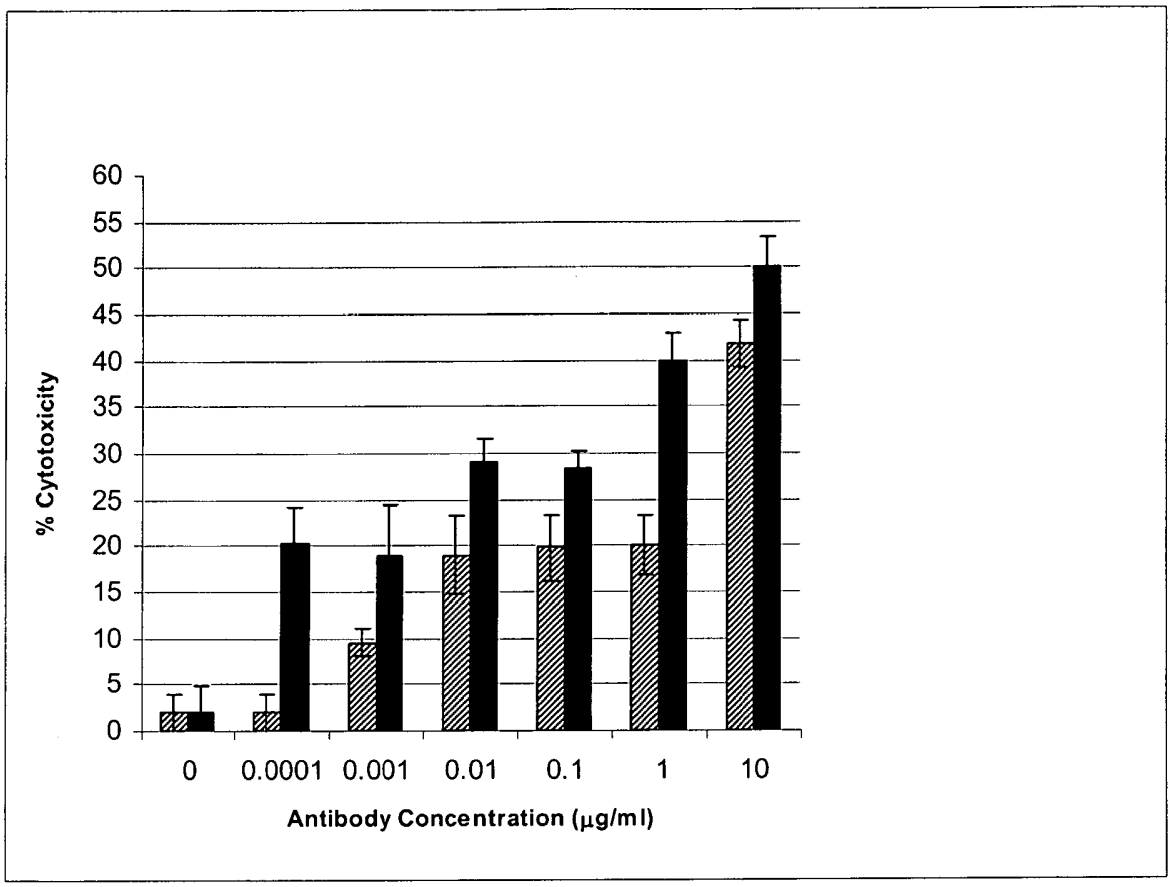
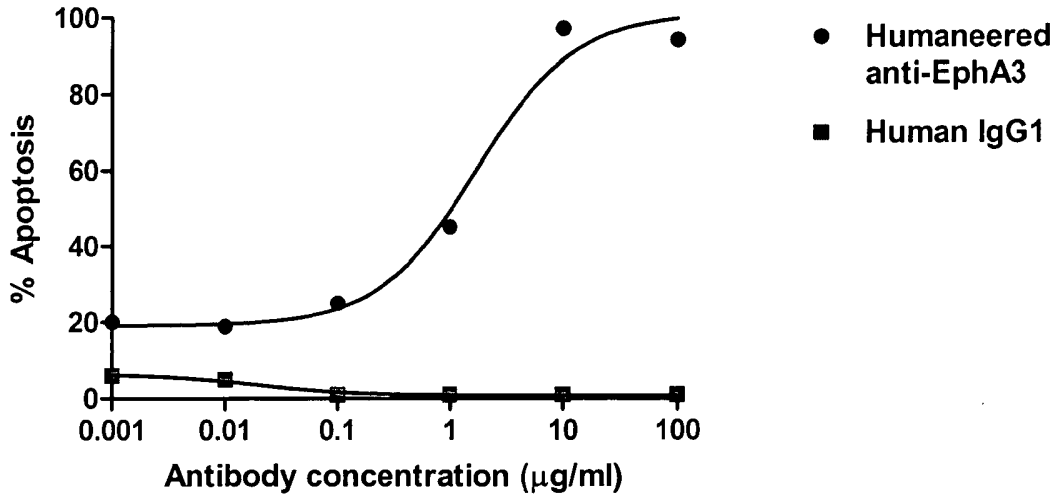

% Cytotoxicity
60
55
50
45
40
35
30
25
20
15
10
5
0
0
0.0001
0.001
0.01
0.1
1
10
Antibody Concentration (µg/ml)

Figure 4


100
80
60
40
20
0
% Apoptosis
0.001
0.01
0.1
1
10
100
Antibody concentration (μg/ml)
Humaneered anti-EphA3
Human IgG1

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026413

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07K16/28 A61K39/395
ADD. A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CILLONI DANIELA ET AL: "EphA3 Kinase Is Constitutively Activated in Chronic Myeloid Leukaemia during Progression to Accelerated and Blast Crisis and It Could Represent a New Molecular Target" BLOOD, vol. 112, no. 11, November 2008 (2008-11), page 399, XP009137279 & 50TH ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; SAN FRANCISCO, CA, USA; DECEMBER 06 -09, 2008 ISSN: 0006-4971	39-49
Y		1-38

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 August 2010	13/08/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Chapman, Rob

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026413

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	WO 2004/069264 A1 (LUDWIG INST CANCER RES [AU]; UNIV MONASH [AU]; QUEENSLAND INST MED RES) 19 August 2004 (2004-08-19) the whole document	1-38
A	LACKMANN MARTIN ET AL: "Expression and function in modulating tumor cell-cell contacts identifies EphA3 as candidate cell-surface receptor for tumor targeting strategies" PROCEEDINGS OF THE ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 45, 27 March 2004 (2004-03-27), page 1015, XP001538538 ISSN: 0197-016X the whole document	1-49
A	VEARING CHRISTOPHER ET AL: "Concurrent binding of anti-EphA3 antibody and ephrin-A5 amplifies EphA3 signaling and downstream responses: Potential as EphA3-specific tumor-targeting reagents" CANCER RESEARCH, AMERICAN ASSOCIATION FOR CANCER REREARCH, US LNKD-DOI:10.1158/0008-5472.CAN-05-0758, vol. 65, no. 15, 1 August 2005 (2005-08-01), pages 6745-6754, XP002493162 ISSN: 0008-5472 The whole document, in particular, p.6746, col.1, para.2	1-49
A	ZHOU Q ET AL: "Development of a simple and rapid method for producing non-fucosylated oligomannose containing antibodies with increased effector function" BIOTECHNOLOGY AND BIOENGINEERING 20080215 JOHN WILEY AND SONS INC. US, vol. 99, no. 3, 15 February 2008 (2008-02-15), pages 652-665, XP009137262 DOI: DOI:10.1002/BIT.21598 the whole document	9

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INTERNATIONAL SEARCH REPORT

International application No
PCT/US2010/026413

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	ARRUGA FRANCESCA ET AL: "EphA3 is abnormally expressed in chronic myeloprolipherative disorders and could represent a new molecular target" PROCEEDINGS OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH ANNUAL MEETING, vol. 50, April 2009 (2009-04), page 692, XP009137278 & 100TH ANNUAL MEETING OF THE AMERICAN-ASSOCIATION-FOR-CANCER-RESEARCH; DENVER, CA, USA; APRIL 18 -22, 2009 ISSN: 0197-016X the whole document	1-49
X,P	PALATH VARGHESE ET AL: "A Recombinant Human Antibody to EphA3 with Pro-Apoptotic and Enhanced ADCC Activity Shows Selective Cytotoxicity against Myeloid Leukemia Cells and CD123-Positive Leukemic Stem Cells." BLOOD, vol. 114, no. 22, November 2009 (2009-11), page 688, XP009137260 & 51ST ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 05 -08, 2009 the whole document	1-49

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2010/026413

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		US 2006140957 A1	29-06-2006

US 20160289321A1

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2016/0289321 A1**

ZHANG et al. (43) **Pub. Date: Oct. 6, 2016**

(54) **IL-17A BINDING AGENT AND USES THEREOF**

(71) Applicants: **SHANGHAI HENGRUI PHARMACEUTICAL CO., LTD.**, Shanghai (CN); **JIANGSU HENGRUI MEDICINE CO., LTD.**, Lianyungang, Jiangsu (CN)

(72) Inventors: **Lianshan ZHANG**, Shanghai (CN); **Jiajian LIU**, Shanghai (CN); **Guoqing CAO**, Shanghai (CN); **Piaoyang SUN**, Lianyungang, Jiangsu (CN)

(73) Assignees: **SHANGHAI HENGRUI PHARMACEUTICAL CO., LTD.**, Shanghai (CN); **JIANGSU HENGRUI MEDICINE CO., LTD.**, Lianyungang, Jiangsu (CN)

(21) Appl. No.: **15/035,550**

(22) PCT Filed: **Oct. 27, 2014**

(86) PCT No.: **PCT/CN2014/089542**

§ 371 (c)(1),
(2) Date: **May 10, 2016**

(30) **Foreign Application Priority Data**

Nov. 18, 2013 (CN) 201310580942.7

Publication Classification

(51) **Int. Cl.**
C07K 16/24 (2006.01)

(52) **U.S. Cl.**
CPC ***C07K 16/244*** (2013.01); *C07K 2317/565* (2013.01); *C07K 2317/567* (2013.01); *C07K 2317/56* (2013.01); *C07K 2317/515* (2013.01); *C07K 2317/51* (2013.01); *C07K 2317/24* (2013.01); *A61K 2039/505* (2013.01)

(57) **ABSTRACT**

Provided is an antibody capable of specially recognizing IL-17A and binding to IL-17A. The antibody can be used for treating inflammation and autoimmune diseases caused by elevated expression of interleukin-17A, such as psoriasis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, and inflammatory arthritis.

IL-17A BINDING AGENT AND USES THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to an IL-17A binding agent and its use as a therapeutic agent, in particular as a therapeutic agent for a variety of inflammatory or autoimmune diseases.

BACKGROUND

[0002] Cytokines of the interleukin-17 family are named IL-17A to IL-17F. Correspondingly, the family of their receptors, named IL-17 receptor A to IL-17 receptor E, have also been identified. The IL-17 cytokines bind to their corresponding receptors and thereby mediate different inflammatory responses.

[0003] The classical member of the family is IL-17A. Lymphocytes that migrate to infection or injury sites can secrete IL-17A. IL-17A induces the expression of inflammatory cytokines and chemokines, thereby recruiting additional immune cells to the inflammation site and exacerbating the inflammatory response. In addition, IL-17A induces the expression of some factors relevant to tissue repair, thus accelerating recovery of the organism. Although interleukin-17A has the effect of amplifying the immune defense response and protecting organisms during the process of anti-infection and tissue repair in the host, interleukin-17A is highly expressed in many patients suffering from autoimmune diseases and cancers, and excessive expression of interleukin-17A plays a negative role in pathologic development because it can induce the expression of various inflammatory factors. Many animal experiments have shown that the pathological severity of various autoimmune diseases can be effectively suppressed by interleukin-17A deficiency or interleukin-17A antibody neutralization. There is evidence that IL-17 signaling could be an effective target for treating autoimmune diseases, including rheumatoid arthritis (RA), psoriasis, Crohn's disease, multiple sclerosis (MS), psoriasis disease, asthma and lupus (see, for example, Aggarwal et al., J. Leukoc. Biol, 71 (1): 1-8 (2002); Lubberts et al.).

[0004] Human IL-17 is a gene encoding a full-length polypeptide having 155 amino acids. The polypeptide comprises a 19-amino-acid signal sequence and a 132-amino-acid mature region. With a relative molecular weight of 17,000Da, human IL-17A is a glycoprotein existing in the form of a homodimer or a heterodimer (Spriggs et al, J. Clin. Immunol, 17: 366-369 (1997)). The IL-17F homolog can combine with IL-17A to form an IL-17A/F heterodimer. The amino acid sequence of IL-17F (IL-24, ML-1) has up to 55% similarity to that of IL-17A, and both have the same receptor, IL-17R. IL-17R is ubiquitously expressed in a variety of cells, including vascular endothelial cells, peripheral T cells, B cells, fibroblasts, myelomonocytes and bone marrow stromal cells (Kolls et al, Immunity, 21: 467-476 (2004); Kawaguchi et al, J. Allergy Clin. Immunol, 114 (6): 1267-1273 (2004); Moseley et al, Cytokine Growth Factor Rev, 14 (2): 155-174 (2003)).

[0005] From the discovery of interleukin-17A, until now, a variety of anti-IL-17A antibodies have been identified, such as CN101001645A, CN101326195A, CN101646690A, but there is still a need for the development of various kinds of improved antibodies to effectively reduce or eliminate IL-17 activity in inflammatory responses and autoimmune diseases.

SUMMARY OF THE INVENTION

[0006] The present invention provides an anti-IL-17A antibody with improved affinity and improved half-life.

[0007] The present invention provides an IL-17A binding agent, comprising:

[0008] An antibody light chain variable region, comprising 0-3 LCDR regions selected from those shown in SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15; and

[0009] An antibody heavy chain variable region, comprising 0-3 HCDR regions selected from those shown in SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12;

[0010] wherein the numbers of CDR regions of the antibody light chain variable region and the antibody heavy chain variable region are not simultaneously 0.

[0011] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 13.

[0012] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 14.

[0013] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 15.

[0014] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 10.

[0015] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 11.

[0016] According to some embodiments of the present invention, the IL-17A binding agent comprises SEQ ID NO: 12.

[0017] According to some embodiments of the present invention, the IL-17A binding agent comprises one LCDR region selected from SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15.

[0018] According to some embodiments of the present invention, the IL-17A binding agent comprises one HCDR region selected from those shown in SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12.

[0019] According to some embodiments of the present invention, the IL-17A binding agent comprises two LCDR regions selected from those shown in SEQ ID NO: 13, SEQ ID NO: 14 and SEQ ID NO: 15.

[0020] According to some embodiments of the present invention, the IL-17A binding agent comprises two HCDR regions selected from those shown in SEQ ID NO: 10, SEQ ID NO: 11 and SEQ ID NO: 12.

[0021] According to some embodiments of the present invention, the IL-17A binding agent comprises three LCDR regions, wherein the amino acid sequence of LCDR1 is shown in SEQ ID NO: 13, the amino acid sequence of LCDR2 is shown in SEQ ID NO: 14 and the amino acid sequence of LCDR3 is shown in SEQ ID NO: 15.

[0022] According to some embodiments of the present invention, the IL-17A binding agent comprises three HCDR regions, wherein the amino acid sequence of HCDR1 is shown in SEQ ID NO: 10, the amino acid sequence of HCDR2 is shown in SEQ ID NO: 11 and the amino acid sequence of HCDR3 is shown in SEQ ID NO: 12.

[0023] According to some embodiments of the present invention, the antibody light chain variable region of the IL-17A binding agent further comprises a light chain framework (FR) region derived from murine κ or λ chain or a variant thereof. In some embodiments, the amino acid sequence of the antibody light chain variable region is SEQ ID NO: 2. In further embodiments, the IL-17A binding agent comprises a light chain constant region derived from murine κ or λ chain or a variant thereof.

[0024] According to some embodiments of the present invention, antibody heavy chain variable region of the IL-17A binding agent further comprises a heavy chain FR region derived from murine IgG1, IgG2, IgG3, IgG4 or a variant thereof In some embodiments, the amino acid sequence of the antibody heavy chain variable region is SEQ ID NO: 1. In further embodiments, the IL-17A binding agent comprises heavy chain constant region derived from murine IgG1, IgG2, IgG3, IgG4 or a variant thereof.

[0025] According to some embodiments of the present invention, the antibody light chain variable region of the IL-17A binding agent further comprises a light chain FR region derived from human κ or λ chain or a variant thereof. In some embodiments, the light chain FR region of the antibody light chain variable region is the human germline light chain A10 FR region, whose amino acid sequence is shown in SEQ ID NO: 4, or a variant thereof In some embodiments, the variant of the antibody light chain variable region FR region refers to a human germline light chain A10 FR region with 0-10 amino acid mutations. In some embodiments, the amino acid mutation in an FR region variant of the light chain variable region is one or more selected from the group consisting of F71Y, K49Y, Y36F, and L47W. In some embodiments, the antibody light chain is selected from SEQ ID NO: 9 and a variant thereof. In further embodiments, the IL-17A binding agent comprises light chain constant region derived from human κ or λ chain or a variant thereof.

[0026] According to some embodiments of the present invention, the antibody heavy chain variable region of the IL-17A binding agent further comprises the heavy chain FR region derived from human IgG1, IgG2, IgG3, IgG4 or a variant thereof. In some embodiments, the heavy chain FR region of the antibody heavy chain variable region is the FR region of the human germline heavy chain VH1-18, whose amino acid sequence is shown in SEQ ID NO: 3, or a variant thereof In some embodiments, a FR region variant of the antibody heavy chain variable region refers to a human germline heavy chain VH1-18 region with 0-10 amino acid mutations. In some embodiments, the amino acid mutation in an FR region variant of the heavy chain variable region is one or more selected from the group consisting of: A93T, T71A, M48I, V67A, M69L, T73D, and S76N; In some embodiments, the antibody heavy chain is selected from SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8. In further embodiments, the IL-17A binding agent comprises heavy chain constant region derived from human IgG1, IgG2, IgG3, IgG4 or a variant thereof.

[0027] Furthermore, according to some embodiments of the present invention, provided is a vector expressing an IL-17A binding agent described above. The host cells express and secrete the IL-17A binding agent after being transfected with the vector.

[0028] According to some embodiments of the present invention, the vector comprises a nucleotide encoding the IL-17A binding agent of the present invention.

[0029] Furthermore, according to some embodiments of the present invention, provided is a pharmaceutical composition that comprises the IL-17A binding agent as described above and a pharmaceutically acceptable excipient, diluent or carrier.

[0030] Furthermore, according to some embodiments, the present invention also provides a use of the described IL-17A binding agent, or of the pharmaceutical composition containing the same, in the preparation of a medicament for the treatment of IL-17-mediated diseases or disorders. The diseases comprise inflammatory or autoimmune diseases and are selected from the group consisting of psoriasis, psoriatic arthritis, ankylosing spondylitis, multiple sclerosis, and inflammatory arthritis. The inflammatory disease is preferably inflammatory arthritis. The inflammatory arthritis is selected from the group consisting of osteoarthritis, rheumatoid arthritis, rheumatic arthritis and osteoporosis, and is preferably rheumatic arthritis.

[0031] According to some embodiments, the present invention also provides the use of the described IL-17A antibody, or a pharmaceutical composition comprising the same, in the preparation of a medicament for the treatment of IL-17-mediated diseases or disorders. The diseases comprise inflammatory or autoimmune diseases. The inflammatory disease is preferably inflammatory arthritis. The inflammatory arthritis is selected from the group consisting of osteoarthritis, rheumatoid arthritis and osteoporosis.

[0032] According to some embodiments, the present invention also provides a method for treating a disease or disorder mediated by IL-17, the method comprising administering to a subject in need thereof a therapeutically effective amount of an IL-17A binding agent as described above, or of a humanized IL-17A antibody or a pharmaceutical composition containing the same.

[0033] So that the invention can be more readily understood, certain technical and scientific terms are specifically defined below. Unless specifically defined elsewhere in this document, all other technical and scientific terms used herein have the meaning commonly understood by one of ordinary skill in the art to which this invention belongs.

[0034] I. Terms

[0035] As used herein, the single-letter code and the three-letter code for amino acids are as described in J. Biol. Chem, 243, (1968) p 3558.

[0036] As used herein, "binding agent" refers to a soluble receptor or fragments or analogs thereof, or to antibodies or fragments or analogs thereof that are capable of binding to the target. "IL-17A binding agent," according to the present invention, refers to an antibody or fragment or analog thereof that is capable of specifically recognizing and binding to IL-17A.

[0037] The term "IL-17A" generally refers to a natural or recombinant human IL-17A, and to non-human homologues of human IL-17A. Unless otherwise indicated, the molecular weight of an IL-17A homodimer is used (for example, 30KDa for human IL-17A) to calculate the molar concentration of IL-17A.

[0038] As used herein, "Antibody" refers to immunoglobulin, a four-peptide chain structure consisting of two identical heavy chains and two identical light chains connected via a disulfide bond. Immunoglobulin heavy chain

constant regions exhibit different amino acid components and orders, and therefore present different antigenicity. Accordingly, immunoglobulins can be divided into five categories, called immunoglobulin isotypes, namely IgM, IgD, IgG IgA and IgE. According to the amino acid components of the hinge region and the number and location of heavy chain disulfide bonds, Ig's in the same category can further be divided into different sub-types, for example, IgG can be divided into IgG1, IgG2, IgG3 and IgG4. Light chains can be divided into κ or λ chains by different constant regions.

[0039] The regions of about 110 amino acids near the N-termini of the antibody heavy and light chains vary widely and are known as the variable regions (V regions); the remainder of the antibody heavy and light chains, near the C-termini, are relatively constant and are known as the constant regions (C regions). The variable regions comprise three hypervariable regions (HVRs) and four relatively conserved framework regions (FR5). The three hypervariable regions determine the specificity of the antibody, and are also known as complementarity determining regions (CDRs). Each light chain variable region (LCVR) and each heavy chain variable region (HCVR) is composed of three CDRs and four FR regions, and the sequential order of the components, from the amino terminus to the carboxy terminus is: FR1, CDR1, FR2, CDR2, FR3, CDR3, and FR4. The three light chain CDR regions, namely the light chain hypervariable regions, are referred to asLCDR1, LCDR2, and LCDR3. The three heavy chain CDR regions, namely the heavy chain hypervariable regions, are referred to asH-CDR1, HCDR2 and HCDR3. The number and location of the CDR amino acid residues in the LCVR and HCVR regions of the antibody or antigen binding fragment thereof disclosed herein comply with known Kabat numbering criteria (LCDR1-3, HCDE2-3), or comply with kabat and chothia numbering criteria (HCDR1).

[0040] As used herein, "antigen-binding fragment" refers to a Fab fragment, Fab' fragment, $F(ab')_2$ fragment or a single Fv fragment having antigen-binding activity. An Fv antibody is a minimum antibody fragment comprising a heavy chain variable region, a light chain variable region and all of the antigen-binding sites, without the constant region. Generally, an Fv antibody further comprises a polypeptide linker between the VH and VL domains, and is capable of forming a structure required for antigen binding.

[0041] As used herein, the term "antigen determinant" refers to the three-dimensional sites, which are distinct on the antigen, that are recognized by the antibody or antigen binding fragment of the present invention.

[0042] "Administration" and "treatment," as they apply to animals, human, experimental subjects, cells, tissues, organs, or biological fluid, refer to contact of animals, humans, subjects, cells, tissues, organs, or biological fluids with exogenous medicaments, therapeutic agents, diagnostic agents, or compositions. "Administration" and "treatment" can refer to, e.g., therapeutic, pharmacokinetic, diagnostic, research, and experimental methods. Treatment of cells encompasses contacting cells with an agent, as well as contacting fluid with an agent, where the fluid is in contact with the cells. "Administration" and "treatment" also mean in vitro and ex vivo treatment of, e.g., cells, by an agent, a diagnostic composition, a binding composition, or by other cells. "Treatment," as it applies to human, veterinary, or research subjects, refers to therapeutic treatment, prophylactic or preventative measures, or to research or diagnostic applications. "Treatment" as it applies to human, veterinary, or research subjects, or cells, tissues, or organs, encompasses contacting human or animal subjects, cells, tissues, physiological compartments, or physiological fluid with an IL-17A agonist or an IL-17 A antagonist. "Treatment of cells" also encompasses situations where the IL-17A agonist or IL-17A antagonist is contacted with an IL-17A receptor, e.g., in the fluid phase or colloidal phase, and also encompasses situations where the agonist or antagonist is not contacted with the cells or the receptors.

[0043] "Treat" means to administer a therapeutic agent, such as a composition containing any of the binding compounds of the present invention, internally or externally to a patient having one or more disease symptoms for which the agent has known therapeutic activity. Typically, the agent is administered in an amount effective to alleviate one or more disease symptoms in the patient or population to be treated, either by inducing the regression of or inhibiting the progression of such symptom(s) by any clinically measurable degree. The amount of a therapeutic agent that is effective to alleviate any particular disease symptom (also referred to as the "therapeutically effective amount") can vary according to various factors, such as the disease state, age, and weight of the patient, and the ability of the drug to elicit a desired response in the patient.

[0044] Four variants of human IL-17 A protein are mentioned herein:

[0045] 1) As used herein, the terms "human IL-17A (huIL-17A)" and "natural human IL-17A" refer to the mature forms (i.e. residues 24-155) of human IL-17A protein with accession numbers NP 002181 and AAT22064, and to naturally occurring variants and polymorphisms thereof.

[0046] 2) As used herein, the term "rhIL-17A" refers to a recombinant human IL-17A. This nomenclature is adopted for convenience to refer to various forms of IL-17A, and may not match usage in the literature.

[0047] 3) As used herein, the term "His-huIL-17A" refers to a recombinant human IL-17A having an N-terminal His tag, "FLAG-huIL-17A" refers to a recombinant human IL-17A having an N-terminal FLAG tag. In some experiments the FLAG-huIL-17A is biotinylated.

[0048] 4) R&D Systems human IL-17A mentioned herein is a recombinant human IL-17A purchased from R&D Systerms.

[0049] As used herein, the term "monoclonal antibody" refers to an antibody secreted by a clone derived from a single cell. Monoclonal antibodies are highly specific and are directed against a single epitope. The cell is not limited to eukaryotic, prokaryotic, or phage clonal cell lines.

[0050] The monoclonal antibody herein specifically includes a "chimeric" antibody, in which a portion of the heavy and/or light chain is identical or homologous to the corresponding sequences of antibodies derived from a particular species or belonging to a particular antibody type or subtype, while the remainder of the chain(s) is identical or homologous to the corresponding sequences of antibodies derived from another species or belonging to another antibody type or subtype, as well as fragment of such antibody, as long as they exhibit the desired biological activity.

[0051] As used herein, the term "humanized antibody" is a variable region-modified form of the murine antibody according to the present invention, having CDRs derived from (or substantially derived from) a non-human antibody

(preferably a mouse monoclonal antibody), and FR regions and constant regions substantially derived from a human antibody; that is, CDR sequences of murine antibody are grafted onto different types of human germline antibody framework sequences. Such framework sequences can be obtained from public DNA databases or published references that include germline antibody gene sequences. For example, germline DNA sequences of human heavy variable region genes and human light chain variable region genes can be found in the human germline sequence database "VBase" (available online at www.mrccpe.com.ac.uk/vbase), as well as found in Kabat, E A, et al. 1991, Sequences of Proteins of Immunological Interest, 5th Ed. Because CDR sequences are responsible for most antibody-antigen interactions, it is feasible to construct an expression vector to express a recombinant antibody that can mimic specific feature of a naturally occurring antibody.

[0052] "Optional" or "optionally" means that the following event or situation can but does not necessarily occur, and the description includes the instances in which the event or situation does or does not occur. For example, "optionally contains 1-3 antibody heavy chain variable regions" means that the antibody heavy chain variable region with specific sequences can be, but is not necessarily, present, and if it is present, there can be 1, 2 or 3 antibody heavy chain variable regions.

[0053] Transformation of the host cell with the recombinant DNA can be carried out by conventional techniques well known to those skilled in the art. The obtained transformants can be cultured by using conventional methods to express the polypeptide encoded by the gene of the invention. Culture medium can be selected from various conventional culture mediums based on the host cells used. The host cells are grown under the appropriate conditions.

[0054] II. Antibodies Specific for Human IL-17A

[0055] The present invention provides engineered anti-IL-17A antibodies and uses thereof to treat various inflammatory, immune and proliferative disorders, including rheumatoid arthritis (RA), osteoarthritis, rheumatoid arthritis osteoporosis, inflammatory fibrosis (e.g., scleroderma, lung fibrosis, and cirrhosis), inflammatory bowel disorders (e.g., Crohn's disease, ulcerative colitis and inflammatory bowel disease), asthma (including allergic asthma), allergies, COPD, multiple sclerosis, psoriasis and cancer.

[0056] Any suitable method for generating monoclonal antibodies can be used to generate the anti-IL-17A antibodies of the present invention. For example, an animal recipient can be immunized with a linked or naturally occurring IL-17A homodimer, or a fragment thereof. Any suitable method for immunization can be used. Such methods can include adjuvants, other immunostimulants, repeated booster immunizations, and the use of one or more immunization routes.

[0057] Any suitable form of IL-17A can be used as the immunogen (antigen) for the generation of the non-human antibody specific for IL-17A, and the antibody can be screened for its biological activity. The eliciting immunogen can be full-length mature human IL-17A, including naturally occurring homodimers, or peptides thereof encompassing a single epitope or multiple epitopes. The immunogen can be used alone or in combination with one or more immunogenicity enhancing agents known in the art. The immunogen can be purified from a natural source or produced in genetically modified cells. DNA encoding the immunogen can be derived from genomic or non-genomic (e.g., cDNA) DNA. Suitable genetic vectors can be used to express the DNAs encoding the immunogen, and the vectors can include but are not limited to adenoviral vectors, adeno-associated viral vectors, baculoviral vectors, plasmids, and non-viral vectors.

[0058] An exemplary method for producing anti-human IL-17A antibodies of the present invention is described at Example 1.

[0059] III. Humanization of IL-17A-Specific Antibodies

[0060] The humanized antibody can be selected from any type of immunoglobulins, including IgM, IgG, IgD, IgA, and IgE. In one embodiment, the antibody is an IgG antibody. Any isotype of IgG can be used, including IgG1, IgG2, IgG3, and IgG4. Variants of the IgG isotypes are also contemplated. The humanized antibody can comprise sequences derived from more than one type or isotype. Optimization of the necessary constant domain sequences to generate the desired biological activity is readily achieved by screening the antibodies in the biological assays described in the Examples below.

[0061] Likewise, any type of light chain can be used in the compounds and methods herein. Specifically, kappa (κ), lambda (λ), or a variant thereof is useful in the present compounds and methods.

[0062] An exemplary method of humanizing anti-human IL-17A antibodies of the present invention is described at Example 2.

DETAILED DESCRIPTION OF THE INVENTION

[0063] Hereinafter, the present invention is further described with reference to examples. However, the scope of the present invention is not limited thereto.

[0064] In the examples of the present invention, where specific conditions are not described, the experiments are generally conducted under conventional conditions, or under conditions proposed by the material or product manufacturers. See Sambrook et al., Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Laboratory; Current Protocols in Molecular Biology, Ausubel et al, Greene Publishing Associates, Wiley Interscience, NY. Where the source of the reagents is not specifically given, the reagents are commercially available conventional reagents.

EXAMPLE 1

Mouse Anti-Human IL-17A Monoclonal Antibody

[0065] Monoclonal antibodies against human IL-17A were obtained as follows. 6-8 week old female BALB/c mice (Shanghai Super B&K Laboratory Animal Corp. Ltd, laboratory animal production Certificate No: SCXK (HU) 2008-0016) and 6-8 week old female SJL mice (Beijing Weitong Lihua Experimental Animal Technology Co. Ltd, laboratory animal production Certificate No: SCXK (Beijing) 2012-0001) were divided into two groups, a high dose group and a low dose group. 10 BALB/c mice and 10 SJL mice were in each group.

[0066] The high and low dose groups were serially immunized with natural hIL-17A variants (His-hIL-17A; the amino acid sequence of hIL-17A refers to human IL-17A protein Genbank accession number NP-002181, and the resulting protein was purified by Ni affinity column (Super-

dex) and 75SEC, sequentially) that were His-tagged at the N-terminus and generated using a HEK293E (293-EBNA, Invitrogen, Lot Num: 493985) expression system. The inoculations were performed on days 0, 14, 35, and 56.

[0067] On day 0, the high dose group was administered with His-huIL-17A, at 500 μg/mouse, via subcutaneous (s.c.) injection, and Complete Freund's Adjuvant (CFA) was administered via intraperitoneal (i.p.) injection at the same time. On days 14 and 35, 25 μg/mouse His-hIL-17A was administered via s.c. injection, and Incomplete Freund's Adjuvant (IFA) was administrated via i.p. injection at the same time. On day 56, before fusing the splenocytes, a booster immunization was performed by i.p. injection of 25 μg/mouse His-hIL-17A dissolved in saline. The time schedule and method for the immunization of the low dose group was the same as those for high dose group, except that the administered dose of His-hIL-17A on day 0 was 10 μg/mouse, and the administered dose of His-hIL-17A on days 14, 35, and 56 was 5 μg/mouse.

[0068] Blood tests were performed on days 22 and day 43. Mouse serum was tested using an ELISA Test described in Test Example 1 to determine the antibody titers in the serum. On day 56, mice with higher antibody titers in their serum were selected for splenocyte fusion. Hybridoma cells were obtained by fusing splenic lymphocyte with myeloma Sp2/0 cells (ATCC® CRL-8287™) using an optimized PEG-mediated fusion procedure.

[0069] The procedures for immunization were as follows:

[0070] Scheme 1, high dose, 10 Balb/c mice and 10 SJL mice—

Day 0	Pre-blood sampling 15-30 μL serum/mouse; primary immunization, IP, CFA 50 μg/mouse
14	Boost 1 (booster immunization 1): IP, IFA 25 μg/mouse
21	Blood sampling (15-30 μL serum/mouse)
22	ELISA test
35	Boost 2 (booster immunization 2): IP, IFA 25 μg/mouse
42	Blood sampling (15-30 μL serum/mouse)
43	ELISA test
44	Data analysis and interim conclusion
56	Pre-fusion booster immunization, IP, 25 μg/mouse of saline

[0071] Scheme 2, low dose—

Day 0	Pre-blood sampling 15-30 μL serum/mouse; primary immunization, IP, CFA 10 μg/mouse
14	Boost 1 (booster immunization 1): IP, IFA 5 μg/mouse
21	Blood sampling (15-30 μL serum/mouse)
22	ELISA test
35	Boost 2 (booster immunization 2): IP, IFA 5 μg/mouse
42	Blood sampling (15-30 μL serum/mouse)
43	ELISA test
44	Data analysis and interim conclusion
56	Pre-fusion booster immunization, IP, 5 μg/mouse of saline

[0072] Primary screening of the resulting hybridomas was performed by an antigen-antibody indirect ELISA test in Test Example 1. Monoclonal cell lines were obtained by limiting the dilution of positive cell lines.

[0073] The obtained monoclonal cell lines were further analyzed by methods including:

[0074] 1. A receptor blocking test (see Test Example 2): the results, shown in Table 5, revealed that a monoclonal cell line, IL17-mAb049, having superior activity compared to the positive control was obtained;

[0075] 2. Affinity test (see Test Example 3): the results, shown in Table 6, revealed that the monoclonal cell line IL17-mAb049 obtained in the present invention demonstrated comparable or improved activity when compared to the positive control;

[0076] 3. Bioassay at cellular level (GROa analysis, see Test Example 4): the results, shown in Table 8, revealed that the monoclonal cell line IL17-mAb049 obtained in the present invention demonstrated comparable or improved activity when compared to the positive control.

[0077] Twelve of the monoclones were studied further. One lead monoclone (lead mAb), IL17-mAb049, was selected based on epitope grouping and biological activity testing. The specific sequences of the heavy chain (VH) and light chain (LH) of the murine IL-17A mouse antibody mAb049 (IL-17mAb) were as follows:

IL-17 mAb049 VH

SEQ ID NO: 1

HVQLQQSGADLVRPGASVTLSCKASGYIFTDYEVHWVKQTPVHGLEWIGV

IDPGTGGVAYNQKFEGKATLTADDSSNTAYMELRSLTSEDSAVYYCTRYS

LFYGSSPYAMDYWGQGTSVTVSS

IL-17mAb 049 VL

SEQ ID NO: 2

QIVLTQSPAIMSASPGEKVTITCSASSSVNYMHWFQQKPGTSPKLWIYRT

SNLASGVPVRFSGSGSGTSYSLTISRMEAEDAATYYCQQRSSYPWTFGGG

TNLEIK

EXAMPLE 2

Humanization of Murine-Anti-Human IL-17A Antibodies

[0078] The humanization of murine-anti-human IL-17A monoclonal antibody mAb049 was performed essentially as described in many publications known to those skilled in the art. Briefly, human constant domains were used to replace the parental (murine antibody) constant domains. The human germline sequences used for humanization were selected according to homology between the murine antibody and the human antibody.

[0079] 1. CDR Regions of Murine anti-IL-17A Antibody

[0080] VH/VL CDR amino acid residues were identified and annotated by the Kabat numbering system. CDR sequences of murine mAb049 in the present invention are listed in the following table:

TABLE 1

CDR sequences of mouse anti-IL-17A antibody

		mAb049	
Domain		Sequence	SEQ ID NO
VH	CDR1	DYEVH	10
	CDR2	VIDPGTGGVAYNQKFEG	11
	CDR3	YSLFYGSSPYAMDY	12

TABLE 1-continued

CDR sequences of mouse anti-IL-17A antibody

		mAb049	
Domain		Sequence	SEQ ID NO
VL	CDR1	SASSSVNYMH	13
	CDR2	RTSNLAS	14
	CDR3	QQRSSYPWT	15

[0081] 2. Selection of Human Germline FR Sequences

[0082] On the basis of characteristic structures of the obtained murine antibody VH/VL CDRs, the sequences of the heavy and light chain variable regions were compared to an antibody database. Human germline heavy chain VH1-18 (SEQ ID NO: 3) and light chain A10 (SEQ ID NO: 4) with high homology were selected based on their high degree of homology, and were used as humanized FR sequences. The specific sequences were as follows:

VH1-18

SEQ ID NO: 3

QVQLVQSGAEVKKPGASVKVSCKASGYTFTSYGISWVRQAPGQGLEWMGW

ISAYNGNTNYAQKLQGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCAR

A10

SEQ ID NO: 4

EIVLTQSPDFQSVTPKEKVTITCRASQSIGSSLHWYQQKPDQSPKLLIKY

ASQSFSGVPSRFSGSGSGTDFTLTINSLEAEDAATYYCHQSSSLP

[0083] 3. Design of Humanized Antibodies:

[0084] The amino acid residues forming the ring conformation and the VH interface were determined. Using that information, a Q1E mutation was introduced to eliminate the formation of N-terminal pyroglutamic acid. Other mutations were made to maintain consistency within the selected VH family, to maintain the characteristic CDR structure and VH/VL interface, and to avoid the N-glycosylation pattern (N-{P}-S/T) present in the humanized structure.

[0085] The design of the humanized mutations in the variable regions of the murine antibody mAb049 are summarized as follows:

TABLE 2

Design of humanized sites in murine antibody mAb049

Design of humanized sites in heavy chain VH (VH1-18) + JH4/FW4		Design of humanized sites in light chain Vk(A10) + JK2/FW4	
Mutation type	Humanized back mutation site	Mutation type	Humanized back mutation site
Hu049 VH.1	CDR-grafted*	Hu049 Vk.1	CDR-grafted*
Hu049 VH.1A	A93T	Hu049 Vk.1A	F71Y
Hu049 VH.1B	A93T, T71A	Hu049 Vk.1B	F71Y, K49Y
Hu049 VH.1C	A93T, T71A, M48I	Hu049 Vk.1C	F71Y, K49Y, Y36F, L47W

TABLE 2-continued

Design of humanized sites in murine antibody mAb049

Design of humanized sites in heavy chain VH (VH1-18) + JH4/FW4		Design of humanized sites in light chain Vk(A10) + JK2/FW4	
Mutation type	Humanized back mutation site	Mutation type	Humanized back mutation site
Hu049 VH.1D	A93T, T71A M48I, V67A, M69L, T73D, S76N		

NOTE:

For example, A93T denotes a back mutation from A to T at position 93 according to Kabat numbering system.

* Indicates that the murine antibody CDR was implanted into human germline FR sequences.

TABLE 3

Murine antibody mAb049 humanized sequences

	Hu049 VH.1	Hu049 VH.1A	Hu049 VH.1B	Hu049 VH.1C	Hu049 VH.1D
Hu049 VK.1	Hu049-1	Hu049-2	Hu049-3	Hu049-4	Hu049-5
Hu049 VK.1A	Hu049-6	Hu049-7	Hu049-8	Hu049-9	Hu049-10
Hu049 VK.1B	Hu049-11	Hu049-12	Hu049-13	Hu049-14	Hu049-15
Hu049 VK.1C	Hu049-16	Hu049-17	Hu049-18	Hu049-19	Hu049-20

NOTE:

This table shows various sequence combinations of different mutations. For example, Hu049-8 indicates that two mutations (Hu049VK.1A and Hu049VH.1B) are present in the humanized murine antibody mAb049, and so on.

[0086] 4. Expression and Purification of Humanized Antibody

[0087] The above-mentioned antibodies were cloned, expressed and purified by genetically recombinant methods. Humanized antibodies were assessed by ELISA, a receptor binding inhibition assay, Biacore, a cell viability test etc., and those demonstrating desirable properties were selected. Specific antibodies are indicated in the following table:

TABLE 4

components of humanized IL-17A antibody

Antibody	Heavy chain	SEQ ID NO	Light chain	SEQ ID NO
Hu049-17	Hu049-17.VH	SEQ ID NO: 5	Hu049 VL	SEQ ID NO: 9
Hu049-18	Hu049-18.VH	SEQ ID NO: 6		
Hu049-19	Hu049-19.VH	SEQ ID NO: 7		
Hu049-20	Hu049-20.VH	SEQ ID NO: 8		

[0088] Specific sequences of the humanized antibody mAb049 are listed below:

Hu049-17.VH

SEQ ID NO: 5

EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEVHWVRQAPGQGLEWMGV

IDPGTGGVAYNQKFEGRVTMTTDTSTSTAYMELRSLRSDDTAVYYCTRYS

LFYGSSPYAMDYWGQGTLVTVSS

-continued

Hu049-18.VH

SEQ ID NO: 6

EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEVHWVRQAPGQGLEWMGV

IDPGTGGVAYNQKFEGRVTMTADTSTSTAYMELRSLRSDDTAVYYCTRYS

LFYGSSPYAMDYWGQGTLVTVSS

Hu049-19.VH

SEQ ID NO: 7

EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEVHWVRQAPGQGLEWIGV

IDPGTGGVAYNQKFEGRVTMTADTSTSTAYMELRSLRSDDTAVYYCTRYS

LFYGSSPYAMDYWGQGTLVTVSS

Hu049-20.VH

SEQ ID NO: 8

EVQLVQSGAEVKKPGASVKVSCKASGYTFTDYEVHWVRQAPGQGLEWIGV

IDPGTGGVAYNQKFEGRATLTADDSTNTAYMELRSLRSDDTAVYYCTRYS

LFYGSSPYAMDYWGQGTLVTVSS

Hu049VL

SEQ ID NO: 9

EIVLTQSPDFQSVTPKEKVTITCSASSSVNYMHWFQQKPDQSPKLWIYRT

SNLASGVPSRFSGSGSGTDYTLTINSLEAEDAATYYCQQRSSYPWTFGQG

TKLEIKR

EXAMPLE 3

In Vivo Pharmacokinetics and Pharmacodynamics Tests of Humanized Anti-IL-17 Antibody

[0089] Human IL-17 can bind to and stimulate the mouse IL-17 receptor, resulting in increased expression and subsequent secretion of chemokines KC (CXCL1) in male mice. Experiments covering various time points and various doses were performed to identify an optimal dose of human IL-17 and an optimal time point for KC induction (see Test Example 5). These experiments showed that 150mg/kg of human IL-17 induces the highest level of KC in mouse serum 2 hours after IL-17 administration. Full-length antibodies of the present invention were intravenously administered to mice at the concentrations of 3, 30, 300, 3000 μg/kg, 20 hours before the subcutaneous injection of human IL-17. Two hours after human IL-17 administration, the mice were sacrificed, and KC levels were determined by ELISA according to the manufacturer's specification (Mouse CXCL1/KC Quantikine ELISA Kit, R & D SYSTEM, #SMKC00B). An isotype-matched antibody was used as a negative control. Antibodies block the ability of human IL-17 to stimulate the mouse IL-17 receptor, resulting in the inhibition of increased KC expression in a dose-dependent manner in mice. Compared to the ineffective control antibody, the antibody Hu049-18 of the present invention reduced the average KC level to about ⅙ under the described conditions at the dose of 3000 μg/mice.

[0090] Serum pharmacokinetics in rats and macaque was determined after intravenous or subcutaneous administration of the antibody Hu049-18 of the present invention (see Test Example 6). In rats, the half-life was 9.91 days after intravenous administration of 5 mg/kg, and the half-life was 11.5 days after subcutaneous administration of 5 mg/kg. In macaque, the half-life was 24.4 days after intravenous administration of 1 mg/kg.

TEST EXAMPLES

TEST EXAMPLE 1

Indirect ELSIA

[0091] Purpose:

[0092] An indirect ELISA method was used to ensure the selection of antibodies that can recognize a conformational epitope, and for screening the mouse hybridomas from Example 1 of the present invention.

[0093] Materials:

[0094] Human IL-17A (hIL-17A) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0095] Human IL-17A/F (heterodimer, hIL-17A/F) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181 and the human IL-17F protein sequence with the Genbank Accession No. NP_443104, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0096] The positive controls, murine anti-IL-17 antibodies from Lilly and Novartis (Lilly mAb, Novartis mAb) were cloned using the murine sequences disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821) and U.S. Pat. No. 7,807,155B2 (AIN 457), respectively, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0097] Murine mAbs antibodies derived from the mouse hybridoma disclosed in Example 1 of the present invention.

[0098] Protocol:

[0099] 1. Microtitration plates were directly coated with 1 μg/ml of streptavidin, and incubated at 4° C. overnight;

[0100] 2. Microtitration plates were blocked with 300 μl of PBST containing 2% BSA (v/v), and thermostatically incubated at 37° C. for 1 h, and uncoated wells were blocked as controls;

[0101] 3. The plates were washed with PBST three times, and all of the washing operations were performed using a Biotek (Elx 405) automatic washer;

[0102] 4. 100 μl of PBS containing hIL-17A or hIL-17A/F (1 μg/ ml) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0103] 5. The plates were washed with PBST three times.

[0104] 6. The positive controls, Lilly mAb and Novartis mAb, or murine mAbs antibodies of the present invention were titrated at a 1:5 dilution, with an initial concentration of 1 μg/ml. 100 μl of diluted positive control or murine antibody of the present invention were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h. Each concentration was tested in duplicate;

[0105] 7. The plates were washed with PBST three times;

[0106] 8. 100 μl of HRP anti-murine secondary antibody (Santa Cruz Cat.No.sc-2005) (1:5000) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0107] 9. The plates were washed with PBST three times. 100 μl of TMB Substrate were added to each well, and the plates were thermostatically incubated at 37° C. for 5 min. The reaction was stopped by the addition of 100 μl 2M H_2SO_4 to each well;

[0108] 10. The OD value at a wavelength of 450 nm was read on an ELISA microplate reader (Molecular Devices, Spectra Max).

[0109] 11. The OD values of the murine mAb antibodies were compared to those of the positive controls. Monoclonal cell lines with a ratio greater than 1, including IL17-mAb049, were screened.

TEST EXAMPLE 2

IL-17 Receptor Blocking Assay (RBA)

[0110] Purpose:

[0111] The purpose of the receptor blocking assay was to select the antibodies capable of blocking the binding of IL-17 to the IL-17 receptor (e.g., hIL-17RA). The test is based on a functional test, and it can be used for hybridoma high-throughput screening.

[0112] Materials and Equipment:

[0113] Anti-human Fc antibody (goat anti-human IgG-Fc fragment specific antibody (available from Jackson Immunoresearch, 109-005-008))

[0114] Human IL-17RA-Fc was cloned according to methods known in the art, using the human IL-17A receptor amino acid sequence with the Genbank ID No. ADY18334.1, and the cloned sequence was transiently transfected into HEK293E cells for expression, wherein the Fc fragments were obtained from human IgG1.

[0115] The positive controls, murine anti-IL-17 antibodies from Lilly and Novartis (Lilly mAb, Novartis mAb) were cloned using the murine sequences disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821) and U.S. Pat. No. 7,807,155B2 (AIN 457), respectively, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0116] mIgG: Murine IgG (Millipore Cat.No.PP54), used as a negative control

[0117] ELISA plate reader: Molecular Devices, Spectra Max

[0118] Murine monoclonal cell strains obtained from Example 1 of the present invention .

[0119] Protocol:

[0120] 1. Microtitration plates were directly coated with 10 μg/ml of Anti-human Fc antibody, and incubated at 4° C. overnight;

[0121] 2. Microtitration plates were blocked with 300 μl of PBST containing 2% BSA (v/v), and thermostatically incubated at 37° C. for 1 h, and uncoated wells were blocked as controls;

[0122] 3. The plates were washed with PBST three times, and all of the washing operations were performed using a Biotek (Elx 405) automatic washer;

[0123] 4. 100 μl of PBS containing IL-17 RA-Fc (60 ng/ml) were added to each well, and the plates were thermostatically incubated at 37° C. for 2 h;

[0124] 5. The plates were washed with PBST three times.

[0125] 6. The positive controls, Lilly mAb and Novartis mAb, or antibodies of the present invention were diluted at a 1:5 ratio, with an initial concentration of 40 μg/ml. mIgG was diluted using the same method. 50 μl of diluted positive control, murine antibody of the present invention, or mIgG were added to each well, and, 50 μof 0.2nM biotin-labeled IL-17A were added to the wells containing diluted positive control or the antibody of the present invention, mixed gently and the plates were thermostatically incubated at 37° C. for 1 h.

[0126] 7. The plates were washed with PBST three times; 8. 100 μl of HRP-labeled streptavidin complex (1:5000) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0127] 9. The plates were washed with PBST three times. 100 μl of TMB Substrate were added to each well, and the plates were thermostatically incubated at 37° C. for 5 min. The reaction was stopped by the addition of 100 μl 2M H_2SO_4 to each well;

[0128] 10. The OD value at a wavelength of 450 nm was read on an ELISA microplate reader.

[0129] 11. The IC_{50} value of the antibody being tested was calculated to measure blocking of the binding of IL-17 to IL-17 receptor.

[0130] The IC_{50} value (the antibody concentration when the OD value reduced 50%, i.e. RBA) was obtained according to the gradient curve of OD values versus antibody concentration.

[0131] Experimental Results:

[0132] According to the above method, the hybridoma obtained in Example 1 was screened to obtain a murine monoclonal antibody, designated IL17-mAb049, and the results were as follows:

TABLE 5

Antibody	huIL-17 RBA □ (nM)
Lilly mAb	0.17
Novartis mAb	1.56
IL17-mAb049	0.07

[0133] Conclusion: The murine antibody IL17-mAb 049 screened from the hybridomas showed improved activity compared to the positive control antibodies, Lilly mAb and Novartis mAb.

TEST EXAMPLE 3

Affinity Test

[0134] Purpose:

[0135] The BIACORE method was used in the experiment for determining antigen-antibody binding kinetics and affinity.

[0136] Materials and Equipments:

[0137] 1.1 Proteins:

[0138] Human IL-17A (hIL-17A) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0139] Human IL-17A/F (heterodimer, hIL-17A/F) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181 and human IL-17F protein sequence with the Genbank Accession No. NP_443104, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0140] Mouse IL-17A (Mu IL-17A) and rat IL-17A (Rat IL-17A) were cloned according to methods known in the art, using the mouse IL-17A protein sequence with the Genbank Accession No. NP_034682 and the rat IL-17A protein

sequence with the Genbank Accession No. NP_001100367, respectively, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0141] The positive controls, murine anti-IL-17 antibodies from Lilly and Novartis (Lilly mAb, Novartis mAb) were cloned using the murine sequences disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821) and U.S. Pat. No. 7,807,155B2 (AIN 457), respectively, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0142] The positive control, Lilly humanized anti-IL-17 antibody (Lilly mAb(hu)), was cloned using the humanized sequences disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821), and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0143] Murine monoclonal cell strains obtained from Example 1 of the present invention.

[0144] Humanized IL-17 antibodies obtained from Example 2 of the present invention.

[0145] 1.2BIACORE Model: BIACORE X 100, GE;

[0146] 1.3BIACORE Chips and Reagents (Trade Names are Listed Hereafter, No Acknowledged Translation):

Materials and Reagents	Company	Product list
1. Sensor Chip CM5 Research Grade	GE Healthcare	BR-1000-14
2. Amine Coupling Kit	GE Healthcare	BR-1000-50
3. HBS buffer BIA Certified	GE Healthcare	BR-1001-88
4. Acetate (100 ml)	GE Healthcare	BR-1003-51
5. Mouse Antibody Capture Kit	GE Healthcare	BR-1008-38
6. Regeneration buffer Glycine 1.5	GE Healthcare	BR-1003-54
7. BIAmaintenance Kit	GE Healthcare	BR-1006-66

[0147] Protocol:

[0148] 1. An antibody of the present invention was immobilized on a CM5 chip. A 1:1 solution of 50 mM NETS: 200 mM EDC was prepared and injected into FC2 (Flow cell 2) channel at a rate of 10 μL/min, for 7 min, to activate the CM5 sensor chip. The Antibody of the present invention was dissolved in 10 mM sodium acetate buffer at a concentration of 30 μg/ml, pH 5.0, and injected into the activated chip (HBS-EP mobile phase buffer: 10 mM HEPES, 150 mM NaCl, 3.4 mM EDTA, 0.005% surfactant P20, pH 7.4) at a rate of 5 μL/min. 1M ethanolamine was injected at a rate of 10 μL/min, for 7 min, to seal the remaining activated coupling positions. About 8000RU was generated.

[0149] 2. Binding kinetics Test: FC1 (Flow cell 1) was used as the reference channel, FC2 (Flow cell 2) was used as the sample channel, and murine or humanized control antibody or the antibody of the present invention was captured in the FC2 channel at 300RU, followed by the injection of different concentrations of IL-17 (including hIL-17A, MuIL-17, Rat IL-17). Cycle conditions were: injecting analytes into all FC channels at 30 μl/min for 3min, dissociation for 20 min, injecting 10 mM Glycine, pH 1.5, for 60 s (at rate of 10 μl/min) for surface regeneration. The difference between the signal with captured antibody and the signal without captured antibody was calculated using Biacore X100 evaluation software ver 2.0 (Biacore), and the running buffer was 10 mM Hepes, 650 mM NaCl, 3 mM EDTA, 0.05% Tween-20.

[0150] Experimental Results:

[0151] 1. Hybridomas obtained in Example 1 were tested using the above method, and the results were as follows:

TABLE 6

Antibody	人 IL-17A □ KD (M)
Lilly mAb	2.18E−11
Novartis mAb	4.24E−10
IL17-mAb049	2.62E−11

[0152] Conclusion: The affinity of the murine antibody IL17-mAb 049 obtained from hybridomas is equivalent to that of the positive control Lilly mAb antibody, and is stronger than that of the positive control Novartis mAb antibody.

[0153] 2. Humanized IL-17 antibodies obtained from Example 2 were tested using the above method, and the results were as follows:

TABLE 7

Humanized antibody	Human IL-17A □ KD (M)	Mu IL-17 KD (M)	Rat IL-17 □ KD (M)
Lilly's mAb (hu)	1.48E−11		
Hu049-17	<1 pM	1.37E−10	1.06E−09
Hu049-18	<1 pM	6.81E−11	4.77E−10
Hu049-19	2.68E−12	7.71E−11	6.00E−11

[0154] Conclusion: The affinity of the humanized antibody 10 times higher than that of Lilly's positive control antibody (1.48E-11M).

TEST EXAMPLE 4

Cellular Bioassay (GROα Assay)

[0155] Purpose:

[0156] The following experiment was intended to assess the cellular biological activity of the anti-IL-17A antibody in inhibiting IL-17-stimulated secretion of GROα from Hs27 cells.

[0157] Materials and Equipment:

[0158] Hs27 cells: ATCC Cat.No.CRL-1634 (Note: cells cultured for more than six weeks are not recommended for the bioassay);

[0159] Hs27 cell culture medium: DMEM+10% FBS

[0160] DMEM: ATCC Cat.No.30-2002;

[0161] FBS: GIBCO Cat.No.10099, lot 8122818;

[0162] Recombinant human IL-17A (rhIL-17A): R&D Systems Cat.No.317-ILB, lot SOA161109B;

[0163] Recombinant human IL-17A/F (rhIL-17A/F): R&D System Cat No.5194-IL/CF, lot RXT101109A;

[0164] Human CXCL1/GRO alpha Quantikine PharmPak kit: R&D system Cat. No. PDGR00

[0165] Equipment: Biotek ELx808 microplate reader.

[0166] Murine monoclonal cell strain obtained from Example 1 of the present invention.

[0167] Humanized IL-17 antibody obtained from Example 2 of the present invention.

[0168] Protocol:

[0169] 1. Hs27 Cell Culture:

[0170] Hs27 cells were cultured in 50 ml of DMEM+10% FBS medium in T175 flasks, and the cells (at a density of about 90%) were diluted at a ratio of 1:3 every 3 days. The

cells were used for the bioassay within a month, or they were re-thawed from liquid nitrogen. The re-thawed cells were cultured for at least a week before use in the bioassay.

[0171] 2. Bioassay (IL-17A) Experimental Procedure

[0172] 2.1 Hs27 cells were centrifuged at 950 rpm for 4 min (for complete removal of trypsin-EDTA) and collected. Cell viability was analyzed using a trypan blue stain, and only cells with >80% vitality were used for the experiment;

[0173] 2.2 Medium was added into a 96-well plate at 50 μl/well;

[0174] 2.3 Hs27 cells were diluted with DMEM+10% FBS and added into a 96-well plate at a density of 10000 cells/50 μl/well;

[0175] 2.4 25 μl of the IL-17 human antibody were added into each well in duplicate, and the antibody was diluted at a ratio of 1:3 with an initial concentration of lOnM;

[0176] 2.5 25 μl of recombinant human IL-17A were added into each well with a final concentration of 0.3 nM, and the 96-well plate was centrifuged at 500 rpm for 1 min;

[0177] 2.6 Cells were thermostatically incubated at 37° C. for 17 h;

[0178] 2.7 Cell culture supernatant was collected, and the concentration of GROα was detected in the supernatant using a human CACL1/GRO alpha Quantikine kit (according to the manufacturer's instructions);

[0179] 3. Experimental procedure of the Bioassay (IL-17A/F):

[0180] The procedure of IL-17A/F bioassay was similar to that of IL-17A bioassay, except that IL-17A was substituted by IL-17A/F.

[0181] Experimental Results:

[0182] 1. The hybridoma obtained in Example 1 was tested according to the above methods, and the results were as follows:

TABLE 8

Antibody	huIL-17 Bioassay (IC50, nM)	huIL-17A/F Bioassay (IC50, nM)
Lilly mAb	0.04	0.69
Novartis mAb	0.22	1.15
IL17-mAb049	0.04	0.46

[0183] Conclusion: The biological activity of the IL17-mAb049 antibody obtained from the hybridoma is equivalent to that of the positive control Lilly mAb antibody, and is higher than that of the positive control Novartis mAb antibody.

[0184] 2. Thumanized antibodies obtained from Example 2 were tested according to the above methods, and the results were as follows:

TABLE 9

Antibody	huIL-17 Bioassay (IC50, nM)	huIL-17A/F Bioassay (IC50, nM)	Cyno IL-17A
Lilly's mAb (hu)	0.033	0.83	
Hu049-17	0.061	0.406	0.03
Hu049-18	0.04	0.684	0.033
Hu049-19	0.066	0.411	0.039
Hu049-20	0.065	0.674	0.028

[0185] Conclusion: These results indicate that all of the humanized antibodies exhibit cellular biological activity. Hu049-17, 18, 19 and 20 have IC50 values (0.04 nM-0.066 nM) similar to that of the positive control antibody (0.04 nM). In addition, these antibodies display cross-reaction with cynomolgus IL-17A (IC50 is 0.03 nM-0.039 nM). The activity against human IL-17A/F is about 10 times weaker than that against IL-17A.

TEST EXAMPLE 5

Neutralization Test of Human IL-17 In Vivo

[0186] Purpose:

[0187] The aim of the in vivo neutralization test is to verify that the antibodies of the invention can block the in vivo the binding of IL-17 to the IL-17 receptor (e.g., hIL-17RA), thereby inhibiting the CXCRlexpression induced by IL-17.

[0188] Materials and Equipment:

[0189] Protein: Human IL-17A (hIL-17A) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0190] The positive control, Lilly humanized anti-IL-17 antibody (Lilly mAb (hu)), was cloned using humanized sequence disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821), and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0191] Human IgG (HuIgG): (Millipore Cat.No.AG711).

[0192] Animals: 7-week-old C57/B6 male mice (purchased from SINO-BRITSH SIPPR/BK LAB. ANIMAL LTD., CO, Certificate No.: SOCK (Shanghai) 2008-0016), 6 mice per group.

[0193] Reagents: Ab dilution solution: citrate buffer (pH 5.0): 10 mM sodium citrate, 50 mM NaCl

[0194] hIL-17A dilution solution: PBS (sodium phosphate buffer, pH 7.2).

[0195] Mouse CXCL1/KC Quantikine ELISA Kit, 6-well plates, R&D SYSTEM, #SMKC00B.

[0196] Protocol:

[0197] 1) Mice were divided into 15 groups, with 6 mice in each group.

[0198] 2) 100 uL of Hu049-18 or control antibody (HuIgG or Lilly mAb (hu)), or a diluted solution thereof, was intraperitoneally (LP.) administered to each mouse, and administration doses of the antibody were 3000 μg/kg, 300 μg/kg, 30 ug/kg and 3 μg/kg.

[0199] 3) 20 hours later, each mouse was subcutaneously (SC) injected with 100 uL of 150 μg/kg hIL-17A.

[0200] 4) 2 hours later, blood samples were collected and incubated at room temperature for 2 hours, until coagulation, or at 2-8° C. overnight, until coagulation, and the samples were then centrifuged at 2000×g for 20 min. The supernatant was discarded, and analysis was performed immediately or aliquots of sample were stored at −20° C. Repeated freezing and thawing was avoided.

[0201] 5) Samples obtained from Step 4 were analyzed using a mouse CXCL1/KC Quantikine ELISA Kit.

[0202] Experimental Results:

[0203] Humanized antibody Hu049-18 obtained from Example 2 was tested according to the above method, and the results were as follows:

TABLE 10

Antibody (injection dosage 3000 μg/mouse)	KC mean value (pg/mll)
HuIgG	937
Lilly mAb(hu)	158
Hu049-18	145

[0204] Conclusion: Compared to the negative control antibody, the Hu-049-18 antibody of the present invention reduced the average KC level by about ⅙ at a dose of 3000 μg/mice under the described condition.

TEST EXAMPLE 6

Determination of the Half-Life (T1/2) of the Antibodies In Vivo

[0205] Purpose:

[0206] To determine the pharmacokinetics parameters of the Hu049-18 antibody of the present invention in rats or cynomolgus monkeys in vivo.

[0207] Materials and Reagents:

[0208] Protein: Human IL-17A (hIL-17A) was cloned according to methods known in the art, using the human IL-17A protein sequence with the Genbank Accession No. NP-002181, and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0209] The positive control, Lilly humanized anti-IL-17 antibody (Lilly mAb (hu)), was cloned using the humanized sequence disclosed in U.S. Pat. No. 7,838,638B2 (LY 2439821), and the cloned sequence was transiently transfected into HEK293E cells for expression.

[0210] Human IgG (HuIgG): Human IgG Polyclonal, Millipore Cat.No.AG711

[0211] Animals: 230-250g SD male rats (purchased from Shanghai SLAC laboratory Animal Co., Ltd., Certificate No: SCXK (Shanghai) 2007-0005), were divided into two groups: an intravenous injection (IV) group (dorsum of foot), and a subcutaneous injection (SC) group; 5 rats were in each group.

[0212] Macaque: 2-3kg cynomolgus monkeys (Hainan Jingang Biotechnology Co., Ltd. Certificate No: SCXK (HN) 2010-0001, 0000152.)

[0213] Reagents: antibody dilution solution: citrate buffer (pH 5.0): 10 mM sodium citrate, 50 mM NaCl

[0214] hIL-17A dilution solution: PBS (sodium phosphate buffer, pH 7.2)

[0215] Goat anti-human IgG (Fab-specific) peroxidase conjugated antibody, Sigma Cat.No.121M4811

[0216] Protocol:

[0217] 1. Procedures for detection in rat:

[0218] (1) In Vivo Administration

[0219] SD rats were randomly divided into two groups (an intravenous injection (IV) (dorsum of foot) group and a subcutaneous injection (SC) group), 5 rats per group;

[0220] Under sterile conditions, Hu049-18 was dissolved in a citrate buffer solution (pH 5.0) to a final concentration of 2.5 mg/mL;

[0221] Each rat was IV or SC administered with a dose of 5 mg/kg;

[0222] For the IV group, 200 uL blood samples (equivalent to 80 uL serum) were taken through the tail vein at 0 min, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 24 hr, 2 d, 4 d, 7 d, 10 d, 14 d, 21 d, and 28 d after administration; For the SC group, 200 uL blood samples (equivalent to 80 uL serum) were taken through the tail vein at 0 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 12 hr, 24 hr, 2 d, 4 d, 7 d, 10 d, 14 d, 21 d, and 28 d after administration;

[0223] Blood samples were collected and incubated for half an hour at room temperature until coagulation, and then centrifuged at 4° C., at 10000×g for 5 minutes. The supernatant was collected for immediate testing, or aliquots of the sample were stored at −80° C. Repeated freezing and thawing was avoided.

[0224] (2) Serum Samples Obtained in Step (1) were Detected by ELISA

[0225] 1) Standard Curve

[0226] a) Microtitration plates were directly coated with 1μg/ml of streptavidin, and incubated at 4° C. overnight;

[0227] b) Microtitration plates were blocked with 300 μl of PBST containing 2% BSA (v/v), and thermostatically incubated at 37° C. for 1 h, and uncoated wells were blocked as controls;

[0228] c) Plates were washed with PBST three times, and all of the washing steps were performed using a Biotek (Elx 405) automatic washer;

[0229] d) 100 μl of PBS containing hIL-17A (0.2 μg/mL) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0230] e) Plates were washed with PBST three times.

[0231] f) Hu049-18 titration: 1:2 dilutions of Hu049-18 were titrated, with an initial concentration of 0.8 μg/ml. 100 μl of diluted Hu049-18 were added into each well, and the standard curve was plotted. The 96-well plate was thermostatically incubated at 37° C. for 1 h.

[0232] g) Plates were washed with PBST three times;

[0233] h) 100 μl of goat anti-human IgG (Fab-specific) peroxidase conjugated antibody (Sigma Cat. No. 121M4811) (1:5000) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0234] i) Plates were washed with PBST three times. 100 μl of TMB Substrate were added to each well, and the plates were thermostatically incubated at 37° C. for 5 min. The reaction was stopped by the addition of 100 μl M HCl to each well;

[0235] j) The OD value at a wavelength of 450 nm/630 nm was read on an ELISA microplate reader (Molecular Devices, Spectra Max).

[0236] 2) Sample Test:

[0237] a) Microtitration plates were directly coated with 1 μg/ml of streptavidin, and incubated at 4° C. overnight;

[0238] b) Microtitration plates were blocked with 300 μl of PBST containing 2% BSA (v/v), and thermostatically incubated at 37° C. for 1 h, and uncoated wells were blocked as controls;

[0239] c) Plates were washed with PBST three times, and all of the washing steps were performed using a Biotek (Elx 405) automatic washer;

[0240] d) 100 μl of PBS containing hIL-17A (0.2 μg/mL) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0241] e) Plates were washed with PBST three times.

[0242] f) Serum samples titration: Before the experiment, a rat serum sample was diluted by different ratios to obtain an optimal dilution ratio at which the antibody concentration in the serum was in the middle of the standard curve. Serum samples were diluted in accordance with the optimal dilution

ratio, and Hu049-18 was diluted to 25 ng/mL. 100 μl of diluted serum sample and Hu049-18 were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h. Each concentration was titrated in duplicate;

[0243] g) Plates were washed with PBST three times;

[0244] h) 100 μl of goat anti-human IgG (Fab-specific) peroxidase conjugated antibody (Sigma Cat. No. 121M4811) (1:5000) were added to each well, and the plates were thermostatically incubated at 37° C. for 1 h;

[0245] i) Plates were washed with PBST three times. 100 μl of TMB Substrate were added to each well, and the plates were thermostatically incubated at 37° C. for 5 min. The reaction was stopped by the addition of 100 μl M HCl to each well;

[0246] j) The OD value at a wavelength of 450 nm/630 nm was read on an ELISA microplate reader (Molecular Devices, Spectra Max).

[0247] 2. Detection procedure for Macaques :

[0248] The in vivo detection procedure for Macaque (Macaca fascicularis) was similar to that for rats, with the following differences: the administration to cynomolgus monkey was only via intravenous injection (IV) at a dose of 1 mg/kg; 500 μL blood samples were taken through the tail vein at 0 min, 5 min, 15 min, 30 min, 1 hr, 2 hr, 4 hr, 8 hr, 24 hr, 32 hr, 3 d, 4 d, 5 d, 6 d, 9 d, 12 d, 14 d, 17 d, 21 d, 28 d, and 35 d after administration; and after centrifugation, the serum sample was divided into 3 parts (ensuring 2 parts containing 60 μL serum sample), and the samples were frozen at −80° C. for analysis.

[0249] Experimental Results:

[0250] The humanized antibody Hu049-18 obtained from Example 2 was tested according to the above method, and the results were as follows:

TABLE 11

Animal	Administration route	T1/2 (Hu049-18) (Day)	T1/2 (Lilly mAb(hu)) (Day)
SD rat	IV (5 mg/kg)	9.91	5.05
	SC (5 mg/kg)	11.5	5.53
cynomolgus monkeys	IV (1 mg/kg)	24.4	

[0251] Conclusion: These results showed that, compared to the positive control antibody of Lilly (T1/2 value of positive control antibody in cynomolgus monkeys was reported as 6.5 days (iv) and 10.3 days (sc)), the Hu049-18 antibody of the present invention had a much longer in vivo half-life under the described condition.

SEQUENCE LISTING

<160> NUMBER OF SEQ ID NOS: 15

<210> SEQ ID NO 1
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 1

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His Val Gln Leu Gln Gln Ser Gly Ala Asp Leu Val Arg Pro Gly Ala
1               5                   10                  15

Ser Val Thr Leu Ser Cys Lys Ala Ser Gly Tyr Ile Phe Thr Asp Tyr
            20                  25                  30

Glu Val His Trp Val Lys Gln Thr Pro Val His Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Glu Gly Lys Ala Thr Leu Thr Ala Asp Asp Ser Ser Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Thr Ser Glu Asp Ser Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Ser Leu Phe Tyr Gly Ser Ser Pro Tyr Ala Met Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Ser Val Thr Val Ser Ser
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```

<210> SEQ ID NO 2
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<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 2

```
Gln Ile Val Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly
1               5                   10                  15
```

-continued

```
Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Asn Tyr Met
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Gly Thr Ser Pro Lys Leu Trp Ile Tyr
        35                  40                  45

Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Val Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Ser Tyr Ser Leu Thr Ile Ser Arg Met Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Trp Thr
                85                  90                  95

Phe Gly Gly Gly Thr Asn Leu Glu Ile Lys
            100                 105


<210> SEQ ID NO 3
<211> LENGTH: 98
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 3

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
            20                  25                  30

Gly Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Ser Ala Tyr Asn Gly Asn Thr Asn Tyr Ala Gln Lys Leu
    50                  55                  60

Gln Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg


<210> SEQ ID NO 4
<211> LENGTH: 95
<212> TYPE: PRT
<213> ORGANISM: homo sapiens

<400> SEQUENCE: 4

Glu Ile Val Leu Thr Gln Ser Pro Asp Phe Gln Ser Val Thr Pro Lys
1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Gly Ser Ser
            20                  25                  30

Leu His Trp Tyr Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Leu Ile
        35                  40                  45

Lys Tyr Ala Ser Gln Ser Phe Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Ser Leu Glu Ala
65                  70                  75                  80

Glu Asp Ala Ala Thr Tyr Tyr Cys His Gln Ser Ser Ser Leu Pro
                85                  90                  95


<210> SEQ ID NO 5
<211> LENGTH: 123
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<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: mAb049 humanized sequence Hu049-17.VH

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Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
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Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe
50 55 60

Glu Gly Arg Val Thr Met Thr Thr Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Ser Leu Phe Tyr Gly Ser Ser Pro Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
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<210> SEQ ID NO 6
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<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: mAb049 humanized sequence Hu049-18.VH

<400> SEQUENCE: 6

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1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
20 25 30

Glu Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe
50 55 60

Glu Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65 70 75 80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Thr Arg Tyr Ser Leu Phe Tyr Gly Ser Ser Pro Tyr Ala Met Asp Tyr
100 105 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

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<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: mAb049 humanized sequence Hu049-19.VH

<400> SEQUENCE: 7

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala

-continued

```
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Glu Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Glu Gly Arg Val Thr Met Thr Ala Asp Thr Ser Thr Ser Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Ser Leu Phe Tyr Gly Ser Ser Pro Tyr Ala Met Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 8
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: mAb049 humanized sequence Hu049-20.VH

<400> SEQUENCE: 8

Glu Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1               5                   10                  15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Asp Tyr
            20                  25                  30

Glu Val His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Ile
        35                  40                  45

Gly Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe
    50                  55                  60

Glu Gly Arg Ala Thr Leu Thr Ala Asp Asp Ser Thr Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Arg Ser Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Arg Tyr Ser Leu Phe Tyr Gly Ser Ser Pro Tyr Ala Met Asp Tyr
            100                 105                 110

Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 9
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: mAb049 humanized sequence Hu049VL

<400> SEQUENCE: 9

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1               5                   10                  15

Glu Lys Val Thr Ile Thr Cys Ser Ala Ser Ser Ser Val Asn Tyr Met
            20                  25                  30

His Trp Phe Gln Gln Lys Pro Asp Gln Ser Pro Lys Leu Trp Ile Tyr
        35                  40                  45
```

-continued

```
Arg Thr Ser Asn Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Asp Tyr Thr Leu Thr Ile Asn Ser Leu Glu Ala Glu
65                  70                  75                  80

Asp Ala Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Ser Tyr Pro Trp Thr
                85                  90                  95

Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys Arg
            100                 105


<210> SEQ ID NO 10
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 10

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<210> SEQ ID NO 11
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 11

Val Ile Asp Pro Gly Thr Gly Gly Val Ala Tyr Asn Gln Lys Phe Glu
1               5                   10                  15

Gly


<210> SEQ ID NO 12
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 12

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1               5                   10


<210> SEQ ID NO 13
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 13

Ser Ala Ser Ser Ser Val Asn Tyr Met His
1               5                   10


<210> SEQ ID NO 14
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 14

Arg Thr Ser Asn Leu Ala Ser
1               5
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-continued

<210> SEQ ID NO 15
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: mus musculus

<400> SEQUENCE: 15

Gln Gln Arg Ser Ser Tyr Pro Trp Thr
1 5

1. An IL-17A binding agent, comprising:

an antibody light chain variable region, comprising 0-3 LCDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15; and

an antibody heavy chain variable region, comprising 0-3 HCDR regions having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, SEQ ID NO:

11, and SEQ ID NO: 12;

wherein the number of CDR regions of the antibody light chain variable region and the number of CDR regions of the antibody heavy chain variable region are not simultaneously 0.

2-5. (canceled)

6. The IL-17A binding agent according to claim **1**, comprising three LCDR regions, wherein the amino acid sequence of LCDR1 is shown in SEQ ID NO: 13, the amino acid sequence of LCDR2 is shown in SEQ ID NO: 14, and the amino acid sequence of LCDR3 is shown in SEQ ID NO: 15.

7. The IL-17A binding agent according to claim **1**, comprising three HCDR regions, wherein the amino acid sequence of HCDR1 is shown in SEQ ID NO: 10, the amino acid sequence of HCDR2 is shown in SEQ ID NO: 11, and the amino acid sequence of HCDR3 is shown in SEQ ID NO: 12.

8. The IL-17A binding agent according to claim **1**, wherein the antibody light chain variable region further comprises a light chain FR region derived from murine κ chain or a variant thereof, or a light chain FR region derived from a murine λ-chain or a variant thereof.

9. The IL-17A binding agent according to claim **8**, wherein the amino acid sequence of the antibody light chain variable region is shown in SEQ ID NO: 2.

10. The IL-17A binding agent according to claim **8**, further comprising a light chain constant region derived from a murine κ chain or a variant thereof, or a light chain constant region derived from a murine λ chain or a variant thereof.

11. The IL-17A binding agent according to claim **1**, wherein the antibody heavy chain variable region further comprises a heavy chain FR region derived from murine IgG1 or a variant thereof, a heavy chain FR region derived from murine IgG2 or a variant thereof, a heavy chain FR region derived from murine IgG3 or a variant thereof, or a heavy chain FR region derived from murine IgG4 or a variant thereof.

12. The IL-17A binding agent according to claim **11**, wherein the amino acid sequence of the antibody heavy chain variable region is shown in SEQ ID NO: 1.

13. The IL-17A binding agent according to claim **11**, further comprising a heavy chain constant region derived from murine IgG1 or a variant thereof, a heavy chain constant region derived from murine IgG2 or a variant thereof, a heavy chain constant region derived from murine IgG3 or a variant thereof, or a heavy chain constant region derived from murine IgG4 or a variant thereof.

14. The IL-17A binding agent according to claim **1**, wherein antibody light chain variable region further comprises a light chain FR region derived from a human κ chain or a variant thereof, or a light chain FR region derived from a human λ chain or a variant thereof.

15. The IL-17A binding agent according to claim **14**, wherein the light chain FR region is a human germline light chain A10 FR region whose amino acid sequence is shown in SEQ ID NO: 4, or a variant thereof.

16. The IL-17A binding agent according to claim **15**, wherein the variant of a human germline light chain A10 FR region refers to a human germline light chain A10 FR region having 0-10 amino acid mutations.

17. The IL-17A binding agent according to claim **16**, wherein the amino acid mutations are one or more selected from the group consisting of F71Y, K49Y, Y36F and L47W.

18. The IL-17A binding agent according to claim **14**, wherein the antibody light chain is a light chain of SEQ ID NO: 9 or a variant thereof.

19. The IL-17A binding agent according to claim **14**, further comprising a light chain constant region derived from a human κ chain or a variant thereof, or a light chain constant region derived from a human λ chain or a variant thereof.

20. The IL-17A binding agent according to claim **1**, wherein the heavy chain variable region further comprises a heavy chain FR region derived from human IgG1 or a variant thereof, a heavy chain FR region derived from human IgG2 or a variant thereof, a heavy chain FR region derived from human IgG3 or a variant thereof, or a heavy chain FR region derived from human IgG4 or a variant thereof.

21. The IL-17A binding agent according to claim **20**, wherein the heavy chain FR region is a human germline heavy chain VH1-18 FR region whose amino acid sequence is shown in SEQ ID NO: 3, or a variant thereof.

22. The IL-17A binding agent according to claim **21**, wherein the variant refers to a heavy chain VH 1-18 FR region having 0-10 amino acid mutations.

23. The IL-17A binding agent according to claim **22**, wherein the amino acid mutations are one or more selected from the group consisting of A93T, T71A, M48I, V67A, M69L, T73D and S76N.

24. The IL-17A binding agent according to claim **21**, wherein the heavy chain is comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7 and SEQ ID NO: 8, or a variant thereof.

25. The IL-17A binding agent according to claim **20**, further comprising a heavy chain constant region derived from human IgG1 or a variant thereof, a heavy chain constant region derived from human IgG2 or a variant thereof, a heavy chain constant region derived from human IgG3 or a variant thereof, or a heavy chain constant region derived from human IgG4 or a variant thereof.

26. A vector expressing the IL-17A binding agent according to claim **1**.

27. A vector comprising a nucleotide encoding the IL-17A binding agent according to claim **1**.

28. A pharmaceutical composition comprising the IL-17A binding agent according to claim **1** and a pharmaceutically acceptable excipient, diluent or carrier.

29-30. (canceled)

31. A method for treating a disease or disorder mediated by IL-17, the method comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition according to claim **28**.

32. The method according to claim **31**, wherein:

the disease is an inflammatory disease or an autoimmune disease.

33. An IL-17A binding agent comprising:

an antibody light chain variable region comprising 3 light chain complementarity determining (LCDR) regions having the amino acid sequences of SEQ ID NO: 13, SEQ ID NO: 14, and SEQ ID NO: 15, respectively; and

an antibody heavy chain variable region comprising 3 heavy chain complementarity determining (HCDR) regions having the amino acid sequences of SEQ ID NO: 10, SEQ ID NO: 11, and SEQ ID NO: 12, respectively.

* * * * *

US007883705B2

(12) **United States Patent**
Yamazaki et al.

(10) **Patent No.: US 7,883,705 B2**
(45) **Date of Patent: Feb. 8, 2011**

(54) **ANTI FGF23 ANTIBODY AND A PHARMACEUTICAL COMPOSITION COMPRISING THE SAME**

(75) Inventors: **Yuji Yamazaki**, Gunma (JP); **Itaru Urakawa**, Gunma (JP); **Hitoshi Yoshida**, Gunma (JP); **Yukiko Aono**, Gunma (JP); **Takeyoshi Yamashita**, Tokyo (JP); **Takashi Shimada**, Gunma (JP); **Hisashi Hasegawa**, Gunma (JP)

(73) Assignee: **Kyowa Hakko Kirin Co., Ltd.**, Tokyo (JP)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 358 days.

(21) Appl. No.: **12/030,593**

(22) Filed: **Feb. 13, 2008**

(65) **Prior Publication Data**

US 2009/0148461 A1 Jun. 11, 2009

(30) **Foreign Application Priority Data**

Feb. 14, 2007 (JP) 2007-034018

(51) **Int. Cl.**
A61K 39/395 (2006.01)

(52) **U.S. Cl.** **424/145.1**; 530/388.24; 530/388.25

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Zachary Skelding
(74) *Attorney, Agent, or Firm*—Stephen A. Bent; Foley & Lardner LLP

(57) **ABSTRACT**

To provide an antibody against FGF23 and a pharmaceutical composition such as a preventive or therapeutic agent which can prevent or treat by suppressing an action of FGF23 by using the antibody. An antibody or its functional fragment against human FGF23 produced by hybridoma C10 (Accession No. FERM BP-10772).

10 Claims, 19 Drawing Sheets

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FIG. 1

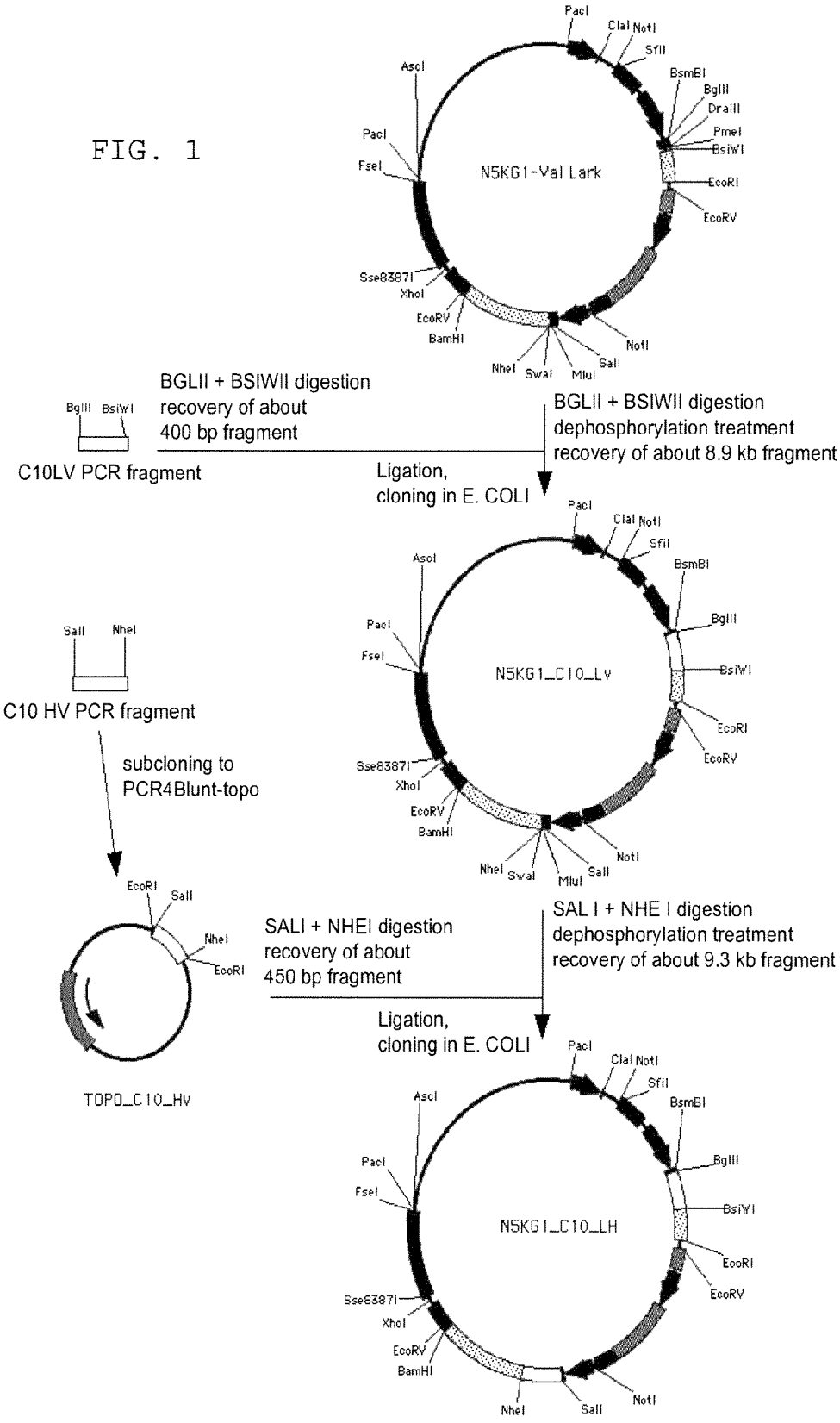
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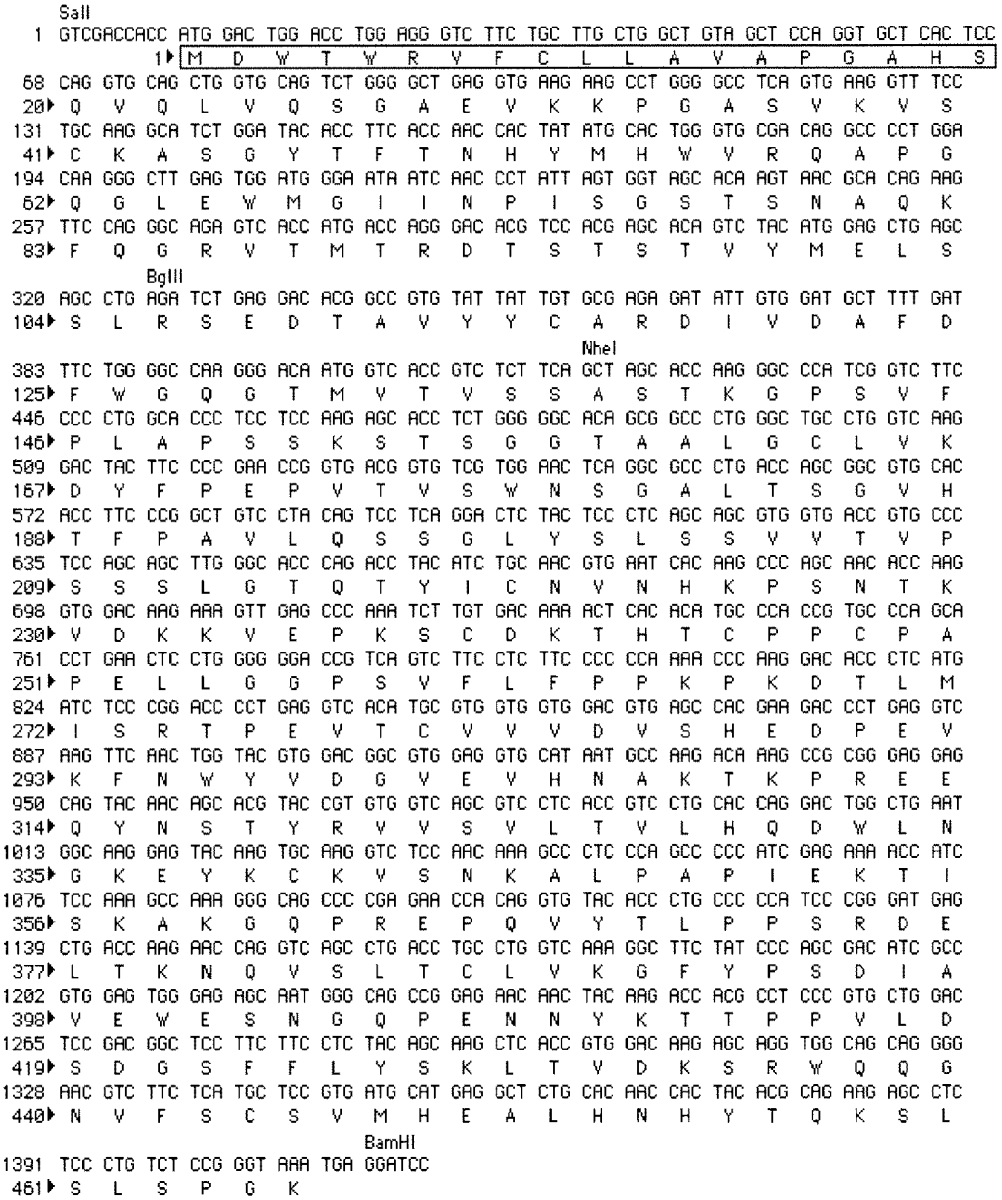
FIG. 2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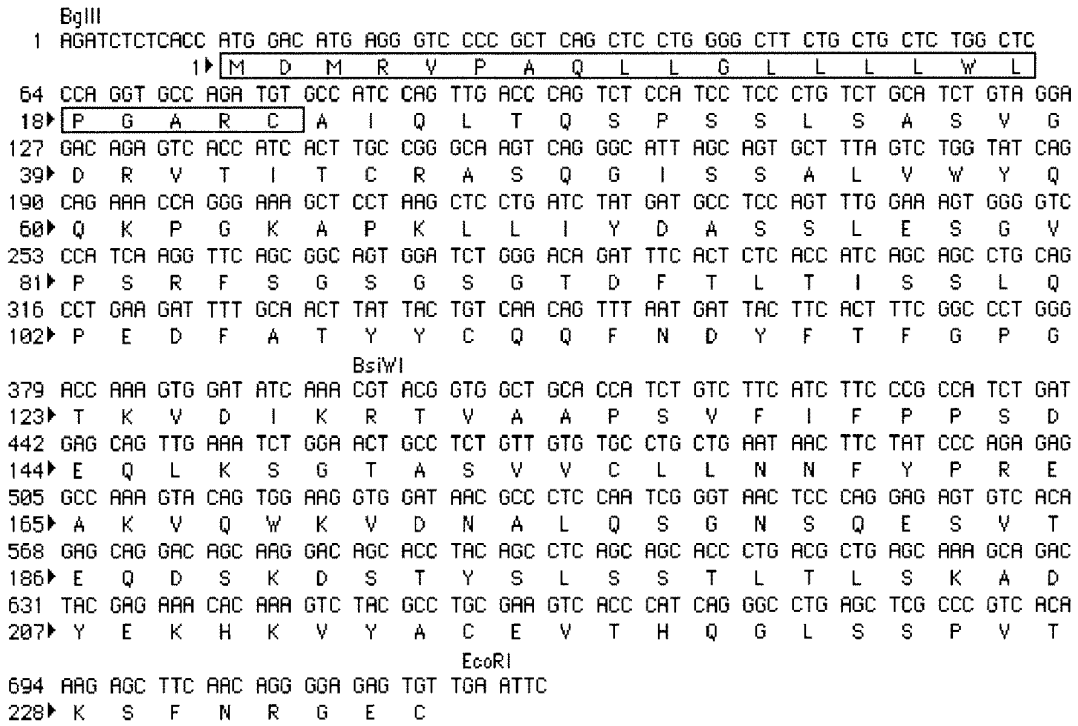
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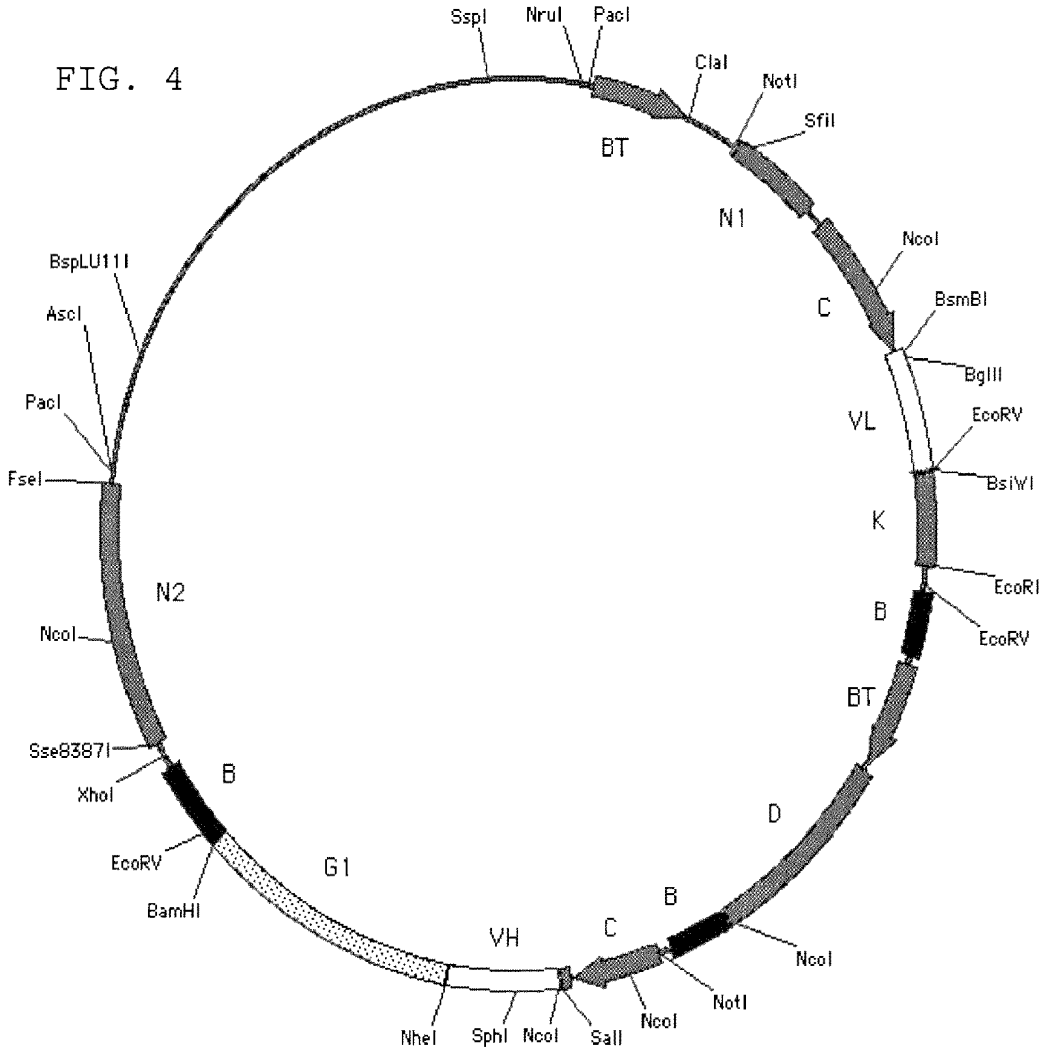
60 Q K P G K A P K L L I Y D A S S L E S G V
253 CCA TCA AGG TTC AGC GGC AGT GGA TCT GGG ACA GAT TTC ACT CTC ACC ATC AGC AGC CTG CAG
81 P S R F S G S G S G T D F T L T I S S L Q
316 CCT GAA GAT TTT GCA ACT TAT TAC TGT CAA CAG TTT AAT GAT TAC TTC ACT TTC GGC CCT GGG
102 P E D F A T Y Y C Q Q F N D Y F T F G P G
BsiWI
379 ACC AAA GTG GAT ATC AAA CGT ACG GTG GCT GCA CCA TCT GTC TTC ATC TTC CCG CCA TCT GAT
123 T K V D I K R T V A A P S V F I F P P S D
442 GAG CAG TTG AAA TCT GGA ACT GCC TCT GTT GTG TGC CTG CTG AAT AAC TTC TAT CCC AGA GAG
144 E Q L K S G T A S V V C L L N N F Y P R E
505 GCC AAA GTA CAG TGG AAG GTG GAT AAC GCC CTC CAA TCG GGT AAC TCC CAG GAG AGT GTC ACA
165 A K V Q W K V D N A L Q S G N S Q E S V T
568 GAG CAG GAC AGC AAG GAC AGC ACC TAC AGC CTC AGC AGC ACC CTG ACG CTG AGC AAA GCA GAC
186 E Q D S K D S T Y S L S S T L T L S K A D
631 TAC GAG AAA CAC AAA GTC TAC GCC TGC GAA GTC ACC CAT CAG GGC CTG AGC TCG CCC GTC ACA
207 Y E K H K V Y A C E V T H Q G L S S P V T
EcoRI
694 AAG AGC TTC AAC AGG GGA GAG TGT TGA ATTC
228 K S F N R G E C

FIG. 4



BT: Mouse beta globulin major promoter
N1: Neomycin phosphotransferase exon 1
C: Cytomegalovirus promoter/enhancer
B: Bovine growth hormone polyadenylation
VL: C10 light chain variable region
K: Human immunoglobulin kappa constant region
D: Dihydrofolate reductase
VH: C10 heavy chain variable region
G1: Human immunoglobulin gamma 1 constant region
N2: Neomycin phosphotransferase exon 2

FIG. 5A

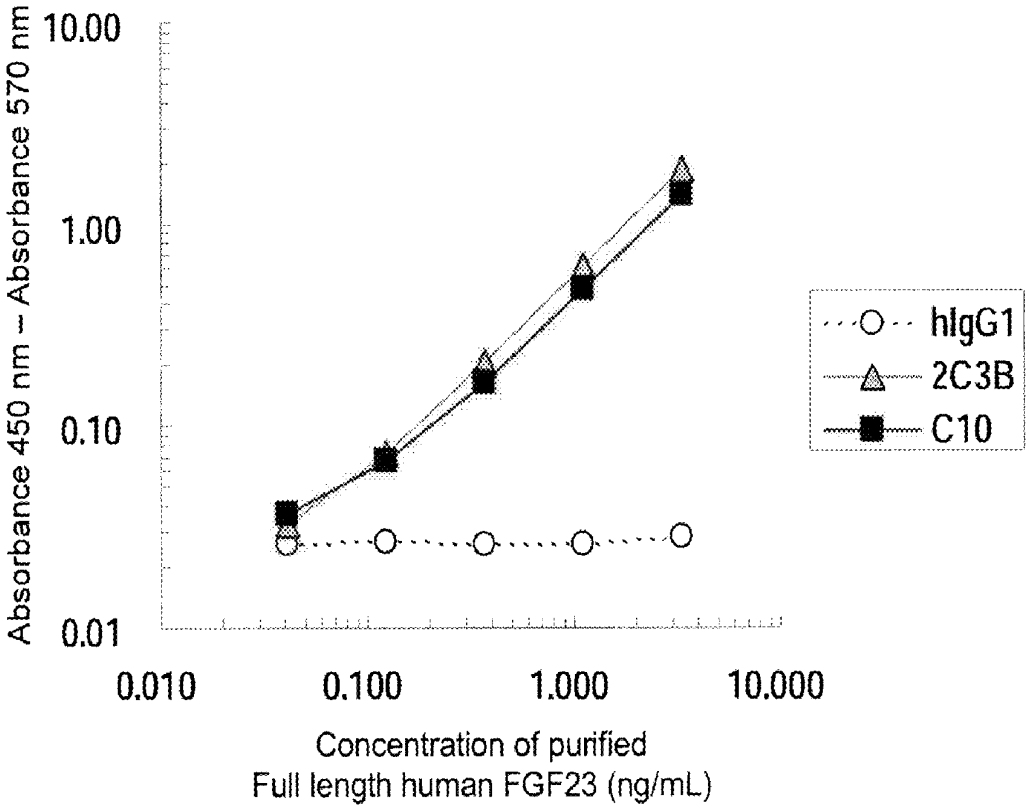

Absorbance 450 nm – Absorbance 570 nm
10.00
1.00
0.10
0.01
0.010
0.100
1.000
10.000
Concentration of purified
Full length human FGF23 (ng/mL)
hIgG1
2C3B
C10

FIG. 5B

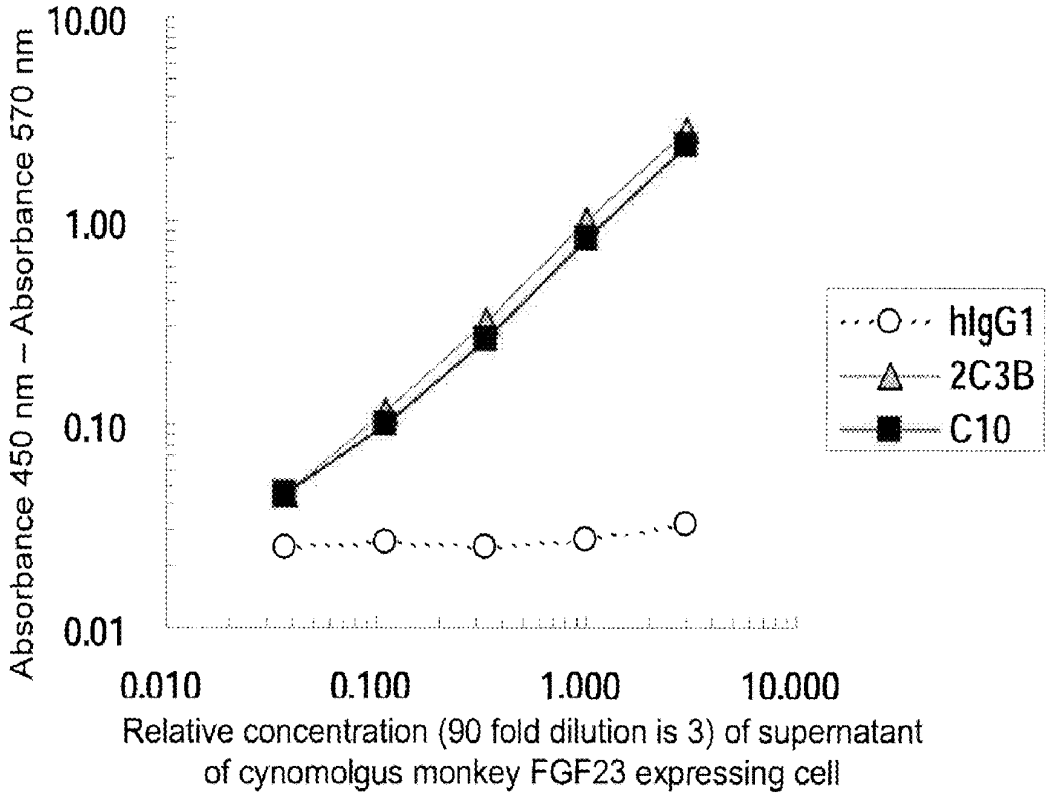
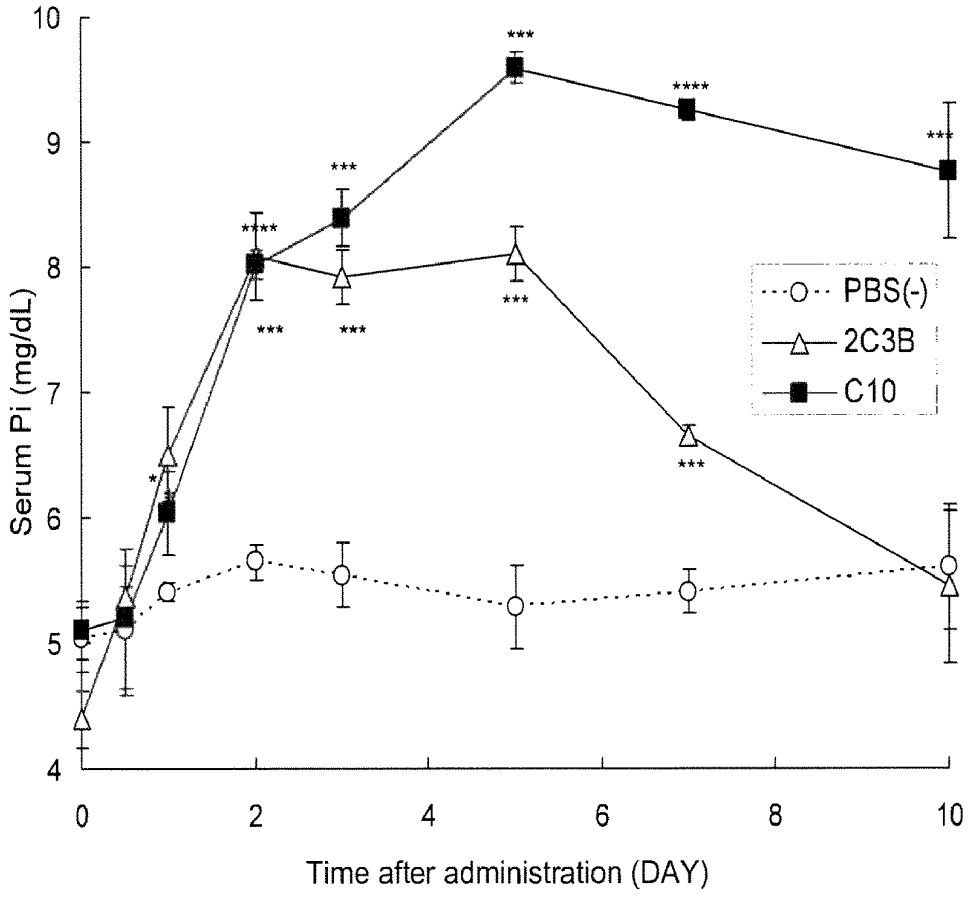

10.00
1.00
0.10
0.01
Absorbance 450 nm – Absorbance 570 nm
0.010
0.100
1.000
10.000
Relative concentration (90 fold dilution is 3) of supernatant of cynomolgus monkey FGF23 expressing cell
hIgG1
2C3B
C10

FIG. 6



* p<0.05

** p<0.01

*** p<0.005

**** p<0.001

student-t

FIG. 7

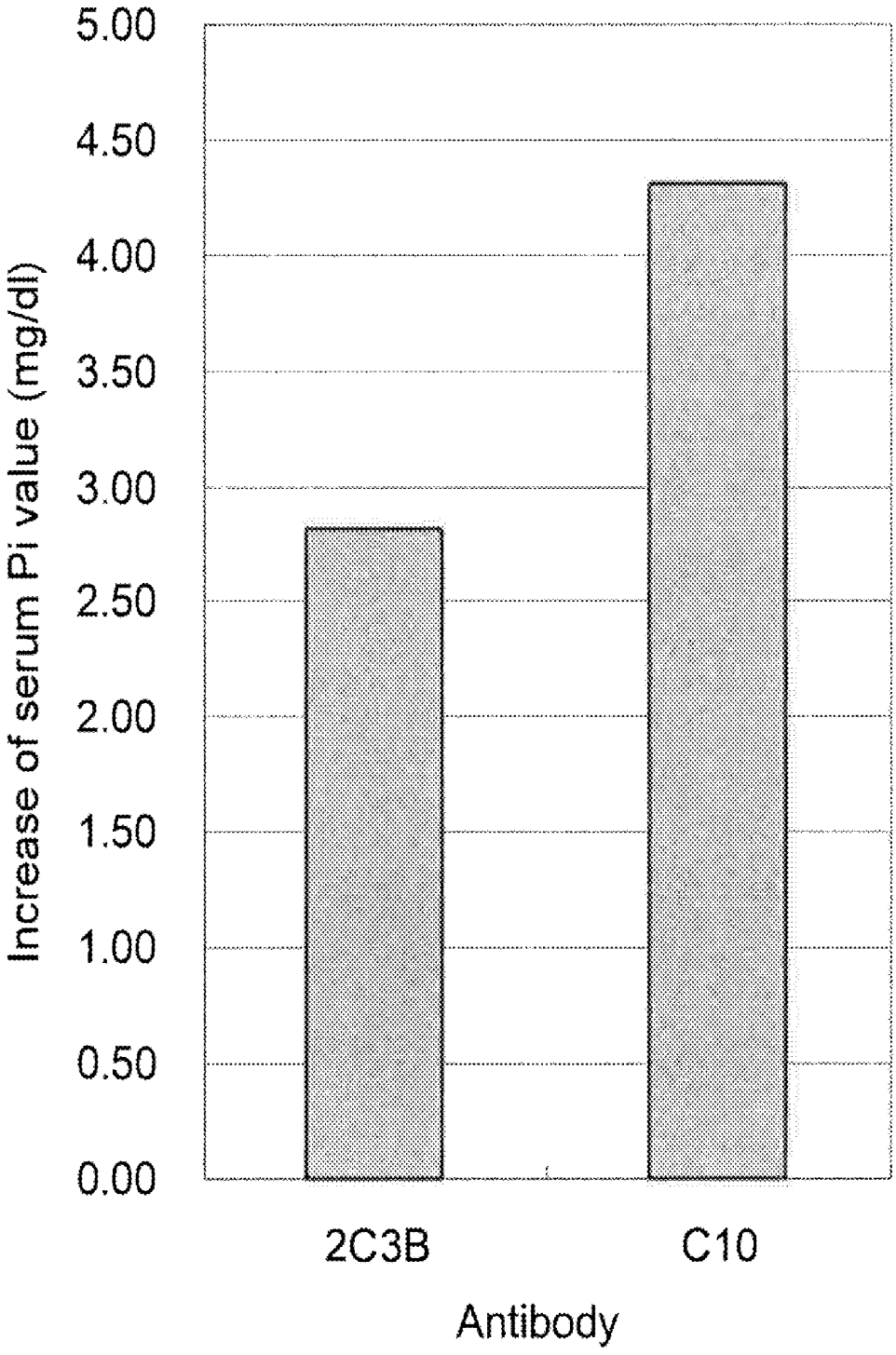
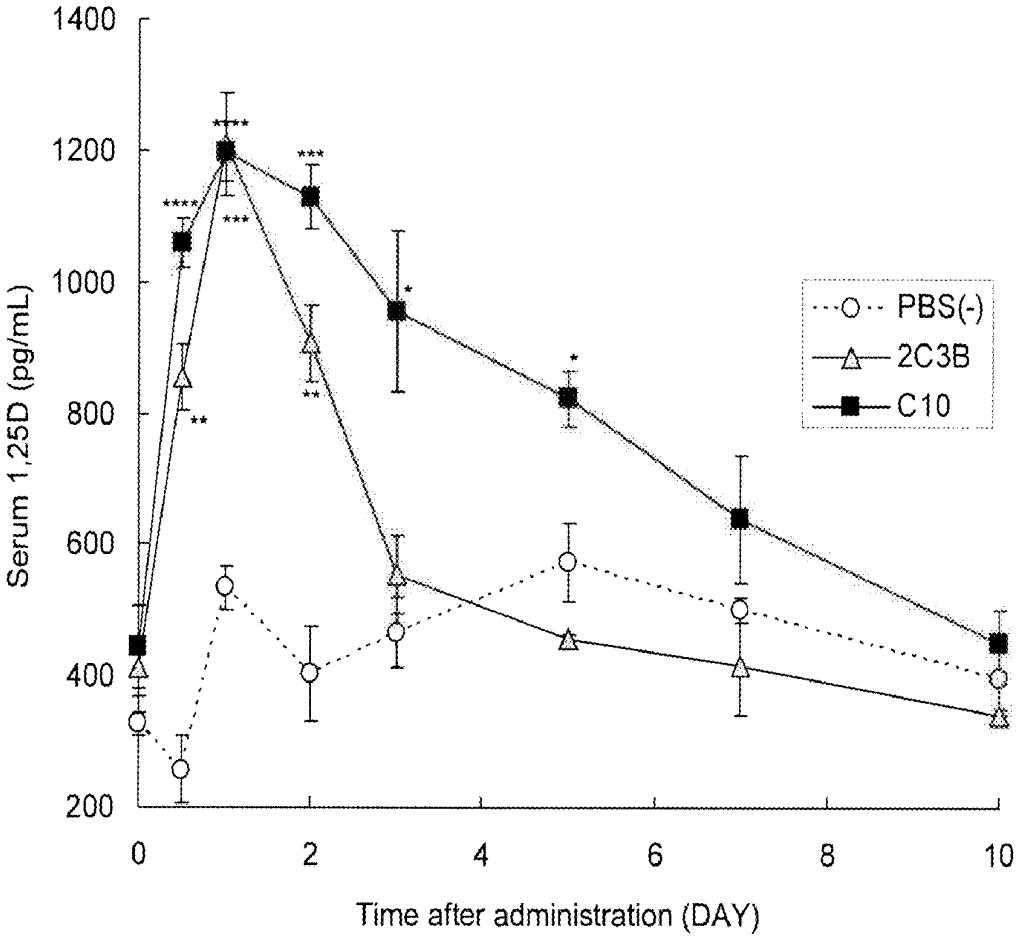

5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
Increase of serum Pi value (mg/dl)
2C3B
C10
Antibody

FIG. 8



*p<0.05

**p<0.01

***p<0.005

****p<0.001

student-t

FIG. 9

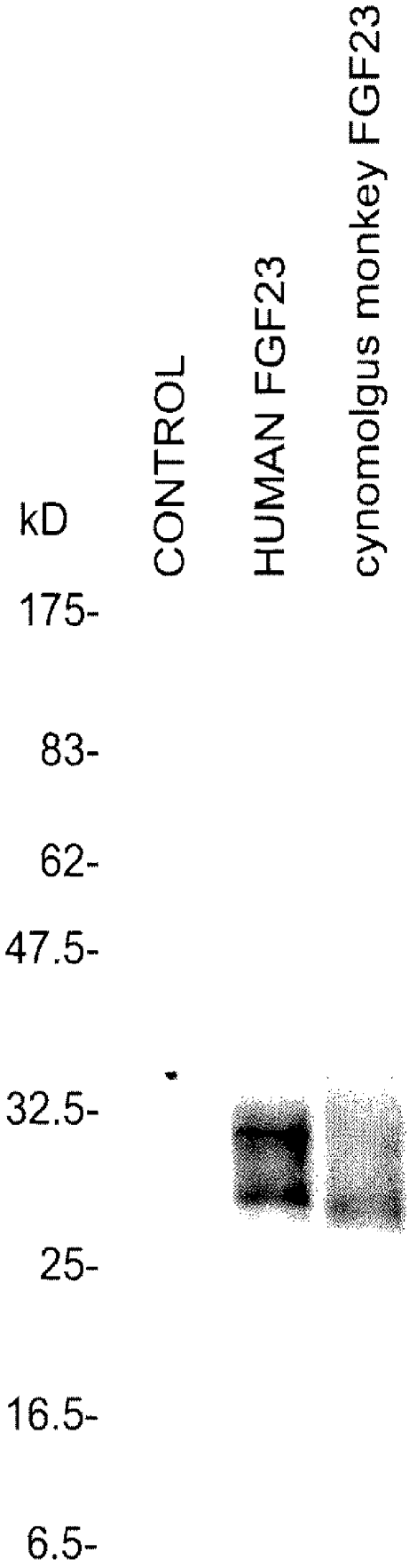
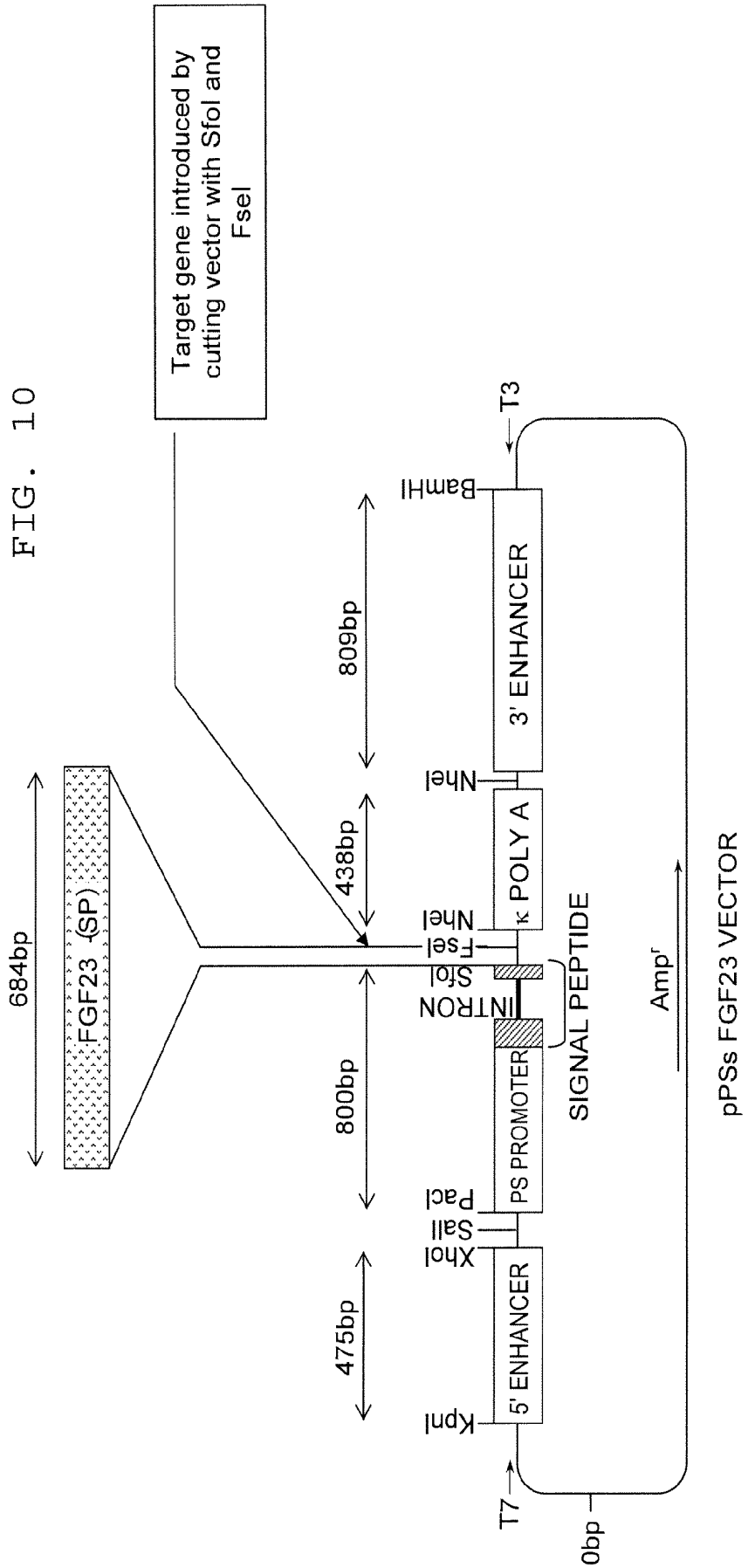

kD
CONTROL
HUMAN FGF23
cynomolgus monkey FGF23
175-
83-
62-
47.5-
32.5-
25-
16.5-
6.5-

FIG. 10


Target gene introduced by cutting vector with SfoI and FseI
T3
BamHI
3' ENHANCER
NheI
κ POLY A
NheI
FseI
SfoI
INTRON
SIGNAL PEPTIDE
PS PROMOTER
PacI
SalI
XhoI
5' ENHANCER
KpnI
T7
0bp
Amp^r
pPSs FGF23 VECTOR
809bp
438bp
800bp
475bp
684bp
FGF23 (SP)

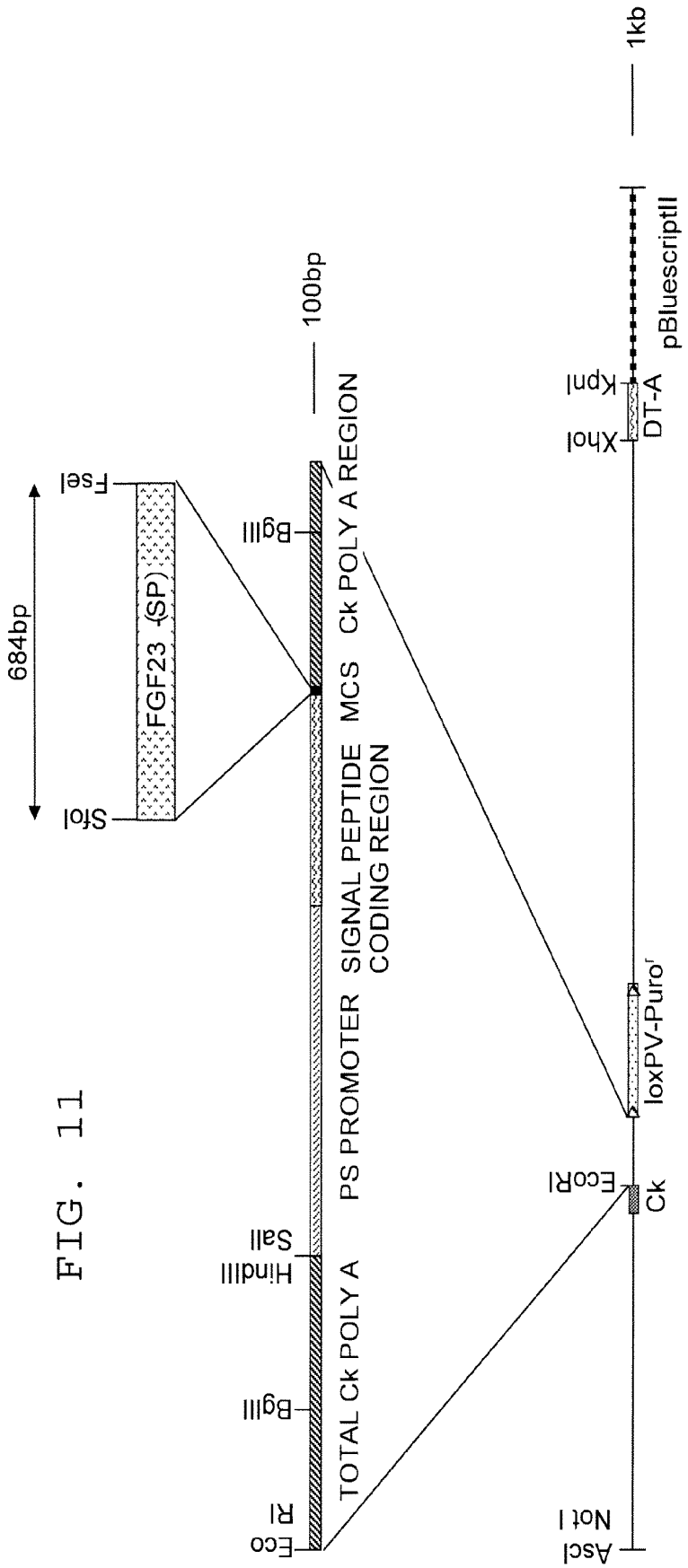

1kb
pBluescriptII
DT-A
KpnI
XhoI
100bp
FseI
SfoI
684bp
FGF23 (SP)
BglII
PS PROMOTER SIGNAL PEPTIDE MCS Ck POLY A REGION
CODING REGION
loxPV-Puro^r
EcoRI
Ck
SalI
HindIII
BglII
TOTAL Ck POLY A
EcoRI
NotI
AscI

FIG. 11

FIG. 12

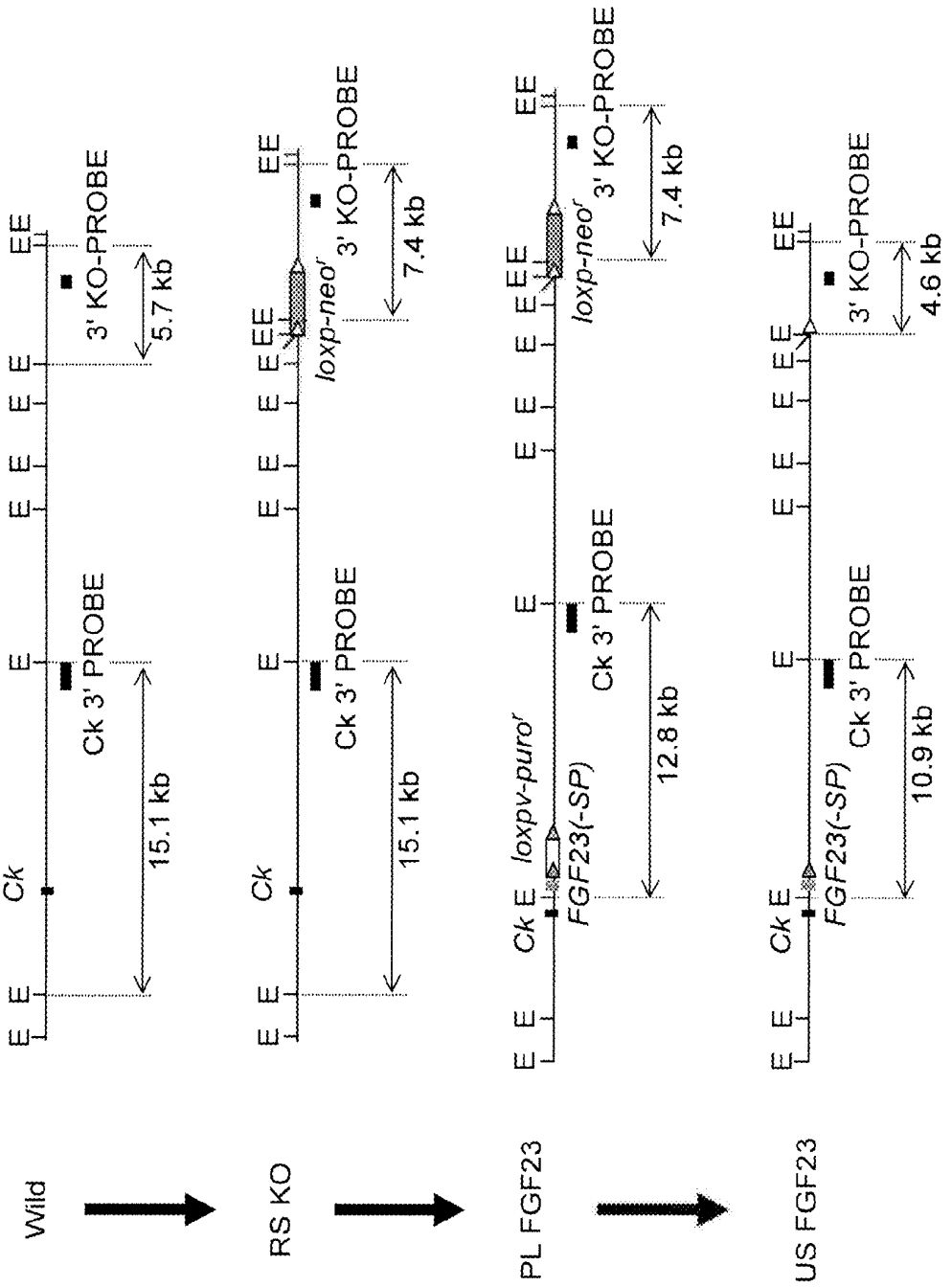

Wild
RS KO
PL FGF23
US FGF23
Ck
E
EE
Ck 3' PROBE
3' KO-PROBE
15.1 kb
5.7 kb
7.4 kb
12.8 kb
10.9 kb
4.6 kb
loxp-neor
loxpv-puror
FGF23(-SP)

FIG. 13

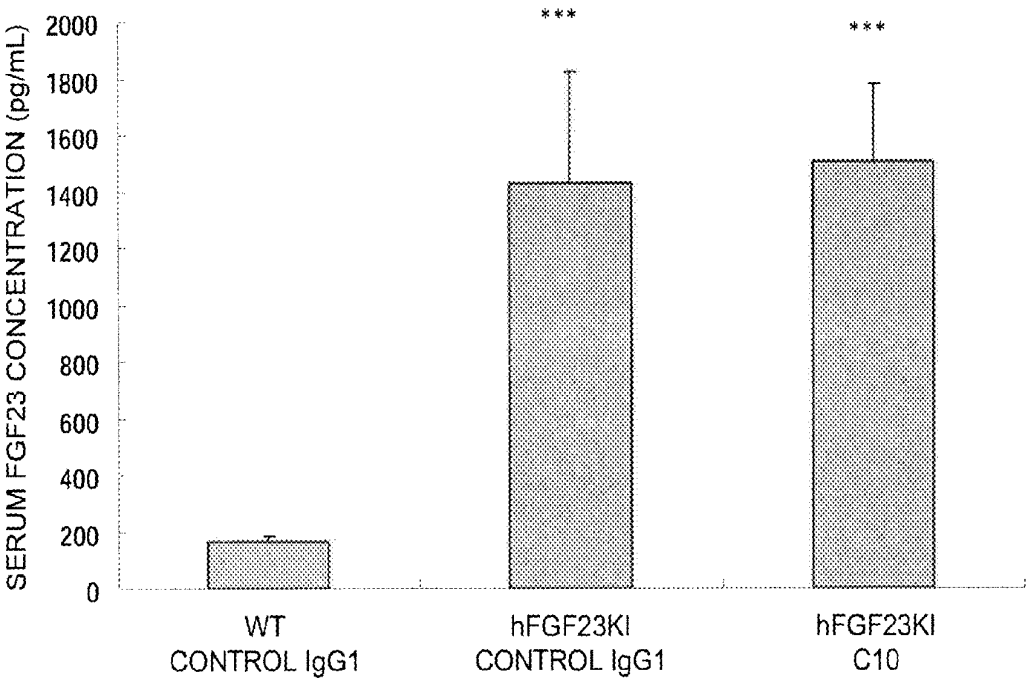

SERUM FGF23 CONCENTRATION (pg/mL)
2000
1800
1600
1400
1200
1000
800
600
400
200
0
***
***
WT
CONTROL IgG1
hFGF23KI
CONTROL IgG1
hFGF23KI
C10

FIG. 14

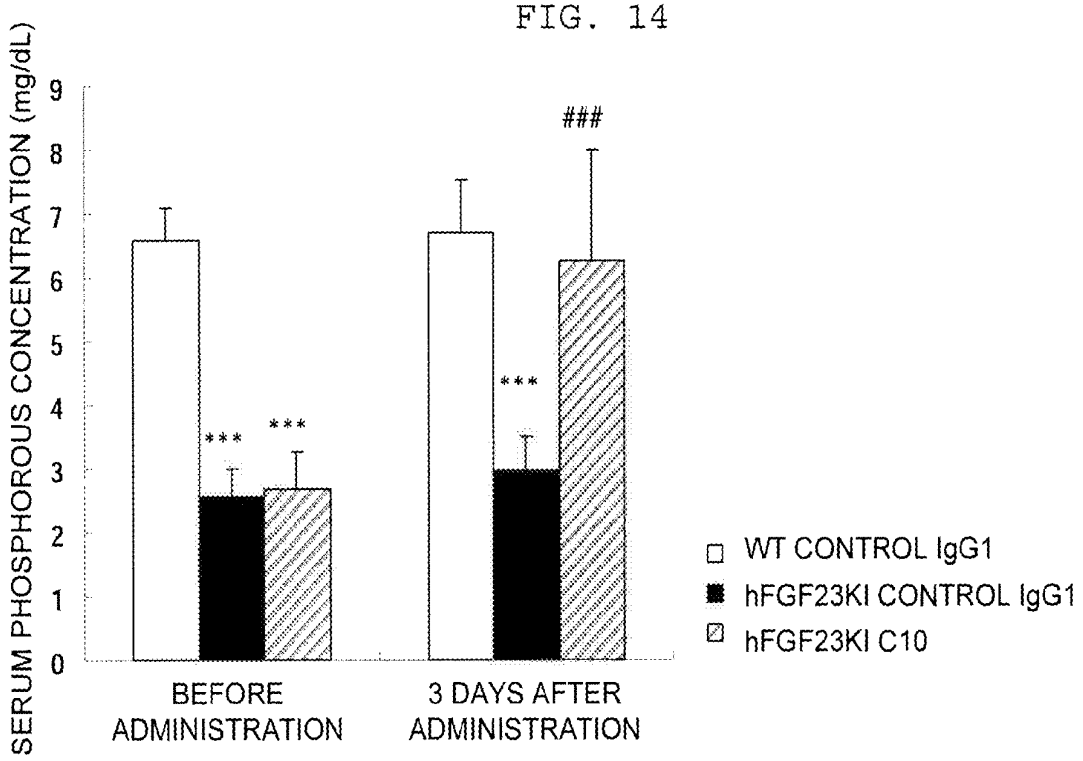

SERUM PHOSPHOROUS CONCENTRATION (mg/dL)
0
1
2
3
4
5
6
7
8
9
***
***
***
###
BEFORE ADMINISTRATION
3 DAYS AFTER ADMINISTRATION
WT CONTROL IgG1
hFGF23KI CONTROL IgG1
hFGF23KI C10

FIG. 15

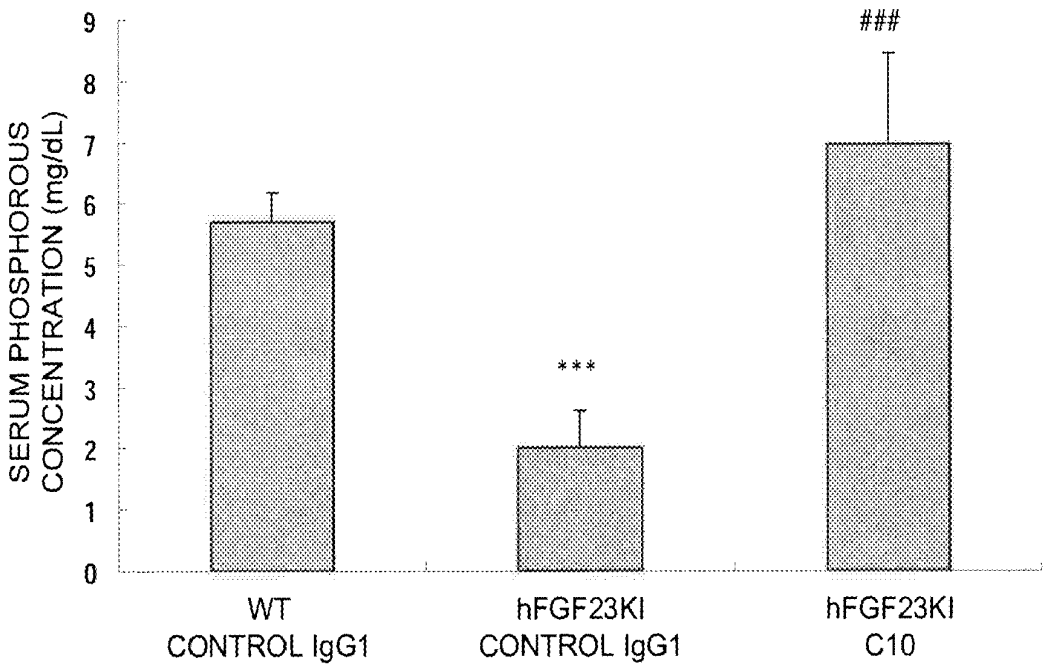

SERUM PHOSPHOROUS CONCENTRATION (mg/dL)
9
8
7
6
5
4
3
2
1
0
###
***
WT CONTROL IgG1
hFGF23KI CONTROL IgG1
hFGF23KI C10

FIG. 16

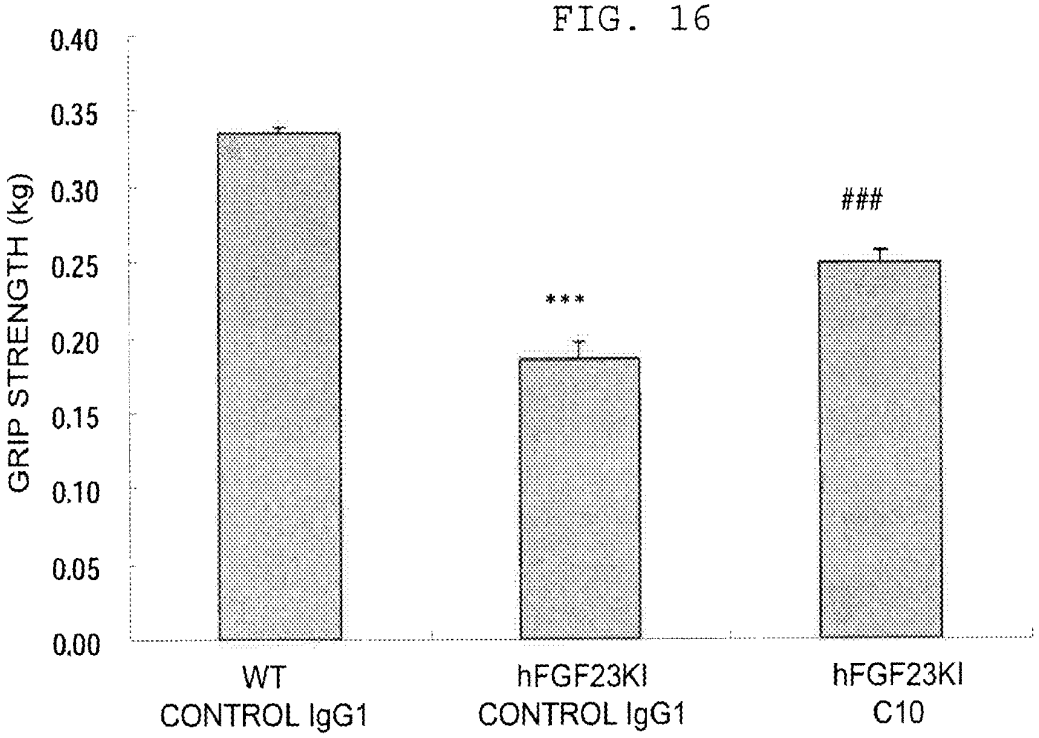

GRIP STRENGTH (kg)
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
***
###
WT
CONTROL IgG1
hFGF23KI
CONTROL IgG1
hFGF23KI
C10

FIG. 17

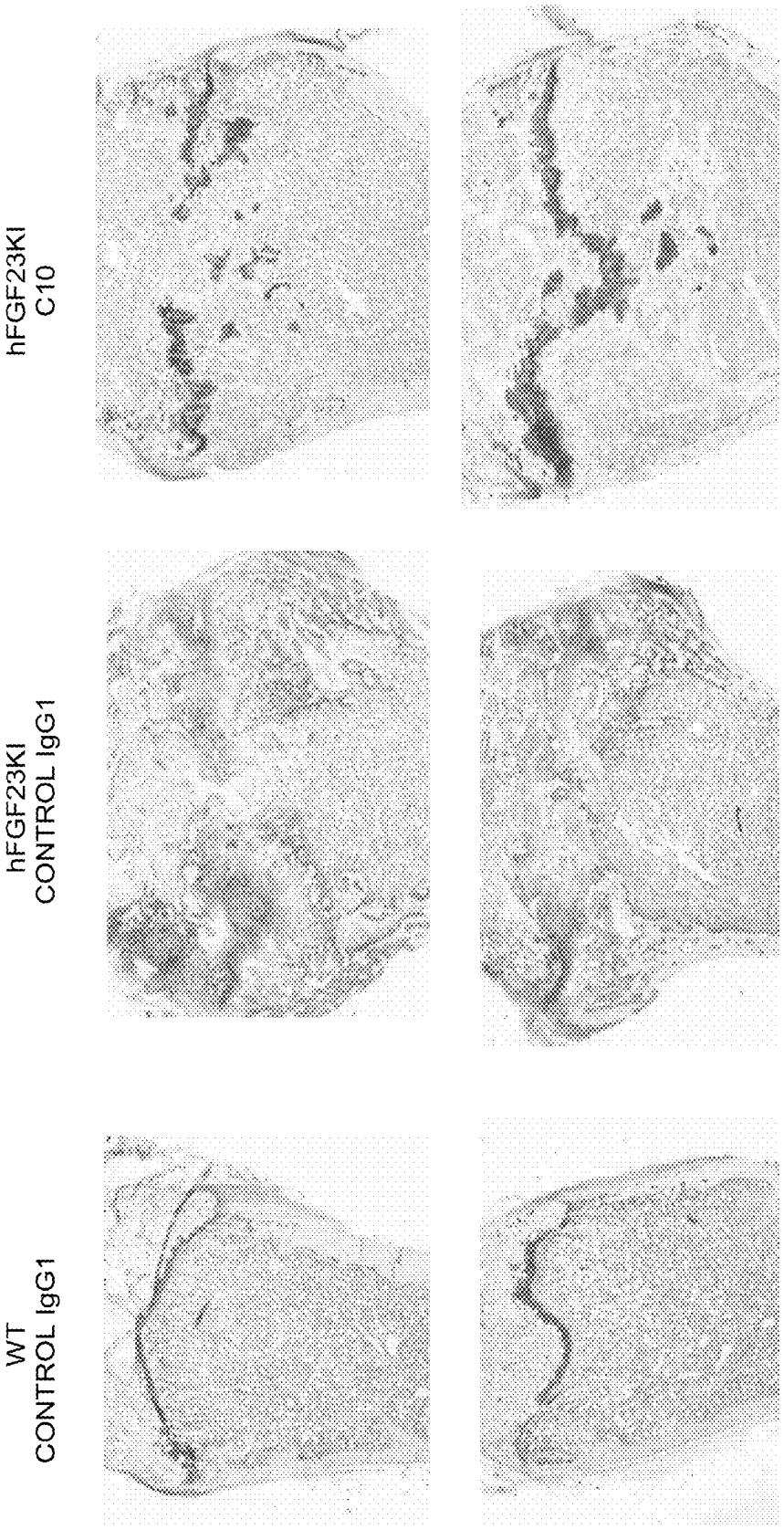
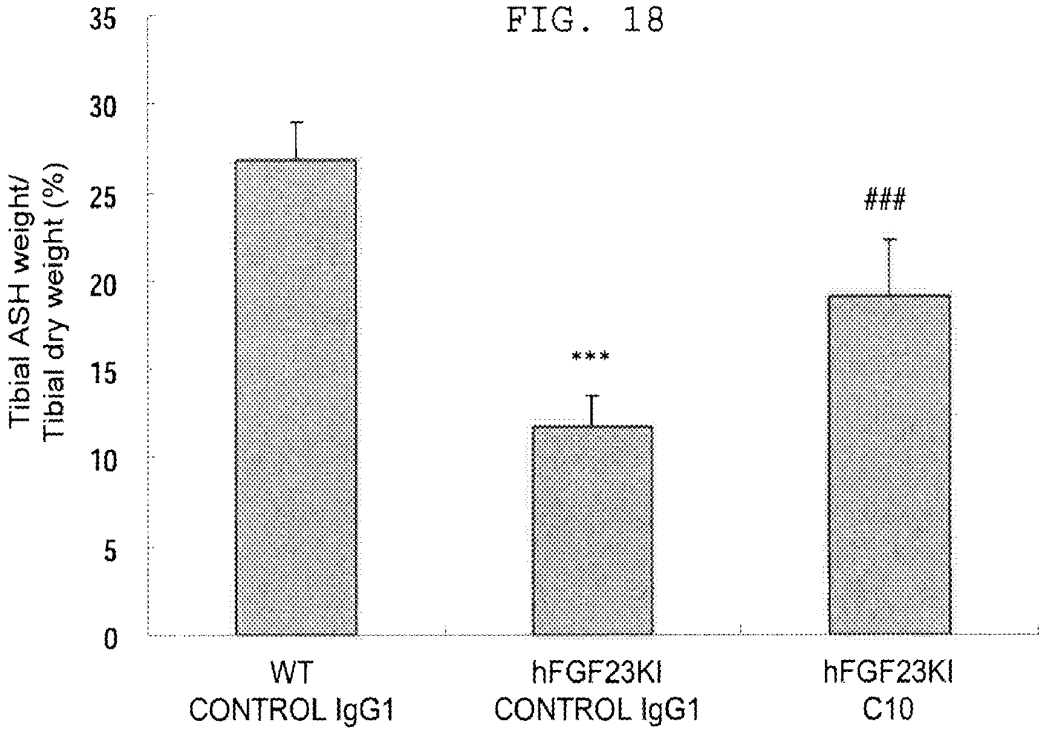


FIG. 18


35
30
25
20
15
10
5
0
Tibial ASH weight/
Tibial dry weight (%)
***
###
WT
CONTROL IgG1
hFGF23KI
CONTROL IgG1
hFGF23KI
C10

ANTI FGF23 ANTIBODY AND A PHARMACEUTICAL COMPOSITION COMPRISING THE SAME

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to an anti-FGF23 antibody which specifically binds to an FGF23 antigen. Furthermore, the present invention relates to an agent for prevention or treatment of mineral metabolic disorders due to excessive production of FGF23 or other causes comprising as an active ingredient the anti-FGF23 antibody. In particular, the present invention relates to an agent for treatment of hypophosphatemic rickets and osteomalachia treatment agent.

2. Background Art

Fibroblast growth factor was first purified from a bovine pituitary gland as a substance that stimulates an increase in fibroblast cell line NIH3T3. Since then, similar proteins have been identified various tissues, and a group of the substances compose a polypeptide family (FGF family). Up until now, 22 proteins have been identified in vertebrates as belonging to the FGF family. With regard to the biological activity of these proteins, not only do they have fibroblast growth activity, but these proteins are also known to have divergent actions such as growth of the mesoblast and the neuroectoderm, and angiogenesis action, and limb bud formation in the developmental stage. FGF is also varied in the gene expression site and expression time. They are often expressed only at certain sites only in the developmental stage or in adults. At least 4 genes encoding the FGF receptor are known, FGFR1, FGFR2, FGFR3, and FGFR4. In addition, with regards to FGFR1, FGFR2, and FGFR3, it is known that there are receptor proteins for each with differing extracellular domains due to differences in splicing. In addition, heparin and heparan sulfate proteoglycan are known to control the action by interaction with FGF and FGF receptors. In addition, there are many, which, due to structural similarities, belong to the FGF family, but whose biological activities and receptor binding properties and the like have not been known. The characteristics of this FGF family have been summarized in a review (see Ornitz, D. et al., Genome biology, 2: 3005.1-3005.12, 2001).

FGF23 (in general, may also be represented as FGF-23) was cloned initially from a mouse by a database search using homology with FGF15 and the PCR method. Further, human FGF23 was cloned by using the sequence homology with mouse FGF23. Human FGF23 is a polypeptide with 251 amino acid residues. In addition, as the secretory signal sequence, an amino acid sequence at amino terminal side up to 24 amino acids is predicted to be cleaved at the time of secretion (see Yamashita, T. et al., Biochem. Biophy. Res. Commun., 277: 494-498, 2000). Next, in research on autosomal dominant hypophosphatemic rickets/osteomalachia (henceforth referred to as ADHR), the mutated gene region in ADHR patients was narrowed down and with advancement in the identification of the responsible gene, a mis-sense mutation in the FGF23 gene was discovered characteristically in ADHR patients (see White, K. E. et al., Nature Genet., 26: 345-348, 2000). With this discovery, there was a strong suggestion that FGF23 was physiologically important in the body. On the other hand, what determined the biological activity of FGF23 was research into neoplastic osteomalachia which is one of the hypophosphatemia rickets and osteomalachia diseases. In this disease, the culprit neoplasm of the disease produces and secretes a liquid disease initiating factor, and it is thought that pathologies such as hypophosphatemia, osteomalachia and the like are caused by the disease initiating factor.

In the search for the disease initiating factor produced by this culprit neoplasm, FGF23 was cloned as a gene which is overexpressed in the tumor. Furthermore, by administering this factor, it was shown that hypophosphatemia and osteomalachia were reproduced (see Shimada, T. et al., Proc. Natl. Acad. Sci., 98: 6500-6505, 2001 and International Publication Number WO02/14504 pamphlet). Based on this research, FGF23 has been shown to be related in the metabolic control related to phosphorus and calcium in the body. In addition, it was suggested that this acts as a systemic factor which expresses its action by circulating in the body. Furthermore, later research also showed that the blood of actual neoplastic osteomalachia patients had a higher value of FGF23 concentration as compared to healthy subjects (see Yamazaki, Y. et al., J. Clin. Endocrinol. Metab., 87: 4957-4960, 2002 and Jonsson, K. B., et al., N. Engl. J. Med., 348: 1656-1663, 2003).

In addition, X-linked hypophosphatemic rickets (henceforth referred to as XLH) is a disease which is known to have a similar presentation as ADHR and neoplastic osteomalachia in terms of clinical findings. In this disease as well, the FGF23 concentration in the blood was shown to be at a high value (see Yamazaki, Y. et al., J. Clin. Endocrinol. Metab., 87: 4957-4960, 2002 and Jonsson, K. B., et al., N. Engl. J. Med., 348: 1656-1663, 2003).

In other words, the cause for vitamin D resistant rickets and osteomalachia which were observed in neoplastic osteomalachia, XLH, and the like had been previously unknown, but the secreted disease causing factor was shown to be FGF23. Furthermore, with regard to other mineral metabolic diseases such as fibrous dysplasia, McCune-Albright syndrome, autosomal recessive hypophosphatemia rickets, and the like, high concentrations of FGF23 in the blood have been reported to be associated with hypophosphatemia and rickets and osteomalachia (See Riminucci, M. et al., J. Clin. Invest., 112: 683-692, 2003; Yamamoto, T. et al., J. Bone Miner. Metab., 23: 231-237, 2005; Lorenz-Depiereux, B. et al., Nat. Genet., 38: 1248-1250, 2006).

From the above report, the condition of having excessive FGF23 in the body has been shown to induce hypophosphatemia and the accompanying rickets and osteomalachia and the like. Furthermore, for chronic renal insufficiency hyperphosphatemia, abnormally high serum FGF23 values have been reported. Excessive FGF23 has been suggested to be possibly related to a portion of the mineral metabolic diseases during renal insufficiency (see Gupta, A. et al., J. Clin. Endocrinol. Metab., 89: 4489-4492, 2004 and Larsson, T. et al., Kidney Int., 64: 2272-2279, 2003). With regard to these diseases induced due to excessive FGF23, suppressing the action of FGF23 or removing FGF23 is thought to be a possible way to treat the diseases. Up to now, anti-FGF23 mouse monoclonal antibody has been reported to be a way to suppress the action of FGF23 (see Yamashita, T. et al., Biochem. Biophy. Res. Commun., 277: 494-498, 2000). When the anti-FGF23 mouse monoclonal antibody 2C3B and 3C1E used in this report were administered to normal mice, the function of the endogenous mouse FGF23 was inhibited, and the phosphorus excretion from the kidney was suppressed. By fluctuating the expression of vitamin D-metabolizing enzyme in the kidney, this was shown to result in increased concentrations for phosphorus and 1 α,25 dihydroxy vitamin D (henceforth referred to as 1,25D) in the serum. Furthermore, repeated administration of anti-FGF23 mouse monoclonal antibody was conducted on Hyp mouse which is a model

mouse for XLH which has a high serum concentration of FGF23 and has hypophosphatemia and has bone elongation dysfunction and calcification dysfunction. As a result, in the Hyp mice, a rise in the phosphorus concentration in the blood was seen, and in addition, there were improvements in bone elongation dysfunction and calcification dysfunction. From these results, the use of FGF23 action suppressing antibody was thought to be appropriate as a medicine for FGF23 excess diseases. However, the 2C3B and 3C1E antibodies used in this report are mouse-derived antibodies. Mouse antibodies which are recognized as foreign by human host initiates a so-called "human anti-mouse antibody" (in other words HAMA) response, and there may be situations where serious side-effects are seen (see Van Kroonenbergh, M. J. et al., Nucl. Med. Commun. 9: 919-930, 1988).

In order to avoid this type of problem, one approach was to develop a chimera antibody (see European Patent Application Publication Number 120694 Specification and European Patent Application Publication Number 125023 Specification). Chimera antibodies include a portion of antibody derived from 2 or more species (for example, variable region of the mouse antibody and the constant region of the human antibody and the like). The advantage of this type of chimera antibody is that the binding to the antibody which was the characteristic of the original mouse antibody is maintained, but on the other hand, "a human-anti chimera antibody" (in other words "HACA") response is still induced (see Bruggemann, M. et al., J. Exp. Med., 170: 2153-2157, 1989).

Furthermore, a recombinant antibody has been developed where only a portion of the substituted antibody is a complementarity determining region (CDR) (see British Patent Number GB2188638A specification and U.S. Pat. No. 5,585,089 specification). Using CDR transplant technology, an antibody consisting of mouse CDR, the framework of the human variable region and constant region (in other words "humanized antibody") was produced (see Riechmann, L. et al., Nature, 332: 323-327, 1988). It has been known that using this method, anti-FGF23 mouse antibody such as 2C3B antibody can be humanized by substituting mouse antibody with a human antibody sequence. However, when humanized, there is the possibility that the affinity to the antigen may be reduced. In addition, for the current treatment of hypophosphatemia rickets in XLH and the like, the main method is periodic oral administration of Vitamin D formulation and phosphoric acid. However, there is the problem that the patients are forced to have a substantial burden due to the size of each dose and the dosage frequency per day. Therefore, in order to lessen the burden on the patients and their families, a hypophosphatemia treatment drug which shows a sustained raising action for serum phosphate concentration and serum 1,25D concentration is desired in order to extend the time between doses.

SUMMARY OF THE INVENTION

The object of the present invention is to provide human antibody against FGF23 and to provide a pharmaceutical composition such as an agent for prevention or treatment or the like with few side effects by using the antibody to suppress the action of FGF23 and thereby preventing or treating disease.

Furthermore, the object of the present invention is to provide an antibody which is an anti-FGF23 antibody which can be used as a hypophosphatemia treatment medicine having a more sustained raising action for serum phosphate concentration and serum 1,25D concentration with a single dose as compared to existing anti-FGF23 antibodies. Another object of the present invention is to provide a pharmaceutical composition such as an agent for prevention or treatment of a disease related to FGF23 using this antibody.

Currently, the mainstream treatment method for hypophosphatemia rickets is oral administration of vitamin D formulation together with phosphate periodically several times a day. However, because of the large amount of each dose and the frequency of doses per day, there is the problem that the patients are forced to have a large burden. The anti-FGF23 human monoclonal antibody, the C10 antibody, obtained by the present invention is shown to have a more sustained raising action for the blood phosphate concentration and 1,25D concentration, in other words, a stronger FGF23 neutralizing activity. With a single administration of the C10 antibody in the present research, there was observed a sustained raising action for serum phosphate concentration and serum 1,25D concentration. This suggests that as compared to the current treatment for hypophosphatemia, the C10 antibody has the potential for being a dramatically superior treatment.

The present invention is as follows.

[1] An antibody against human FGF23 or a functional fragment thereof, comprising a heavy chain variable region and/or a light chain variable region of an antibody produced by hybridoma C10 (Accession No. FERM BP-10772)

[2] An antibody against human FGF23 or a functional fragment thereof, comprising a heavy chain amino acid sequence shown by an amino acid sequence from Q at position 20 to S at position 136 of SEQ ID NO: 12 and/or a light chain amino acid sequence shown by an amino acid sequence from A at position 23 to K at position 128 of SEQ ID NO: 14.

[3] An antibody against human FGF23 or a functional fragment thereof, wherein: the antibody against human FGF23 or the functional fragment thereof contains a heavy chain variable region and/or a light chain variable region amino acid sequence; and the heavy chain variable region amino acid sequence is shown by an amino acid sequence from Q at position 20 to S at position 136 of SEQ ID NO: 12; and the light chain variable region amino acid sequence is shown by an amino acid sequence from A at position 23 to K at position 128 of SEQ ID NO: 14.

[4] An antibody against human FGF23 produced by hybridoma C10 (Accession No. FERM BP-10772) or a functional fragment thereof.

[5] An antibody or a functional fragment thereof binding to all or part of epitope on human FGF23, to which an antibody produced by hybridoma C10 (Accession No. FERM BP-10772) binds.

[6] The antibody against human FGF23 or a functional fragment thereof, comprising a heavy chain variable region of the above [3] having any one of complementarity determining region (CDR) 1 shown by the amino acid sequence of SEQ ID NO: 40, CDR2 shown by the amino acid sequence of SEQ ID NO: 41 and CDR3 shown by the amino acid sequence of SEQ ID NO: 42, or a heavy chain variable region of the above [3] having all of the above.

[7] The antibody against human FGF23 or a functional fragment thereof, comprising a light chain variable region of the above [3] having any one of CDR 1 shown by the amino acid sequence of SEQ ID NO: 43, CDR2 shown by the amino acid sequence of SEQ ID NO: 44 and CDR3 shown by the amino acid sequence of SEQ ID NO: 45, or a light chain variable region of the above [3] having all of the above.

[8] An antibody against human FGF23 or a functional fragment thereof, wherein the antibody against human FGF23 or the functional fragment thereof contains a heavy chain variable region having any one of complementarity determining region (CDR) 1 shown by the amino acid

sequence of SEQ ID NO: 40, CDR2 shown by the amino acid sequence of SEQ ID NO: 41 and CDR3 shown by the amino acid sequence of SEQ ID NO: 42, or a heavy chain variable region having all of the above; and a light chain variable region having any one of complementarity determining region (CDR) 1 shown by the amino acid sequence of SEQ ID NO: 43, CDR2 shown by the amino acid sequence of SEQ ID NO: 44 and CDR3 shown by the amino acid sequence of SEQ ID NO: 45, or a light chain variable region having all of the above.

[9] The antibody against human FGF23 or a functional fragment thereof as described in any one of [1]-[8], wherein the functional fragment is a peptide fragment selected from the group consisting of Fab, Fab', F (ab')2, disulfide stabilized Fv (dsFv), dimerized V region (diabody), single chain Fv (scFv) and CDR.

[10] The antibody against human FGF23 or a functional fragment thereof, as described in any one of [1]-[8], comprising: a heavy chain and/or light chain having an amino acid sequence in which one or several amino acids are deleted, substituted or added.

[11] The antibody against human FGF23 as described in any one of [1]-[10], wherein the class of the antibody is IgG, IgA, IgE, or IgM.

[12] The antibody against human FGF23 as described in [11], wherein the subclass of the antibody is IgG1, IgG2, IgG3, or IgG4.

[13] A pharmaceutical composition, comprising as an active ingredient, the antibody against human FGF23 or a functional fragment thereof as described in any one of [1]-[12].

[14] A pharmaceutical composition which can control phosphorus metabolism and/or vitamin D metabolism by FGF23 and comprises, as an active ingredient, the antibody against human FGF23 or a functional fragment thereof as described in any one of [1]-[12].

[15] A pharmaceutical composition for prevention or treatment of diseases that are associated with mineral metabolism disorders comprising as an active ingredient, the antibody against human FGF23 or a functional fragment thereof as described in any one of [1]-[12].

[16] The pharmaceutical composition as described in [15], wherein the disease which is associated with mineral metabolism abnormalities is selected from the group consisting of neoplastic osteomalachia, ADHR, XLH, fibrous dysplasia, McCune-Albright syndrome, and autosomal recessive hypophosphatemia.

[17] A pharmaceutical composition for prevention or treatment of a disease selected from the group consisting of osteoporosis, rickets, hypocalcaemia, hypocalcaemia, heterotrophic calcification, osteosclerosis, Paget's disease, hyperparathyroidism, hypoparathyroidism, and pruritis, comprising as an active ingredient, the antibody against human FGF23 or a functional fragment thereof as described in any one of [1]-[12].

[18] A hybridoma C10 (Accession No. FERM BP-10772).

[19] Nucleic acids which encode an amino acid sequence of a heavy chain variable region encoded by a base sequence from C at position 58 to A at position 408 represented by SEQ ID NO: 11.

[20] Nucleic acids which encode an amino acid sequence of a light chain variable region encoded by a base sequence from G at position 67 to A at position 384 represented by SEQ ID NO: 13.

[21] A vector containing the nucleic acid described in [19] or [20].

[22] A host cell containing the vector described in [21].

[23] A method for producing an antibody against human FGF23 or a functional fragment thereof, comprising the step of culturing the host cell described in [22] to express an antibody against human FGF23 or a functional fragment thereof.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a schematic diagram of the construction steps of C10 expression vector.

FIG. **2** shows the nucleotide sequence (SEQ ID NO: 30) and amino acid sequence (SEQ ID NO: 31) of the antibody heavy chain gene in N5KG1_C10_LH. The amino acid sequence surrounded by a rectangular line represents the secretion signal sequence (leader sequence).

FIG. **3** shows the nucleotide sequence (SEQ ID NO: 32) and amino acid sequence (SEQ ID NO: 33) of the antibody light chain gene in N5KG1_C10_LH. The amino acid sequence surrounded by a rectangular line represents the secretion signal sequence (leader sequence).

FIG. **4** shows the structure of C10 expression vector.

FIG. **5**A shows the result of the measurement for detecting purified full length human FGF23 protein by the sandwich ELISA method using 2C3B antibody or C10 antibody as the immobilizes antibody, and 3C1E antibody as the detection antibody.

FIG. **5**B shows the result of the measurement for detecting the culture supernatant of cynomolgus monkey FGF23 expressing cells by the sandwich ELISA method using 2C3B antibody or C10 antibody as the solid phase antibody, and 3C1E antibody as the detection antibody.

FIG. **6** is a graph showing chronological measurements of serum phosphorous concentration in cynomolgus monkeys administered with solvent, 2C3B antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the solvent administered group and the test groups was conducted at the same date using Student-test, values found to be significant difference ($p<0.05$) are marked with * on the graph.

FIG. **7** is a graph showing an increase in the serum phosphorous concentration of cynomolgus monkeys 5 days after 2C3B antibody or C10 antibody administration, based on the serum phosphorous concentration of cynomolgus monkey 5 days after the administration of the solvent as the standard.

FIG. **8** is a graph showing chronological measurements of serum 1,25D concentration in cynomolgus monkeys administered with solvent, 2C3B antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the solvent administered group and the test groups was conducted at the same date using Student-test, values found to be significant difference ($p<0.05$) are marked with * on the graph.

FIG. **9** is a picture showing the detection of the culture supernatant of the cells with no forced expression (control) and the culture supernatant of the human and cynomolgus monkey FGF23 expression cells by C15 antibody using the Western blotting method.

FIG. **10** shows the structure of pPSs FGF23 vector.

FIG. **11** shows the structure of pUS FGF23 KI vector.

FIG. **12** represents an allele structure in which the drug resistance gene (loxp-neor) is targeted, an allele structure in which human FGF23 (−SP)+drug resistance gene (loxpv-puror) is targeted by using pUS hFGF23 KI vector, an allele structure in which the drug resistance genes (loxp-neor, loxpv-puror) are deleted, and the position of Southern analysis probe. Terms used in the figures are described in detail as follows:

hFGF23 (−SP): Human FGF23 gene having no specific signal peptide code region,

Cκ: constant region of mouse Igκ gene, loxpv-puro: puromycin resistance gene having loxPV sequence which is a partially mutated loxP sequence at both ends thereof,

loxp-neor: neomycin resistance gene having loxP sequence at both ends thereof,

Ck3' probe: Southern blotting analysis probe for selection of clones having hFGF23 (−SP)+loxpv-puror gene introduced and having loxpv-puror gene deleted,

3'KO-probe: Southern blotting analysis probe for selection of clones having loxp-neor gene introduced and deleted, and

E: EcoRI restriction enzyme site.

FIG. **13** is a graph showing the serum FGF23 concentration 7 days before the control antibody or C10 antibody administration. Measured values are shown in average +/− standard error. Further, when significant difference test between the WT mice group and the test groups was conducted using Student's t-test, groups found to be significant difference ($p<0.001$) are marked with *** on the graph.

FIG. **14** is a graph showing the serum phosphorous concentration 7 days before the control antibody or C10 antibody administration and 3 days after the first administration of control antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the WT mice group and the test groups was conducted in one day using Student's t-test, groups found to be significant difference ($p<0.001$) are marked with *** on the graph. In addition, when significant difference test between the hFGF23KI mouse control antibody administered group and the test groups was conducted in one day, hFGF23KI mouse C10 antibody administered groups found to be significant difference ($p<0.001$) are marked with ### on the graph.

FIG. **15** is a graph showing the serum phosphorous concentration 1 day after the fifth administration of control antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the WT mice group and the test groups was conducted using Student's t-test, groups found to be significant difference ($p<0.001$) are marked with *** on the graph. In addition, when significant difference test between the hFGF23KI mouse control antibody administered group and the test groups was conducted, hFGF23KI mouse C10 antibody administered groups found to be significant difference ($p<0.001$) are marked with on the graph.

FIG. **16** is a graph showing the grip strength 1 day after the fourth administration of control antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the WT mice group and the test groups was conducted using Student's t-test, groups found to be significant difference ($p<0.001$) are marked with *** on the graph. In addition, when significant difference test between the hFGF23KI mouse control antibody administered group and the test groups was conducted, hFGF23KI mouse C10 antibody administered groups found to be significant difference ($p<0.001$) are marked with ### on the graph.

FIG. **17** is a picture showing the histological staining image of femur collected from mice 1 day after the fifth administration of control antibody or C10 antibody, wherein the staining was performed by Villanueva-Goldner method.

FIG. **18** is a graph showing the ratio of ash weight to dry weight of tibia collected from mice 1 day after the fifth administration of control antibody or C10 antibody. Measured values are shown in average +/− standard error. Further, when significant difference test between the WT mice group and the test groups was conducted using Student's t-test, groups found to be significant difference ($p<0.001$) are marked with *** on the graph. In addition, when significant difference test between the hFGF23KI mouse control antibody administered group and the test groups was conducted, hFGF23KI mouse C10 antibody administered groups found to be significant difference ($p<0.001$) are marked with ### on the graph.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Below, by clarifying the definitions for the terms used in the present invention, we will describe the present invention in detail.

I. Antibody of the Present Invention

1. Anti-FGF23 Antibody and its Functional Fragment

The antibody of the present invention is an antibody against FGF23 which is a member of the fibroblast growth factor (FGF) family.

In the present invention, "antibody against FGF23" is an antibody which binds to FGF23 or a portion thereof, an antibody which is reactive to FGF23 or a portion thereof, or an antibody which recognizes FGF23 or a portion thereof. Antibody against FGF23 is also termed an anti-FGF23 antibody. In the present invention, an antibody is an immunoglobulin in which all of the regions which construct the immunoglobulin of the heavy chain variable region and heavy chain constant region and the light chain variable region and light chain constant region are derived from a gene which encodes the immunoglobulin. The antibody is preferably a monoclonal antibody. Here, a portion of FGF23 signifies a partial amino acid sequence of a full-length amino acid sequence of FGF23 represented by SEQ ID NO: 4 and is a fragment peptide of FGF 23 comprising a continuous amino acid sequence. Preferably, the antibody contains the amino acid sequence from Q at position 20 to S at position 136 of SEQ ID NO: 12 and/or the amino acid sequence from A at position 23 to K at position 128 of SEQ ID NO: 14. More preferably, the antibody is an antibody produced by hybridoma C10. SEQ ID NO: 12 is the amino acid sequence that comprises the leader sequence of the heavy chain variable region of the antibody against FGF23. The amino acid sequence from Q at position 20 to S of number 136 of SEQ ID NO: 12 is the mature portion of the amino acid sequence with the leader sequence portion removed. In addition, SEQ ID NO: 14 is the amino acid sequence that comprises the leader sequence of the light chain variable region of the antibody against FGF23. The amino acid sequence from A at position 23 to K at position 128 of SEQ ID NO: 14 is the mature portion of the amino acid sequence with the leader sequence removed. With regard to the class of antibody, immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin E (IgE), and immunoglobulin M (IgM) are used. Preferably, it is IgG. Furthermore, for the IgG subclass, IgG1, IgG2, IgG3, IgG4 are used. It is preferably IgG1, IgG2, and IgG4. More preferably, it is IgG1.

The antibody of the present invention also includes an anti-FGF23 antibody which comprises an amino acid sequence of a novel complementarity determining region (CDR).

A CDR is present in the variable region of an antibody, and the part is responsible for the specificity of antigen recognition. The part other than the CDR in the variable region has a role in maintaining the structure of the CDR, and is referred to

as the framework region (FR). A constant region is present in the C terminal side of a heavy chain and a light chain, and is referred to as the heavy chain constant region (CH) and the light chain constant region (CL), respectively.

Three complementarity determining regions are present in the heavy chain variable region, which are a first complementarity determining region (CDR1), a second complementarity determining region (CDR2), and a third complementarity determining region (CDR3). The three complementarity determining regions in the heavy chain variable region are collectively referred to as the heavy chain complementarity determining region. Similarly, three complementarity determining regions are present in the light chain variable region, which are a first complementarity determining region (CDR1), a second complementarity determining region (CDR2), and a third complementarity determining region (CDR3). The three complementarity determining regions in the light chain variable region are collectively referred to as the light chain complementarity determining region. The sequences of these CDRs can be determined by using the methods described in Sequences of Proteins of Immunological Interest, US Dept. Health and Human Services (1991) and the like.

The antibody of the present invention preferably has at least any one or all of CDR1 shown by SEQ ID NO: 40, CDR2 shown by SEQ ID NO: 41, and CDR3 shown by SEQ ID NO: 42 as the heavy chain complementarity determining region. In addition, the antibody of the present invention preferably has at least any one or all of CDR1 shown by SEQ ID NO: 43, CDR2 shown by SEQ ID NO: 44, and CDR3 shown by SEQ ID NO: 45 as the light chain complementarity determining region. More preferably, the antibody of the present invention is an antibody which binds to FGF23 and has CDR1 shown by SEQ ID NO: 40, CDR2 shown by SEQ ID NO: 41, and CDR3 shown by SEQ ID NO: 42 as the heavy chain complementarity determining region, and CDR1 shown by SEQ ID NO: 43, CDR2 shown by SEQ ID NO: 44, and CDR3 shown by SEQ ID NO: 45 as the light chain complementarity determining region.

The CDR sequence of the antibody of the present invention is not specifically limited. However, the antibody of the present invention is an antibody preferably comprising any one or more CDRs, more preferably three CDRs of the heavy chain, and even more preferably six CDRs of the CDR sequences represented by SEQ ID NO: 40 through 45. The amino acid sequence other than the CDR is not specifically limited. The antibody of the present invention includes so called CDR transplantation antibodies, wherein the amino acid sequence other than the CDR is derived from other antibodies, and particularly antibodies in other species. Among these, a humanized antibody or human antibody, wherein the amino acid sequence other than the CDR is derived from human, is preferred. An addition, deletion, substitution and/or insertion of 1 amino acid residue or more can be introduced into the FR according to need. A publicly known method can be applied as the method for producing a humanized antibody or human antibody.

"Functional fragment" is a portion of an antibody (partial fragment) and has one or more of the actions of the antibody to the antigen. In other words, it refers to a fragment which retains binding ability to the antigen, reactivity to the antigen, or recognition capability to the antigen. Examples include Fv, disulfide stabilized Fv (dsFv), single chain Fv (scFv), and polymers of these and the like. Stated more specifically, examples include peptides which contain Fab, Fab', F (ab')2, scFv, diabody, dsFv, and CDR [D. J. King., Applications and Engineering of Monoclonal Antibodies., 1998 T. J. International Ltd].

Of the fragments which are obtained by treating an antibody which binds to FGF23 with the protease papain, Fab is the antibody fragment of molecular weight approximately 50,000 with antigen binding activity, in which approximately half of the amino-terminal side of the H chain with all of the L chain by a disulfide bond.

The Fab of the present invention can be obtained by treating the antibody which binds to FGF23 with the protease papain. Alternatively, Fab can be produced by inserting DNA which encodes Fab of the antibody into an expression vector for prokaryotic organisms or an expression vector for eukaryotic organisms and expressing this vector by introducing into a prokaryotic organism or eukaryotic organism.

Of the fragments obtained by treating IgG with the protease pepsin, F (ab')2 is the antibody fragment of molecular weight approximately 100,000 with antigen binding activity and which is larger than that of Fab bonded via disulfide bonds of the hinge region.

The F (ab')2 of the present invention can be obtained by treating antibody that binds with FGF23 with the protease pepsin. Alternatively, it can be produced through a thioether bond or disulfide bond of Fab' described below.

Fab' is an antibody fragment of a molecular weight of approximately 50,000 having antigen binding activity and in which the disulfide bond of the hinge region of the above F (ab')2 is cleaved.

Fab' of the present invention is obtained by treating F (ab')2 of the present invention, which binds to FGF23, with a reducing agent dithiothreitol. Alternatively, DNA which encodes the Fab' fragment of this antibody is inserted into an expression vector for prokaryotic organisms or into an expression vector for eukaryotic organisms, and this vector is introduced into prokaryotic organisms or eukaryotic organisms and thereby is expressed to produce Fab'.

scFv is an antibody fragment having antibody binding activity with a single heavy chain variable region (hereinafter referred to as VH) and a single light chain variable region (henceforth written as VL) which are linked using a suitable peptide linker (henceforth written as P) and is a VH-P-VL or VL-P-VH polypeptide.

The scFv of the present invention can be produced by obtaining the cDNA which encodes VH and VL of the antibody of the present invention which binds with FGF23 and constructing the DNA which encodes scFV and inserting the DNA into the expression vector for prokaryotic organisms or the expression vector for eukaryotic organisms and introducing and expressing the expression vector in prokaryotic organisms or eukaryotic organisms.

A diabody is an antibody fragment in which scFv is dimerized and is an antibody fragment having a bivalent antibody binding activity. Each binding activity of the bivalent antibody can be the same or different.

The diabody of the present invention can be produced by obtaining the cDNA which encodes the VH and VL of the antibody of the present invention which binds to FGF23, constructing the DNA which encodes scFV such that the length of the amino acid sequence for the peptide linker is 8 residues or less, inserting this DNA into an expression vector for prokaryotic organism or expression vector for eukaryotic organism, and expressing this expression vector by introducing into a prokaryotic organism or eukaryotic organism.

In dsFv, 1 amino acid residue in each of VH and VL is substituted with a cystine residue, and the polypeptides are bonded through a disulfide bond between these cysteine resi-

dues. The amino acid residue which is substituted with the cysteine residue can be selected based on the predicted tertiary structure of the antibody according to the method indicated by Reiter et al (Protein Engineering, 7: 697-704, 1994).

The dsFv of the present invention can be produced by obtaining the cDNA which encodes VH and VL of the antibody of the present invention which binds to FGF23, constructing the DNA which encodes the dsFv, inserting this DNA into an expression vector for a prokaryotic organism or an expression vector for a eukaryotic organism, and introducing and expressing this expression vector in a prokaryotic organism or eukaryotic organism.

The peptide which comprises CDR is constructed comprising at least 1 region or more of CDR of VH or VL. Peptides which comprise multiple CDR's can be linked together directly or through a suitable peptide linker.

The peptide which comprises the CDR of the present invention can be produced by constructing a DNA which encodes the CDR of the VH and VL of the antibody of the present invention which binds to FGF23, inserting this DNA into an expression vector for prokaryotic organisms or expression vector for eukaryotic organisms, and introducing and expressing this expression vector in prokaryotic organisms or eukaryotic organisms.

In addition, the peptide which contains CDR can be produce by a chemical synthesis method such as Fmoc method (fluorenylmethyloxycarbonyl method) and tBoc method (t-butyloxycarbonyl method) and the like.

Furthermore, "functional fragment" is a fragment of the antibody which can bind to the antigen (FGF23). Preferably, the "functional fragment" is a fragment which can bind to FGF23 and comprises an amino acid sequence from Q at position 20 to S at position 136 of SEQ ID NO: 12, and/or an amino acid sequence from A at position 23 to K at position 128 of SEQ ID NO: 14. Preferably, the "functional fragment" is a fragment which comprises at least one or all of CDRs represented by SEQ ID NO: 40 through 45 and can bind to FGF23. More preferably, the "functional fragment" is derived from the variable region of an antibody produced by hybridoma C10 and is a fragment which can bind to FGF23.

The antibody of the present invention includes derivatives of the antibody in which radioisotopes, low molecular weight drugs, macromolecular drugs, proteins, and the like is bound chemically or through genetic engineering to the antibody against FGF23 of the present invention or functional fragments of the antibody.

The derivatives of the antibody of the present invention can be produced by bonding radioisotopes, low molecular weight drugs, macromolecular drugs, proteins and the like to the amino terminal side or carboxy terminal side of the H chain (heavy chain) or L chain (light chain) of the antibody against FGF23 of the present invention or the functional fragment of the antibody, to a suitable substituted group or side chain in the antibody or functional fragment of the antibody, and further, to a sugar chain in the antibody or functional fragment of the antibody and the like by chemical methods (Koutai Kogaku Nyuumon, Osamu Kanamitsu, Chijin Shokan, 1994) and the like.

In addition, the derivative of the antibody bonded with protein is produced by linking the DNA which encodes the antibody against FGF23 of the present invention and the functional fragment of the antibody and the DNA which encodes the protein to be bonded, inserting this DNA into an expression vector, and introducing and expressing the expression vector in a suitable host cell.

For the radioisotope, examples include 131I, 125I. For example, the radioisotope can be bonded to the antibody by the chloramine T method and the like.

Low molecular weight drugs include alkylating agents including nitrogen mustard, cyclophosphamide; antimetabolites such as 5-fluorouracil and methotrexate; antibiotics such as daunomycin, bleomycin, mitomycin C, daunorubicin and doxorubicin; plant alkaloids, such as vincristine, vinblastine and vindesine; anti cancer agents such as hormone agents such as tamoxifen and dexamethasone (Clinical oncology; Japanese Clinical Oncology Research Meeting, Japanese Journal of Cancer and Chemotherapy Co., 1996); steroids such as hydrocortisone, prednisone, and the like; non-steroid agents including aspirin and indomethacin; immunomodulators such as gold thiomalate, penicillamine, and the like; immunosuppressors such as cyclophosphamide, azathioprine, and the like; anti-inflammatories such as anti-histamines such as chlorpheniramine maleate, clemastine, and the like (Inflammation and anti-inflammatory treatment method, Ishiyaku Publishing Corp. Ltd., 1982). The bonding of the antibody with these low molecular weight drugs is conducted by known methods. Examples of methods for bonding daunomycin with antibody include a method for bonding between amino groups of the daunomycin and antibody via glutaraldehyde, and a method for bonding the amino group of daunomycin and carboxyl group of the antibody via water-soluble carbodiimide. By bonding these low molecular weight drugs with the antibody, a derivative of an antibody having the function of the low molecular weight drug is obtained.

For the macromolecular drug, examples include polyethylene glycol (hereinafter referred to as PEG), albumin, dextran, polyoxyethylene, styrene maleate copolymer, polyvinyl pyrrolidone, pyran copolymer, hydroxypropyl methacrylamide, and the like. By bonding these macromolecular compounds with antibody or a functional fragment of an antibody, the following effects are anticipated (1) the stability with respect to various chemical, physical, and biological factors is improved (2) half life in blood is dramatically extended, (3) immunogenicity is lost, antibody production is suppressed, and the like (Bioconjugate Pharmaceutical, Hirokawa Shoten, 1993). An example of a method for bonding PEG to an antibody is a method of reacting with PEG-modifying reagent (Bioconjugate Pharmaceutical, Hirokawa Shoten, 1993). Examples of PEG-modifying reagent include ε-amino group modifier of lysine (Laid-Open Patent Publication Number S61-178926), carboxyl group modifier of aspartic acid and glutamic acid (Laid-Open Patent Publication Number S56-23587), guanidino group modifier of arginine (Laid-Open Patent Publication Number H2-117920), and the like.

The antibody which has bonded to the protein can be obtained as a fusion antibody. In other words, the cDNA which encodes the antibody or a functional fragment of the antibody is linked with the cDNA which encodes a specific protein, and DNA which encodes the fused protein of the specific protein and antibody is constructed. This DNA is inserted into an expression vector for a prokaryotic organism or eukaryotic organism. This expression vector can be introduced and expressed in the prokaryotic organism or eukaryotic organism in order to produce the fused antibody which is bonded with the specific protein.

With regard to the antibody against FGF23 of the present invention or the functional fragment of the antibody, by taking measurements through immunological methods such as ELISA (Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Chapter 14, 1988; Monoclonal Antibodies: Principles and Practice, Academic Press Limited, 1996) or measuring the binding dissociation constant by biosensor

Biacore (Journal of Immunological Methods, 145: 229-240, 1991), and measuring the inhibition activity (Nature, 444: 770-774, 2006) of the promoter activity of the Early growth response gene-1 by human FGF23 stimulation using klotho expression cells, human FGF23 binding activity and the activity of inhibiting the function of human FGF23 can be evaluated.

In the present invention, "human antibody" is defined as an antibody which is an expression product of an antibody gene derived from humans. Human antibody, as will be described later, can be obtained by introducing the human antibody gene locus and by administering antigen to transgenic animals having the ability to produce human antibody. Examples of these transgenic animals include mice. The method of creation of mice which can produce human antibody is described, for example, in International Publication Number WO02/43478 pamphlet.

For the antibody of the present invention, examples include an antibody (C10 antibody) produced by C10 hybridoma as will be described in Examples later. C10 hybridoma has had an international deposition based on the Budapest treaty with accession No. FERM ABP-10772 (a display for identification: C10) at the Patent Organism Depository Center (Central 6, 1-1 Higashi 1-chome, Tsukuba-shi, Ibaraki-ken, Japan) on Feb. 2, 2007 at the independent administrative institution of the Advanced Industrial Science and Technology.

The antibody or functional fragment of the present invention also included monoclonal antibodies or functional fragments thereof comprising the heavy chain and/or light chain consisting of amino acid sequences with 1 or several amino acid deletions, substitutions, and additions in each of the amino acid sequences for the heavy chain and/or light chain which constructs the antibody or functional fragment. Here, of the "1 or several", "several" is 9 or less, preferably 5 or less, and more preferably 3 or less. Having 2 is especially preferred. A partial modification (deletion, substitution, insertion, addition) of the amino acid as described previously can be introduced into the amino acid sequence of the antibody of the present invention or functional fragment by partially modifying the nucleotide sequence which encodes the amino acid sequence. Partial modification of this nucleotide sequence can be introduced using the conventional method of known site specific mutagenesis [Proc Natl Acad Sci USA., 81: 5662-5666, 1984]. The antibody of the present invention includes antibodies of all immunoglobulin classes and isotypes.

The antibody against FGF23 of the present invention can be produced by the following production method. For example, FGF23 or a portion of FGF23 or a conjugate of a portion of FGF23 and a suitable carrier substance for increasing antigenicity (for example, bovine serum albumin and the like) are immunized together with an adjuvant (Freund's complete or incomplete adjuvant and the like) as necessary into non-human mammals such as human antibody producing transgenic mice. For FGF23, natural FGF23 or recombinant FGF23 can be used. Alternatively, immune sensitization can be conducted by introducing the gene encoding FGF23 into an expression vector and expressing the FGF23 protein inside the animal. The monoclonal antibody is obtained by culturing the hybridoma obtained by fusing antibody producing cells obtained from immune sensitized animals and myeloma cells which do not have antibody production ability, and by selecting the clones which produce the monoclonal antibodies showing specific affinity for the antigen used for immunization.

The antibody of the present invention includes those that have been converted to a different subclass by genetic engineering modification that is known to those skilled in the art (for example, see European Patent Application EP314161). In other words, using DNA which encodes the variable region of the antibody of the present invention, an antibody which is of a subclass that is different from the original subclass can be obtained using genetic engineering methods.

2. Producing the Antibody of the Present Invention

Producing a monoclonal antibody includes the following steps. In other words, (1) the antigen protein which is to be used as the immunogen or the antigen protein expression vector is prepared, (2) after immunization by injecting the antigen inside the animal or by expressing the antigen inside the animal, blood is sampled and its antibody titer is assayed, and after determining the time for spleen isolation, antibody production cells are prepared, (3) Myeloma cells are prepared, (4) the antibody production cell and myeloma are fused, (5) the hybridoma group which produces the target antibody is selected, (6) the hibridomas are divided into a single cell clone (cloning), (7) optionally, the hybridoma is cultured to produce large amounts of monoclonal antibody, or animals in which the hybridoma has been transplanted are raised, and (8) the biological activity and the recognition specificity of the monoclonal antibody produced in this way is assayed, or the property as a labeling reagent are assayed.

Hereinafter, the production method for the anti-FGF23 monoclonal antibody is described in detail following the above process. However, the production method for this antibody is not limited to this method. For example, antibody producing cells and myeloma from other than spleen cells can also be used.

(1) Purification of the Antibody

Using genetic recombination technique, the DNA sequence which encodes FGF23 is integrated into a suitable expression plasmid. After FGF23 is produced in a host such as *E. coli* or an animal cell or the like, the purified FGF23 protein can be used. Because the primary structure of human FGF23 protein is known [GenBank accession No. AAG09917, SEQ ID NO: 4], a partial peptide from the amino acid sequence of FGF23 is chemically synthesized by methods known to those skilled in the art, and this can also be used as the antigen.

(2) Preparation Step of Antibody Producing Cell

The antigen obtained as mentioned in (1) is mixed with a adjuvant such as complete or incomplete Freund's adjuvant or aluminum potassium, and the mixture is immunized into experimental animals as an immunogen. For the experimental animals, transgenic mice having the ability to produce human derived antibodies are most suitably used. This type of mice is described by the reference by Tomizuka et al [Tomizuka. et al., Proc Natl Acad Sci USA., 97: 722-727, 2000].

The immunogen administration method when immunizing mice can be any of subcutaneous injection, intraperitoneal injection, intravenous injection, intradermal injection, intramuscular injection, foot pad injection, and the like. Intraperitoneal injection, foot pad injection or intravenous injection is preferred.

The immunization can be conducted once or repeated several times at a suitable interval. Afterwards, the antibody titer against the antigen in the serum of the immunized animal is measured. When animals with a sufficiently high antibody titer are used as a supply source for antibody producing cells, the efficiency of later operations is increased. In general, it is preferable to use antibody producing cells derived from animals 3-5 days after the final immunization for the following cell fusion.

Examples of the method used here for measuring antibody titer include known techniques such as radioimmunoassay (hereinafter referred to as "RIA method"), enzyme linked immunoabsorbent assay (hereinafter referred to as "ELISA method"), fluorescent antibody method, passive hemagglutination method, and the like. From the standpoint of detection sensitivity, rapidity, accuracy, and the possibility of automated operation, RIA method or ELISA method is suitable.

According to the ELISA method for example, the measurement of antibody titer of the present invention can be conducted by the following procedure. First, antigen against human antibody is absorbed onto the solid phase surface of an ELISA 96 well plate for example. Furthermore, the solid phase surface which has not absorbed antigen is covered with a protein unrelated to the antigen, such as bovine serum albumin (BSA). After rinsing the surface, it is allowed to contact with a serially diluted reagent as a primary antibody (for example, serum from transgenic mice having the ability to produce human antibodies) to make the antigen described above which binds to the anti-FGF23 antibody in the sample. Furthermore, an enzyme-labeled antibody against human antibody is added as the secondary antibody to be allowed to bind to the human antibody. After washing, a substrate for the enzyme is added. Then, change in the light absorption caused by the color resulted from the substrate breakdown is measured to calculate the antibody titer.

(3) Preparation Step for Myeloma

For the myeloma, cells which do not have antibody production ability by themselves and which are derived from mammals such as mouse, rat, guinea pig, hamster, rabbit, or humans, and the like can be used. In general, cell lines obtained from mice, for example 8-azaguanine resistant mice (BALB/c derived) myeloma line P3X63Ag8U.1 (P3-U1) [Yelton, D. E. et al., Current Topics in Microbiology and Immunology, 81: 1-7, 1978], P3/NSI/1-Ag4-1 (NS-1) [Kohler, G. et al., European J. Immunology, 6: 511-519, 1976], Sp2/O—Ag14 (SP2/O) [Shulman, M. et al., Nature, 276: 269-270, 1978], P3X63Ag8.653 (653) [Kearney, J. F. et al., J. Immunology, 123: 1548-1550, 1979], P3X63Ag8 (X63) [Horibata, K. and Harris, A. W., Nature, 256: 495-497, 1975] and the like are preferably used. These cell lines are subcultured in a suitable medium, for example 8-azaguanine medium [an RPMI-1640 medium supplemented which glutamine, 2-mercaptoethanol, gentamycin, and fetal calf serum (FCS) as well as 8-azaguanine], Iscove's Modified Dulbecco's Medium (IMDM), or Dulbecco's Modified Eagle Medium (DMEM). However, 3-4 days prior to cell fusion, the cell lines are subcultuted in a normal medium (for example DMEM medium containing 10% FCS), and on the day of fusion, a cell number of 2×107 or greater is prepared.

(4) Cell Fusion

The antibody producing cells are plasma cells and lymphocytes which are their precursor cells. These can be obtained from any site from the individuals. In general, the spleen, lymph node, bone marrow, tonsils, peripheral blood, or any of these can be combined. In general, splenic cells are used most often.

After the final immunization, the site where the antibody producing cells is present, for example the spleen, is removed from mice which have achieved a prescribed antibody titer, and the splenic cells which are the antibody producing cells are prepared. Next, splenic cells and myeloma are fused. For the means for fusing the splenic cell and the myeloma obtained in step (3), the method that is used most generally is a method using polyethylene glycol. This method has relatively low cell toxicity and the fusion operation is also easy. This method has the following procedure, for example.

The splenic cell and myeloma is washed well with serum-free medium (for example DMEM) or a phosphate buffered saline (PBS). The splenic cell and myeloma are mixed at a cell number ratio of around 5:1-10:1 and are centrifuged. The supernatant is removed, and after loosening the precipitated cell group, 1 mL of a serum-free medium containing 50% polyethylene glycol (molecular weight 1000-4000) (w/v) is instilled into the cells while stirring. Afterwards, 10 mL of serum-free medium is slowly added, and afterwards, this is centrifuged. The supernatant is again discarded, and the precipitated cells is suspended in a suitable amount of normal medium (referred to as HAT medium) which contains suitable amount of hypoxanthine/aminopterine/thymidine (HAT) solution and human interleukin-6 (IL-6). The cells are aliquoted onto each well of a culturing plate (henceforth referred to as "plate"), and cultured for approximately 2 weeks at 37 degrees C. under 5% carbon dioxide gas. During this time, HAT medium is supplemented as needed.

(5) Selection of Hybridoma Group

When the myeloma cells described above is a 8-azaguanine resistant strain, in other words, if it is a hypoxanthine/guanine/phosphoribosyltransferase (HGPRT) deficient strain, the myeloma cells which were not fused and fused cells of only myeloma cells will not survive in HAT containing medium. On the other hand, fused cells of only antibody producing cells and hybridomas of antibody producing cell and myeloma cell can survive, but for the fused cells of only antibody producing cells have a limited lifespan. Therefore, by continuing to culture in a HAT-containing medium, only the hybridomas which are fused cells between antibody producing cells and myeloma cells will survive. As a result, hybridomas can be selected.

For the hybridoma which is growing in colonies, medium exchange to a medium in which aminopterin is removed from HAT medium (henceforth referred to as HT medium) is conducted. Afterwards, a portion of the medium supernatant is collected, and the anti-FGF23 antibody titer is measured by the ELISA method, for example.

Above, we showed an example of a method using an 8-azaguanine resistant cell line, but other cell lines can also be used according to the selection method for hybridomas. In these cases, the medium composition to be used also changes.

(6) Cloning Step

By measuring the antibody titer with the same method as the antibody titer measuring method as in (2), the hybridoma which has been determined to produce the specific antibody is transferred to another plate, and cloning is conducted. Examples of cloning methods include the limiting dilution method in which the hybridoma are diluted so that there is one hybridoma contained per 1 well of a plate and this is cultured; soft agar method in which the hybridomas are cultured in a soft agar medium and the colonies are collected; a method in which one cell at a time is removed with a micromanipulator and this is cultured; "sorter cloning" in which a single cell is separated by a cell sorter, and the like. The limiting dilution method is simple and is often used.

With regard to the wells in which antibody titer has been seen, for example, cloning is repeated 2-4 times by the limiting dilution method, and cells having a stable antibody titer, these are selected as anti-FGF23 monoclonal antibody producing hybridoma lines.

(7) Preparation of Monoclonal Antibody by Hybridoma Culturing

The hybridomas in which cloning has been completed are cultured by exchanging the medium from HT medium to normal medium. For large-scale culturing, there are rotation culturing using a large-scale culture bottle, spinner culturing,

or culturing using a hollow fiber system, and the like. By purifying the supernatant in large-scale culturing using a method known to those skilled in the art such as gel filtration and the like, anti-FGF23 monoclonal antibody can be obtained. In addition, by growing this hybridoma intraperitoneally in the same strain of mouse (for example BALB/c) or nu/nu mouse, rat, guinea pig, hamster, or rabbit or the like, peritoneal fluid containing large amounts of anti-FGF23 monoclonal antibody can be obtained. A simple method for purification uses commercial monoclonal antibody purification kits (for example, MAbTrap GII kit; GE Healthcare Bioscience Co.) and the like.

The monoclonal antibodies obtained in this way have high antigen specificity against FGF23.

In addition, recombinant antibody can be prepared by cloning the gene which encodes human monoclonal antibody from the antibody producing cells of the hybridoma and the like, incorporating the gene into a suitable vector and introducing into a host (for example, mammalian cell line, *E. coli*, yeast cell, insect cell, plant cell, and the like), and using genetic recombination technology (Delves, P. J., ANTIBODY PRODUCTION ESSENTIAL TECHNIQUES., 1997 WILEY, Shepherd, P. and Dean C., Monoclonal Antibodies., 2000 OXFORD UNIVERSITY PRESS, Goding, J. W., Monoclonal Antibodies: principles and practice., 1993 ACADEMIC PRESS).

The present invention includes the nucleic acids which contain the genetic sequence for the antibody of the hybridoma which produces the antibody of the present invention, in particular the nucleic acid for the heavy chain variable region and light chain variable region of the antibody produced by the hybridoma of the present invention that will be described later. Here, nucleic acid includes DNA and RNA. Furthermore, the present invention includes the nucleic acid of the mature portion in which the region encoding the signal sequence from the nucleic acid of the heavy chain variable region and light chain variable region of the present invention has been removed. Furthermore, in addition to the nucleic acids described above, the nucleic acid of the present invention includes the nucleic acids having the codons corresponding to the amino acids of the amino acid sequence of the antibody of the present invention and to the amino acids of the antibody heavy chain variable region and/or light chain variable region of this antibody.

In order to prepare the gene which encodes the monoclonal antibody from the hybridoma, a method is used in which DNA encoding each of the L chain V region, L chain C region, H chain V region and H chain C region of the monoclonal antibody is prepared by PCR method or the like. For this, oligoDNA designed from the anti-FGF23 antibody gene or the amino acid sequence is used as the primer. For the template, DNA prepared from the hybridoma can be used. These DNAs are incorporated into one suitable vector and this is introduced into a host and is expressed, or else these DNAs are each incorporated into a suitable vector, and co-expressed.

For the vector, phages or plasmids which can grow autonomously in the host microorganisms are used. For the plasmid DNA, examples include plasmids from *E. coli, Bacillus subtilis*, or yeast, and the like. For the phage DNA, examples include λ phage.

The host used in transformation is not limited as long as it is one which can express the target gene. Examples include bacteria (*E. coli, Bacillus subtilis*, and the like), yeast, animal cells (COS cells, CHO cells and the like), and insect cells and the like.

Methods for introducing genes into a host are known, and there are many examples of methods (for example, a method which uses calcium ion, electroporation method, spheroplast method, lithium acetate method, calcium phosphate method, lipofection method, and the like). In addition, examples of methods for introducing the gene into animals which will be described later include microinjection method, method of introducing genes into ES cells using electroporation method and lipofection method, nuclear transplantation, and the like.

In the present invention, the transformant is cultured, and the anti-FGF23 antibody is obtained by collecting from the culture product. Here, "culture product" signifies any of (a) culture supernatant, (b) cultured cells or cultured bacteria or their homogenate, (c) secretions of the transformant. In order to culture the transformant, a medium suitable for the host is used, and stationary culture method, culture method by roller bottle and the like are used.

After culturing, when the target antibody is produced inside the bacteria or inside the cell, the antibody is collected by homogenizing the bacteria or cell. In addition, when the target antibody is produced outside the bacteria or outside the cell, the culture solution can be used directly, alternatively the bacteria or cells are removed by centrifugation or the like. Afterwards, the target antibody can be isolated and purified from the culture product by general biochemical methods using, singly or in combination, various chromatographies used for isolation and purification of proteins.

Furthermore, using transgenic animal creation techniques, animal hosts in which the gene of the target antibody is incorporated into endogenous genes, for example transgenic cattle, transgenic goat, transgenic sheep, or transgenic pig are created. A large amount of monoclonal antibody derived from the antibody gene can be obtained from the milk secreted from these transgenic animals (Wright, G., et al., Bio/Technology 9: 830-834, 1991). When culturing the hybridoma in vitro, the hybridoma is grown, maintained and stored according to the various conditions of the properties of the cultured cell the experimental research and culture methods and the like. Known nutrition medium or various nutrition medium derived and prepared from known basic medium can be used to produce the monoclonal antibody in the culture sup ernatant.

(8) Assay of the Monoclonal Antibody

Determining the isotype and subclass of the monoclonal antibody obtained in this manner can be conducted in the following manner. First, examples of the identification method include Ouchterlony method, ELISA method, or RIA method, and the like. The Ouchterlony method is simple, but when the concentration of the monoclonal antibody is low, a concentrating procedure is necessary. On the other hand, when ELISA method or RIA method is used, the culture supernatant is reacted directly with the antigen absorbed solid phase, and as a secondary antibody, antibodies responding to various immunoglobulin isotypes, and subclasses can be used to identify the isotype and subclass for the monoclonal antibody.

Furthermore, the quantification of the protein can be conducted by Folin/Lowry method and by a method which calculates light absorption at 280 nm [1.4 (OD280)=immunoglobulin 1 mg/mL].

Identification of recognition epitopes of the monoclonal antibody (epitope mapping) is conducted as follows. First, the partial structures of various molecules that monoclonal antibodies recognize are created. For the creation of partial structures, there is a method in which known oligopeptide synthesis techniques are used to create various partial peptides of the molecule, and a method in which, using genetic recombina-

tion techniques, the DNA sequence which encodes the target partial peptide is incorporated in a suitable expression plasmid, and the peptides are produced inside or outside of the host such as *E. coli* or the like. However, in general, both methods are combined for the above objective. For example, a series of polypeptides in which the antigen protein has been sequentially shortened at random lengths from the carboxy terminal or amino terminal is created using genetic recombination techniques known to those skilled in the art. Afterwards, the reactivity of the monoclonal antibody to these polypeptides is studied, and recognition sites are roughly determined.

Afterwards, for further detail, the oligopeptide of the corresponding portion, or variants and the like of these peptides are synthesized by oligopeptide synthesis techniques known to those skilled in the art. In order to define the epitopes, the binding of the monoclonal antibodies contained as an active ingredient in the agent for prevention or treatment of the present invention to these peptides is studied, alternatively the competitive inhibition activity of the peptides to the binding of the monoclonal antibodies to the antigen is studied. As a simple method for obtaining various oligopeptides, commercial kits (for example, SPOTs kit (Genosis Biotechnologies), a series of multipin peptide synthesis kits which uses multipin synthesis method (Chiron Co,) and the like) can be used.

(9) Producing the Antibody Fragment

The antibody fragment is produced by genetic engineering methods or proteochemical methods based on the antibody described in (7) of the above.

For the genetic engineering method, the gene which encodes the target antibody fragment is constructed and expressed using a suitable host such as animal cell, plant cell, insect cell, *E. coli* and the like, and the antibody fragment is purified.

For the proteochemical method, proteases such as pepsin, papain, and the like are used for site specific cleavage, and purification is conducted.

For the antibody fragment, examples include peptides comprising Fab, F (ab')2, Fab', scFv, diabody, dsFv, CDR and the like. The production method for each of the antibody fragments is described in detail below.

(i) Production of Fab

Proteochemically, Fab can be created by treating IgG with protease papain. After treatment with papain, if the original antibody is an IgG subclass having protein A binding ability, by passing through a protein A column, IgG molecules and Fc fragments are separated, and a uniform Fab can be recovered (Monoclonal Antibodies: Principles and Practice, third edition, 1995). If the antibody is an IgG subclass with no protein A binding ability, with ion exchange chromatography, Fab is recovered from the fraction which is eluted at low salt concentrations (Monoclonal Antibodies: Principles and Practice, third edition, 1995). In addition, for genetic engineering of Fab, *E. coli* is used in most cases, or insect cells and animal cells and the like are used to produce Fab. For example, DNA which encodes the V region of the antibody described in 2 (7) above is cloned into a Fab expression vector to construct a Fab expression vector. For the Fab expression vector, anything can be used as long as DNA for Fab can be incorporated and expressed. An example is pIT106 (Science, 240: 1041-1043, 1988) and the like. The Fab expression vector is introduced into a suitable *E. coli*, and Fab can be generated and stored in an inclusion body or periplasma layer. From the inclusion body, the Fab can be activated by a refolding method normally used with proteins. In addition, when expression is in the periplasma layer, active Fab is discharged into the culture supernatant. After refolding or from the culture supernatant, by using a column with bound antigen, a uniform Fab can be purified (Antibody Engineering, A Practical Guide, W.H. Freeman and Company, 1992).

(ii) Production of F (ab')2

Proteochemically, F (ab')2 is produced by treating IgG with protease pepsin. After treating with pepsin, a uniform F (ab')2 is recovered through the same purification operation as with Fab (Monoclonal Antibodies: Principles and Practice, third edition, Academic Press, 1995). In addition, it can be created by a method in which Fab' described in the following (iii) is treated with a maleimide such as o-PDM or bis maleimide hexane and the like, and thioether bonds are formed or it can be created by a method in which it is treated with DTNB [5,5'-dithiobis(2-nitrobenzoic acid)], and S—S bonds are formed (Antibody Engineering, A Practical Approach, IRL PRESS, 1996).

(iii) Production of Fab'

Fab' can be obtained by treating F (ab')2 described in the above (ii) with a reducing agent such as dithiothreitol, and the like. In addition, with genetic engineering, Fab' can be created by using *E. coli* in most cases or insect cells or animal cells and the like. For example, DNA which encodes the V region of the antibody described in the above 2 (7) is cloned into a Fab' expression vector and a Fab' expression vector can be constructed. For the Fab' expression vector, anything can be used as long as DNA for Fab' can be incorporated and expressed. An example is pAK19 (BIO/TECHNOLOGY, 10: 163-167, 1992) and the like. Fab' expression vector is introduced into a suitable *E. coli*. Fab' can be generated and accumulated in an inclusion body or in the periplasma layer. From the inclusion body, Fab' is activated by the refolding method used normally in proteins. In addition, when expressed in the periplasma layer, bacteria is homogenized by treatment with partial digestion by lisozyme, osmotic shock, sonication, and the like, and this can be recovered from outside the bacteria. After refolding or from the bacterial homogenate, a uniform Fab' can be purified by using a protein G column and the like (Antibody Engineering, A Practical Approach, IRL PRESS, 1996).

(iv) Production of scFv

By genetic engineering, scFv can be produced by using a phage or *E. coli* or insect cells or animal cells and the like. For example, DNA which encodes the V region of the antibody described in 2 (7) can be cloned into a scFv expression vector to construct a scFv expression vector. For the scFv expression vector, anything can be used as long as DNA for scFv can be incorporated and expressed. Examples include pCANTAB5E (GE Healthcare Bioscience Co.), pHFA (Human Antibodies & Hybridomas, 5: 48-56, 1994) and the like. scFv expression vector is introduced into a suitable *E. coli*. By infecting with a helper phage, a phage in which scFv is expressed on the phage surface as fused with a phage surface protein can be obtained. In addition, scFv can be generated and accumulated in the inclusion body or in the periplasma layer of the *E. coli* in which the scFv expression vector has been introduced. From the inclusion body, activated scFv can be obtained by the refolding method normally used for proteins. In addition, when expressed in the periplasma layer, bacteria are homogenized by treatment with partial digestion by lisozyme, osmotic shock, sonication, and the like, and this is recovered from outside the bacteria. After refolding or from the bacterial homogenate, a uniform scFv can be purified by using positive ion exchange chromatography and the like (Antibody Engineering, A Practical Approach, IRL PRESS, 1996).

(v) Production of Diabody

By genetic engineering, diabody can be produced mainly using *E. coli* as well as insect cells and animal cells. For

example, DNA is produced in which VH and VL of the antibody described in above 2 (7) are linked so that the amino acid residues encoded by the linker are 8 residues or less and cloned in a diabody expression vector to construct the expression vector for diabody. Any vector can be used as a diabody expression vector as long as it can be integrated with diabody DNA and express diabody DNA. Examples include pCANTAB5E (GE Healthcare Bioscience), pHFA (Human Antibodies Hybridomas, 5, 48, 1994) and the like, diabody can be generated and accumulated in the inclusion body or in the periplasma layer of the *E. coli* in which the diabody expression vector has been introduced. From the inclusion body, activated diabody can be obtained by the refolding method normally used for proteins. In addition, when expressed in the periplasma layer, bacteria are homogenized by treatment with partial digestion by lisozyme, osmotic shock, sonication, and the like, and this is recovered from outside the bacteria. After refolding or from the bacterial homogenate, a uniform diabody can be purified by using positive ion exchange chromatography and the like (Antibody Engineering, A Practical Approach, IRL PRESS, 1996).

(vi) Production of dsFv

dsFv can be created mainly using *E. coli* as well as insect cells and animal cells by genetic engineering. First, mutations are introduced at appropriate sites of DNA which encodesVH and VL of antibody described in (ii), (iv) and (v), and DNA in which the coded amino acid residues are replaced with cysteine is produced. Each DNA produced can be cloned in dsFv expression vector to construct expression vectors for VH and VL. Any vector can be used as an dsFv expression vector as long as it can be integrated with and express dsFv DNA. For example, pUL19 (Protein Engineering, 7: 697-704, 1994) and the like can be used. The expression vector for VH and VL can be introduced into an appropriate *E. coli* and generated products can be accumulated in inclusion body or periplasma layer. VH and VL are obtained from inclusion body and periplasma layer, mixed and converted to dsFv with activity by the refolding method which is employed in normal protein processing. After refolding, further purification by ion-exchange chromatography and gel-filtration can be carried out (Protein Engineering, 7: 697-704, 1994).

(vii) Production of CDR Peptide

Peptides containing CDR can be produced by the chemical synthesis method such as Fmoc method or tBoc method and the like. Also, CDR peptide expression vector can be produced by producing DNA which encodes a peptide containing CDR and by cloning the DNA produced in an appropriate expression vector. Any vector can be used as an expression vector as long as it can be integrated with and express DNA that encodes CDR peptide. For example, pLEX (Invitrogen) and pAX4a+ (Invitrogen) may be used. The expression vector can be introduced into an appropriate *E. coli* and generated products can be accumulated in inclusion body or periplasma layer. CDR peptide is obtained from inclusion body or periplasma layer and can be purified by ion exchange chromatography and gel-filtration (Protein Engineering, 7: 697-704, 1994).

3. Characteristic of the Antibody of the Present Invention and the Functional Fragment Thereof.

The antibody of the present invention and the functional fragment thereof possesses any of the characteristic below.

(a) FGF23 binding test; binds to the full length protein having amino acid residues from 25th to 251st of SEQ ID NO: 4 of FGF protein.

(b) In vitro test; inhibits the action of FGF23 in an assay, by which the action of FGF23 can be detected. An example of the method for detecting the action of FGF23 in vitro is the activation of the promoter of the early growth response gene-1 by human FGF23 stimulation (Nature, 444: 770-774, 2006).

(c) In vivo test; inhibits the activity of endogenous FGF23 and increases serum phosphorous concentration and serum 1,25D concentration when administered to human. The extent of the increase of the serum phosphorous concentration and serum 1,25D concentration is greater compared to conventional antibody, 2C3B antibody (the mouse monoclonal antibody against FGF23 protein disclosed in WO03/057733, anti-FGF23 antibody produced by hybridoma of Accession No. FERM BP-7838) and also the duration of increased level of serum phosphorous concentration and serum 1,25D concentration is long. For example, the duration of elevated serum phosphorous concentration is about 3 times or longer, preferably about 5 times as that of 2C3B antibody, and the duration of elevated serum 1,25D concentration is about 1.5 times or longer, preferably about 2.5 times as that of 2C3B antibody when administered to cynomolgus monkey.

The present invention also includes a nucleic acid which encodes an amino acid sequence of the antibody to FGF23 of the present invention. The nucleic acid may be DNA or RNA. The nucleic acid of the present invention is, preferably, a nucleic acid which encodes an amino acid sequence of antibody produced by hybridoma C10. An example is a nucleic acid encoding the amino acid sequence of the heavy chain variable region (heavy chain nucleotide sequence of C10 antibody), which is coded by the nucleotide sequence from at position 58 C to at position 408 A shown in SEQ ID NO: 11. In addition, another example is a nucleic acid encoding the amino acid sequence of the light chain variable region, which is coded by the nucleotide sequence from G at position 67 to A at position 384 shown in SEQ ID NO: 13.

II. Pharmaceutical Compositions

A formulation which is a pharmaceutical composition comprising the human anti-FGF23 antibody of the present invention or the functional fragment thereof is included in the scope of the present invention. Such a formulation, preferably, includes in addition to the antibody and the functional fragment thereof, a physiologically acceptable diluents or carriers and may be a mixture with other drugs such as other antibody or antibiotics. Appropriate carriers include physiological saline, phosphate buffered saline, phosphate buffered saline glucose solution, and buffered physiological saline, but not limited to these. Further, the antibody may be freeze-dried and may be re-constituted by adding above buffer solution when needed, and then used. Administration routes include oral administration, or parenteral administration such as intraoral, tracheobronchial, endorectal, subcutaneous, intramuscular and intravenous administration, and preferred administration route is intravenous administration. Administration can be conducted in various formulations and the formulations include, aerosol, capsules, tablets, granules, syrup, emulsion, suppositories, injections, ointments and tapes.

Liquid preparations such as emulsion and syrup can be produced using additives for example: water; saccharides such as sucrose, sorbitol and fructose; glycols such as polyethylene glycol, propylene glycol; oils such as sesame oil, olive oil and soy bean oil; preservatives such as p-hydroxybenzoate esters; flavors such as strawberry flavor and peppermint.

Capsules, tablets, powder and granules can be produced using additives for example: excipients such as lactose, glu-

cose, sucrose and mannitol; disintegrators such as starch and sodium alginate; lubricants such as magnesium stearate and talc; binders such as polyvinyl alcohol, hydroxypropyl cellulose and gelatin; surface active agents such as fatty acid ester; plasticizers such as glycerin.

In the injections, additives can be used include; water; saccharides such as sucrose, sorbitol, xylose, trehalose, fructose and the like; sugar alcohols such as mannitol, xylitol and sorbitol; buffers such as phosphate buffer, citrate buffer and glutamate buffer; surface active agents such as fatty acid ester.

An appropriate formulation for parenteral administration includes injections, suppositories, aerosol and the like. In case of injections, it is normally provided in the form of unit dosage ampules or multiple dosage containers. It may be powder which is re-dissolved, when in use, in an appropriate carrier, for example pyrogen-free sterile water. These formulations contain additives such as emulsifier, suspending agent and the like, which are generally used for formulating in these compositions. Methods for injection include, for example intravenous infusion, intravenous injection, intramuscular injection, intraperitoneal injection, subcutaneous injection, intradermal injection and the like. Also, the dosage is different according to the age of the administration subject, administration route, frequency of administration, and can be changed widely.

A suppository is prepared using a carrier such as cacao butter, hydrogenated fat or carboxylic acid. Aerosol can be prepared using the antibody of the present invention of the functional fragment thereof itself, or using a carrier which does not irritate oral and respiratory tract mucosa of a recipient (patient) and can disperse the aforementioned antibody and the functional fragment thereof as fine particles to facilitate absorption.

In particular, examples of a carrier include lactose, glycerin and the like. Depending on the characteristic of the aforementioned antibody or the functional fragment thereof and the characteristic of the carrier to be used, formulation such as aerosol, dry powder and the like can be chosen. Also, the components shown as examples of additives for oral formulation can be added to these parenteral formulations.

The dosage may vary according to symptoms, age, body weight but normally in oral administration, about 0.01 mg-1000 mg per day for an adult is administered. This can be administered once or divided into several batches. In parenteral administration, about 0.01 mg-1000 mg can be administered by subcutaneous, intramuscular or intravenous injection per administration.

The present invention includes the antibody of the present invention, or the functional fragment thereof, or a preventive or therapeutic method for diseases described below using a pharmaceutical composition containing thereof, and furthermore, the present invention include a use of the antibody of the present invention or the functional fragment thereof for manufacturing an agent for preventive or therapeutic of the diseases described below.

Diseases that can be prevented or treated by the antibody of the present invention or the functional fragment thereof include diseases having excessive activity of FGF23 such as tumor-induced osteomalachia, ADHR, XLH, fibrous dysplasia, McCune-Albright syndrome, and a disease accompanying abnormal mineral metabolism such as autosomal recessive hypophosphataemia. Further, improving effects can be expected for syndromes associated with these diseases such as, hypophosphataemia, bone mineralization failure, bone pain, muscle weakness, skeletal deformity, growth disorder, low blood 1,25D and the like. Since FGF23 plays an important role under the physiological condition, the calcium metabolism control activity of FGF23, which is mediated by the control of phosphorous metabolism and vitamin D metabolism, can be regulated by the antibody of the present invention and the functional fragment thereof, and thus, they can be used preventively and therapeutically for diseases caused by abnormality in mineral metabolism and vitamin D metabolism, such as osteoporosis, rickets (including hypophosphatemic rickets and vitamin D-resistant rickets), hypercalcaemia, hypocalcaemia, ectopic calcification, osteosclerosis, Paget's disease, hyperparathyroidism, hypoparathyroidism, pruritus and the like. Further, the antibody of the present invention and the functional fragment thereof can also be used preventively or therapeutically for diseases caused by the complication of kidney failure and dialysis for kidney failure, represented by renal osteodystrophy, dialysis osteopathy, renal tubular dysfunction. On the other hand, 1,25D has been reported to have activities not only on mineral metabolism such as calcium metabolism as described above but also cell growth inhibitory effect, cell differentiation promotion activity and the like. Thus the antibody of the present invention and the functional fragment thereof can be used therapeutically and preventively against diseases caused by the cells whose growth and differentiation are regulated by 1,25D.

Also, it is known that, in tumor-induced osteomalachia, overproduction of FGF23 by the tumor causes pathology. Therefore it may be conceivable that retraction of the tumor may be induced by using the antibody of the present invention linked with a radioactive substance such as radioactive isotope and the like, or with therapeutic reagent of various toxins such as low molecular weight drugs and by accumulating the present antibody in the FGF23 overproducing tumor.

III. Formulation Example

The formulation containing the antibody of the present invention or the functional fragment thereof, is provided as an ampule of sterile solution dissolved in water or pharmacologically acceptable solution or suspension. Also, a sterile powder formulation (it is preferable to freeze dry the molecule of the present invention) may be placed in an ampule and may be diluted in use with a pharmacologically acceptable solution.

EXAMPLES

Following is the detailed description of the present invention by Examples, but it does not mean that the present invention is limited to these descriptions of Examples only.

Example 1

Preparation of an Expression Vector for Recombinant Human FGF23

(1) Construction of an Expression Vector for Human FGF23H Protein

cDNA encoding human FGF23 was amplified by using the human cDNA library of the responsible tumor for tumor-induced osteomalachia as a template, a FlEcoRI primer (SEQ ID NO: 1) and a LH is Not primer (SEQ ID NO: 2) and LA-Taq DNA polymerase and by conducting 35 cycles of a PCR step consisting of heating at 96° C. for 1 min, then at 96° C. for 30 sec, at 55° C. for 30 sec and at 72° C. for 30 sec. The F1EcoRI primer was annealed to a sequence present at further upstream of the 5' side of the nucleotide sequence encoding

human FGF23 and adds an EcoRI restriction site at the 5' side of the nucleotide sequence encoding human FGF23 in the amplified fragment. The LH is Not primer comprises a sequence which anneals to the sequence at the 5' side of the stop codon of the nucleotide sequence encoding human FGF23, a sequence encoding the terminal codon which follows the sequence encoding the His6-tag sequence (His-His-His-His-His-His) and a NotI restriction site. As a result, the amplified fragment encodes human FGF 23 protein in which the His6-tag sequence is added at the carboxy terminal and has a NotI restriction site at the downstream thereof. This amplified fragment was digested with EcoRI and Not I, and ligated to an animal cell expression vector, pcDNA3.1Zeo (Invitrogen) which was similarly digested with EcoRI and NotI. The expression vector constructed in such a way was cloned and the nucleotide sequence was determined to confirm that the expression vector encodes the target, human FGF23 protein to which the His6-tag sequence was added. This vector is called pcDNA/hFGF23H.

F1EcoRI:
CCGGAATTCAGCCACTCAGAGCAGGGCACG (SEQ ID NO: 1)

LHisNot:
ATAAGAATGCGGCCGCTCAATGGTGATGGTGATGAT (SEQ ID NO: 2)

GGATGAACTTGGCGAA

(2) Construction of an Expression Vector for Human FGF23 Protein

A fragment was amplified by using pcDNA/hFGF23H as a template, the F1EcoRI primer and a LNot primer (SEQ ID NO: 3) and LA-Taq DNA polymerase and by conducting 25 cycles of a PCR step consisting of heating at 94° C. for 1 min, then at 94° C. for 30 sec, at 55° C. for 30 sec and at 72° C. for 1 min. After terminating the reaction, the fragment encoding human FGF23 was digested with EcoRI and NotI, and then purified. This was cloned by inserting at the EcoRI and NotI restriction sites of pEAK8/IRES/EGFP vector, an animal cell expression vector, pEAKS (Edge Biosystem), to which the intramolecular ribosomal entry sequence (IRES) and enhanced green fluorescent protein (EGFP) were ligated. The nucleotide sequence of thus obtained plasmid was determined to confirm that it encodes human FGF23 protein. This vector was called pEAK8/IRES/EGFP/hFGF23.

LNot:
ATAAGAATGCGGCCGCTCAGATGAACTTGGCGAA (SEQ ID NO: 3)

Example 2

Expression of Recombinant Human FGF23 and Recombinant Mutant Human FGF23H Protein

(1) pcDNA/hFGF23H was Linearized by Cleaving the FspI Restriction Site

pcDNA/hFGF23H was linearized by cleaving the FspI restriction site in the ampicillin resistant gene in the vector and purified, and then mixed with CHO Ras clone-1 cells (Shirahata, S., et al., Biosci Biotech Biochem, 59: 345-347, 1995) and transfected to the cells by electroporation using Gene Pulser II (Bio Rad). After culturing these cells in MEM a medium (Gibco BRL) containing 10% FCS for 24 h, Zecocin (Invitrogen) was added to a final concentration of 0.5 mg/ml and then the cells were cultured for a week. Cells attached and grown were released by trypsinization and cloned by the limited dilution method in the presence of Zecocin at the final concentration of 0.3 mg/ml to obtain a multiplicity of cloned cells. The cell expressing human FGF23H most efficiently was identified by the Western blotting method. Culture supernatants of each cloned cell were collected and were subjected to SDS-polyacrylamide gel electrophoresis, and then proteins were transferred to a PVDF membrane (Millipore). A signal derived from FGF-23H protein was detected at about 32 kDa by using anti-His-tag (carboxy terminal) antibody (Invitrogen) and ECL photo-luminescent system (GE Healthcare Bioscience). As the result, the highest expression was found in a clone called #20, which was named as CHO-OST311H and deposited at International Patent Organism Depositary (IPOD) National Institute of Advanced Industrial Science and Technology (AIST) Tsukuba Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan on Aug. 11, 2000 (Deposition No.: FERM BP-7273). In the present description, CHO-OST311H is called CHO-hFGF23H.

(2) Obtaining of Human FGF23 Expressing Cells

Transfection of pEAK8/IRES/EGFP/hFGF23 vector to CHO Ras clone-1 cells was carried out by the gene transfection method using a membrane fusion lipid. CHO Ras clone-1 cells were cultured in 6 well plates until about 60% of the bottom of the well was covered by the cells, and then the culture medium was removed and 1 ml of MEMα medium without serum was added. Each of 2.5 μg of the vector to be introduced and 10 μl of Transfectam (Registered Trademark) (Promega) was mixed with 50 μl of MEMα medium without serum, and then both solutions were mixed and left standing for 10 min. The mixtures were added to wells of 6 well plates prepared beforehand. After incubating for 2 hours, the culture medium containing DNA was removed, replaced with a medium containing 10% FCS, and the culture was incubated overnight. Next day, Puromycin (Sigma) was added to a final concentration of 5 μg/ml to select drug resistant cells. The drug resistant cells thus obtained were cloned by the limited dilution method. Further, the cell line expressing the target protein most efficiently was obtained by Western blotting method. This cell line was called CHO-hFGF23.

(3) Expression and Detection of Recombinant Human FGF23 Protein in Animal Cells

Western blotting of the recombinant in the culture supernatant of CHO-hFGF23H using the antibodies against the carboxy terminal anti-His6 tag sequence detected bands of about 32 kDa and about 10 kDa. These 2 bands were excised out of the gel, and the amino acid sequences of the amino terminals were determined. In the larger molecular weight band (about 32 kDa), the sequence from amino acid 25 of SEQ ID NO: 4 was detected and it appeared to be human FGF23 protein from which the signal sequence was removed during the process of excretion. On the other hand, in the band having a smaller molecular weight, the sequence from amino acid 180 of SEQ ID NO: 4 was confirmed and it turned out that this fragment was the carboxy terminal fragment produced by the cleavage between amino acid 179 and 180. Also, the presence of a polypeptide having the sequence from amino acid 179 to the amino terminal (amino terminal fragment) was recognized by detecting it using polyclonal antibody which recognizes the amino terminal side of human FGF23 (International Publication No. WO02/14504 Pamphlet).

Similarly, in the culture supernatant of CHO-hFGF23 having no His6-tag sequence, the cleavage between amino acid

residue 179 and 180 was confirmed (International Publication No. WO02/14504 Pamphlet). Therefore, following operations were carried out to separate and purify the full length human FGF23 protein, which appears not to be cut, having the sequence from amino acid 25 to amino acid 251 of SEQ ID NO: 4 (sometimes referred to as full length FGF23) from the amino terminal or carboxy terminal fragments.

(4) Purification of Recombinant Full Length Human FGF23 Protein

The culture supernatant of CHO-hFGF23 was filtered through SuperCap (Registered Trade Mark) (Pall Gelman Laboratory) which is a membrane filter having 0.2 μm pore size, and the filtrate was passed through SP-Sepharose FF (GE Healthcare Bioscience). Substances having weak affinity to the column was washed and eluted with 50 mM sodium phosphate buffer, pH 6.7. This fraction contained the carboxy terminal fragment generated by the cleavage between amino acid 179 and 180. Protein held by the column was eluted with NaCl concentration gradient from 0 to 0.7 M, and full length human FGF23 protein was observed in the fraction eluted with about 0.3 M NaCl. Next, full length human FGF23 protein was absorbed to Talon Superflow (Registered Trade Mark) (Clonetech), which is a metal affinity column, washed with 50 mM sodium phosphate buffer, pH 6.7 and then eluted by adding imidazole at different concentrations. The fraction containing the target protein was absorbed to a SP sepharose FF column and eluted for further purification.

Human FGF23 amino acid sequence (SEQ ID NO: 4)
MLGARLRLWV CALCSVCSMS VLRAYPNASP LLGSSWGGLI

HLYTATARNS YHLQIHKNGH VDGAPHQTIY SALMIRSEDA

GFVVITGVMS RRYLCMDFRG NIFGSHYFDP ENCRFQHQTL

ENGYDVYHSP QYHFLVSLGR AKRAFLPGMN PPPYSQFLSR

RNEIPLIHFN TPIPRRHTRS AEDDSERDPL NVLKPRARMT

PAPASCSQEL PSAEDNSPMA SDPLGVVRGG RVNTHAGGTG

PEGCRPFAKF I

Example 3

Production of Mice Producing Human Antibody (KM Mice)

Mice producing complete human antibody for preparation of human monoclonal antibody have the homozygous genetic background for destructed endogenous both Ig heavy chain and kappa-light chain and also for having the chromosome 14 fragment (SC20) containing the human Ig heavy chain gene loci and the human Ig kappa chain trans gene (KCo5) at the same time. These mice were produced by cross-breeding the strain A mouse which has the human Ig heavy chain gene loci and the strain B mouse which has the human Ig kappa chain trans gene. The strain A is homozygous for destructed endogenous both Ig heavy chain and the kappa light chain, and is a mouse line having the chromosome 14 fragment (SC20) which can be transmitted to offsprings. This line of mouse is described, for example, in the report by Tomizuka et al., (Tomizuka, et al., Proc Natl. Acad. Sci. USA., 97: 722-727, 2000). Also, the strain B is homozygous for destructed endogenous both Ig heavy chain and the kappa light chain and is a transgenic mouse line having the human Ig kappa chain trans gene (KCo5). This line of mouse is described, for example, in the report by Fishwild et al., (Nat. Biotechnol., 14; 845-851, 1996).

In the following experiments, used are individual mice, which are obtained by crossing a male strain A mouse and a female strain B mouse, or a male strain B mouse and a female strain A mouse, and in which human Ig heavy chain and kappa light chain are detected at the same time in the serum [Ishida & Lonberg, IBC's 11th Antibody Engineering, Abstract 2000]. Furthermore, the mice producing human antibody can be obtained from Kirin Beer Company by contracting.

Example 4

Preparation of Human Monoclonal Antibody Against Human FGF23

(1) Obtaining a Hybridoma Producing Human Monoclonal Antibody Against Human FGF23

Monoclonal antibodies used in the present Examples are prepared according to the general method described in, such as, "Introduction to monoclonal antibody experimental manipulation" by Tamio Ando et al., Published by Kodansha, 1991. Full length human FGF23 protein prepared in Example 2 was used as an immunogen, and the human antibody producing mice produced in Example 3 which produce human immunoglobulin were immunized.

First, to prepare human monoclonal antibody against FGF23, purified full length human FGF23 protein prepared in Example 2 was mixed with RIBI adjuvant (Corixa) and inoculated intraperitoneally to human antibody producing mice at a dose of 20 μg/mouse as the first immunization. Similar to the first immunization, the mixture of purified FGF23 and RIBI adjuvant was inoculated total 3 times at 2 weeks intervals. Five mice were used for immunization, blood samples were collected after the third immunization, and the presence of human IgG antibody against FGF23 in sera was confirmed by the enzyme labeled immunosorbent assay (ELISA) method as described below. The mouse was selected which showed the highest serum value by the ELISA using FGF23 fixed on the solid phase with anti-FGF23 protein mouse monoclonal antibody, 3CIE, which was disclosed in International Publication No. WO03/057733 Pamphlet (anti FGF23 antibody produced by the hybridoma deposited as FERM BP-7839) and was immunized by 20 μg of full length human FGF23 protein/mouse via tail vein administration 3 days before taking the spleen out as described below.

The spleen was surgically taken out of the immunized mice, immersed in 10 ml of the DMEM containing 350 mg/mL of sodium bicarbonate, 50 units/mL of penicillin, 50 μg/mL streptomycin and no serum (Invitrogen, called DMEM without serum, hereinafter) and crushed on a mesh (Cell strainer: Falcon)) using a spatula. The cell suspension which passed through the mesh was centrifuged to precipitate cells, and then the cells were washed twice with DMEM without serum and suspended in DMEM without serum to measure the cell number. While, myeloma cells, SP2/0 (ATCC No. CRL-1581) were cultured in DMEM (Invitrogen) containing 10% FCS (Sigma) (called DMEM with serum, hereinafter) at 37° C. under 5% carbon dioxide gas so that cell density does not exceed 1×106 cells/mL. These myeloma cells were similarly washed with DMEM without serum, suspended in the same medium and counted. Recovered spleen cell suspension and mouse myeloma cell suspension were mixed at the cell number ratio 5:1, centrifuged and the supernatant was completely removed. To this cell pellet, 1 mL

of 50% (w/v) polyethylene glycol 1500 (Boehringer-Manheim) as a fusion agent was added slowly while stirring the pellet with a tip of a pipette, and then 1 mL of DMEM without serum that was pre-warmed at 37° C. was added slowly in 2 portions and further 7 mL of DMEM without serum was added. After centrifuging, the supernatant was removed and the fused cells thus obtained were subjected to screening by the limited dilution method as described below. The hybridoma selection was carried out by culturing in DMEM containing 10% FCS and IL-6 (10 ng/mL)(or 10% hybridoma cloning factor (called HCF, hereinafter): Biobase), and hypoxanthine (H), aminopterin (A) and thymidine (T) (called HAT, hereinafter: Sigma). Further, single clones were obtained by the limited dilution method using DMEM containing HT (Sigma), 10% FCS and 10% HCF. Culturing was conducted in 96 well microtiter plates (Becton, Dickinson). Selection of hybridoma clones producing anti-FGF23 human monoclonal antibody (screening) and characterization of human monoclonal antibody produced by respective hybridomas were conducted by the enzyme labeled immunosorbent assay (ELISA) as described below. As the results, many hybridomas were obtained which contained human immunoglobulin γ chain (hIgγ) and human immunoglobulin light chain κ, and produced human monoclonal antibody having the specific reactivity to human FGF23. Among a number of hybridomas obtained, 2 clones (C10 and C15) were particularly obtained as hybridomas producing an antibody which recognizes the FGF23 protein. Furthermore, in all the Examples described below including this Example, the hybridoma clones that produce the anti-FGF23 human monoclonal antibody of the present invention were designated using symbols. Still further, "antibody" affixed before or after these symbols indicates the antibody produced by the hybridoma or recombinant antibody produced by host cells carrying the antibody gene (full length or variable region) isolated from the hybridoma. Also, to the extent where the context clearly indicates, the name of the hybridoma clone may indicate the name of the antibody. The hybridoma clone C10 has been deposited at International Patent Organism Depositary (IPOD) National Institute of Advanced Industrial Science and Technology (AIST) Tsukuba Central 6, 1-1-1 Higashi, Tsukuba, Ibaraki, Japan on Feb. 2, 2007 (Deposition No.: FERM ABP-10772) (Label for ID: C10).

(2) Purification of C10 and C15 Antibody from the Culture Supernatant of the Hybridoma

C10 and C15 hybridoma obtained in Example 4 was conditioned to eRDF medium (Kyokuto Seiyaku) containing bovine insulin (5 μg/ml, Invitrogen), human transferrin (5 μg/ml, Invitrogen), ethanoamine (0.01 mM, Sigma), sodium selenite (2.5×10-5 mM, Sigma), 1% Low IgG Fetal Bovine Serum (Hyclone). The hybridoma was cultured in a flask and the culture supernatant was recovered. The culture supernatant was affinity-purified using Protein G Fast Flow gel (GE Healthcare, Bioscience), PBS(−) as an absorption buffer and 0.1 M glycine buffer (pH 2.8) as an elution buffer. The eluted fraction was adjusted to about pH 7.2 by adding 1 M Tris (pH 9.0). The antibody solution thus prepared was replaced by PBS using a Sephadex G25 desalting column (NAP column; GE Healthcare Bioscience) and sterilized by filtration with a membrane filter MILLEX-GV with 0.22 μm pore size (Millipore) to obtain purified C10 and C15 antibody. The concentration of the purified antibody was calculated by measuring 280 nm absorption and by assuming 1 mg/mL as 1.4 OD.

Example 5

Obtaining the Antibody Gene Encoding C10 Antibody and Determination of the Sequence Thereof

(1) Synthesis of cDNA of C10 Antibody

To obtain the DNA fragment containing the variable regions of human antibody heavy chain and light chain which are expressed in C10 hybridoma, cloning by the 5' RACE method (5' rapid amplification of cDNA ends) was carried out using primers specific to the constant regions of heavy and light chain of human antibody. More particularly, the cloning was carried out using the BD SMART RACE cDNA Amplification Kit (Becton Dickinson Bioscience Clonetech) following the manufacturer's instruction.

RNA extraction reagent, ISOGEN (Nippon Gene), was added to C10 hybridoma and 15 μg of total RNA was purified as the material for cDNA synthesis according to the manufacturer's instruction. The 1st strand of cDNA was prepared using about 1 μg of each purified total RNA as a template. All the reagents and enzymes except RNA used were provided by the BD SMART RACE cDNA Amplification Kit.

In the 1st strand cDNA synthesis,

Total RNA	1 μg/3 μl
5'CDS	1 μl
SMART Oligo	1 μl

the reaction mixture with the above composition was incubated at 70° C. for 2 min, and then

5 x Buffer	2 μl
DTT	1 μl
dNTP mix	1 μl
PowerScript Reverse Transcriptase	1 μl

were added and incubated at 42° C. fir 1.5 h.

Further, 50 μl of Tricine-EDTA Buffer was added and then incubated at 72° C. for 7 min to obtain the 1st strand of cDNA.

(2) Amplification of the Heavy Chain Gene and the Light Chain Gene by PCR and Confirmation of the Nucleotide Sequences.

(2)-1; Amplification of the Heavy Chain Gene and the Light Chain Gene by PCR.

To amplify the cDNA of the gene encoding C10 antibody, following reaction mixture was prepared and subjected to PCR, using a PCR primer set of the 3' primer having the sequence specific to human antibody (the particular sequence is described later) and the 5' primer (Universal primer A mix) that hybridizes specifically to the sequence added to the 5' terminal of the cDNA synthesized by the BD SMART RACE cDNA Amplification Kit, and KOD-Plus-DNA polymerase (Toyobo) as PCR enzyme.

sterile H2O	28 μl
1st strand cDNA	2.5 μl
KOD-Plus- buffer (10X)	5 μl
dNTP Mix (2 mM)	5 μl
MgSO4 (25 mM)	2 μl
KOD-Plus- (1 unit/μl)	1 μl
Universal primer A mix (UPM) (10X)	5 μl
Gene specific primers (GSP) (10 μM)	1.5 μl
Total volume	50 μl

For the amplification of the heavy chain gene, the set of UPM primer in the SMART RACE cDNA Amplification Kit and IgG1p primer (SEQ ID NO: 5) was used, while for the amplification of the light chain gene, the set of UPM primer and hk-2 (SEQ ID NO: 6) primer was used.

IgG1p:
TCTTGTCCACCTTGGTGTTGCTGGGCTTGTG (SEQ ID NO: 5)

hk-2:
GTTGAAGCTCTTTGTGACGGGCGAGC (SEQ ID NO: 6)

Also, the reaction condition used is as follows.

5 cycles of 94° C./30 sec and 72° C./3 min were repeated,

5 cycles of 94° C./30 sec, 70° C./30 sec and 72° C./3 min were repeated, and

25 cycles of 94° C./30 sec, 68° C./30 sec and 72° C./3 min were repeated.

Further, this reaction mixture 2 μl was diluted by adding 98 μl of Tricine-EDTA Buffer, and the second (nested) PCR was carried out using 5 μl of the diluted mixture as a template. The composition of the PCR reaction solution is as follows:

sterile H2O	30 μl
The first PCR reaction solution (50 fold dilution)	5 μl
KOD-Plus- buffer (10X)	5 μl
dNTP Mix (2 mM)	5 μl
MgSO4 (25 mM)	2 μl
KOD-Plus- (1 unit/μl)	1 μl
Nested Universal primer A (NUP; 10 μM)	1 μl
Gene specific primers (GSP) (10 μM)	1 μl
Total volume	50 μl

As a primer set for the amplification of the heavy chain gene in the above reaction, NUP primer (in the SMART RACE cDNA Amplification Kit; Becton Dickinson Bioscience Clonetech) and hh2 primer (SEQ ID NO: 7) were used, and for the amplification of the light chain gene, UPM primer and hk-5 primer (SEQ ID NO: 8) were used. The reaction temperature condition was as follows: at 94° C. as the initial temperature for 1 min, then 20 cycles of 94° C./5 sec, 68° C./10 sec and 72° C./3 min were repeated. Finally heating at 72° C./7 min was carried out.

hh2:
GCTGGAGGGCACGGTCACCACGC (SEQ ID NO: 7)

hk-5:
AGGCACACAACAGAGGCAGTTCCAGATTTC (SEQ ID NO: 8)

(2)-2; Determination of the Nucleotide Sequence of the Antigen Gene

The amplified heavy chain PCR fragment (hereinafter, referred to as HV[C]: consisting of the 5'-untranslated region-leader sequence, variable region (HV) and a part of constant region ([C]) of the H chain), and the amplified light chain PCR fragment (hereinafter, referred to as LV[C]: consisting of the 5'-untranslated region-leader sequence, variable region (LV) and a part of constant region ([C]) of the L chain) were recovered by ethanol precipitation, and then subjected to agarose gel electrophoresis. Recovered fragments were purified by a DNA purification kit using a membrane, QIAquick Gel Extraction Kit (Qiagen). The purified HV[C] amplified fragment or LV[C] amplified fragment was subcloned in PCR 4 Blunt-TOPO vector of Zero Blunt TOPO PCR Cloning Kit (Invitrogen) and the nucleotide sequence of the insert DNA was analyzed for the plasmid DNA of the clone obtained. The primers used for DNA nucleotide sequence were M13-20FW (SEQ ID NO: 9) and M13RV (SEQ ID NO: 10).

M13-20FW: GTAAAACGAC GGCCAGTG (SEQ ID NO: 9)

M13RV: CAGGAAACAGCTATGAC (SEQ ID NO: 10)

DNA nucleotide sequence encoding the heavy chain variable region and light chain variable region, and amino acid sequence of heavy chain variable region and light chain variable region of C10 antibody are show below.

<C10 heavy chain nucleotide sequence> (from the ATG initiation codon to the DNA sequence encoding the carboxy terminal amino acid residues of the variable region) (SEQ ID NO: 11)

```
        10         20         30         40         50         60
ATGGACTGGA CCTGGAGGGT CTTCTGGTTG CTGGCTGTAG CTCCAGGTGC TCACTCCCAG

        70         80         90        100        110        120
GTGCAGCTGG TGCAGTCTGG GGCTGAGGTG AAGAAGCCTG GGGCCTCAGT GAAGGTTTCC

       130        140        150        160        170        180
TGCAAGGCAT CTGGATACAC CTTCACCAAC CACTATATGC ACTGGGTGCG ACAGGCCCCT

       190        200        210        220        230        240
GGACAAGGGC TTGAGTGGAT GGGAATAATC AACCCTATTA GTGGTAGGAC AAGTAACGCA

       250        260        270        280        290        300
CAGAAGTTCC AGGGCAGAGT CACCATGACC AGGGACACGT CCACGAGCAC AGTCTACATG
```

-continued

```
      310        320        330        340        350        360
GAGCTGAGCA GCCTGAGATC TGAGGACACG GCCGTGTATT ATTGTGCGAG AGATATTGTG

      370        380        390        400        408
GATGCTTTTG ATTTCTGGGG CCAAGGGACA ATGGTCACCG TCTCTTCA
```

<C10 heavy chain amino acid sequence> (to the leader sequence and variable region) (SEQ ID NO: 12) (Underlined amino acid residues represent the leader sequence as a secretion signal)

```
       10         20         30         40         50         60
MDWTWRVFCL LAVAPGAHSQ VQLVQSGAEV KKPGASVKVS CKASGYTFTN HYMHWVRQAP

       70         80         90        100        110        120
GQGLEWMGII NPISGSTSNA QKFQGRVTMT RDTSTSTVYM ELSSLRSEDT AVYYCARDIV

      130      136
DAFDFWGQGT MVTVSS
```

<C10 light chain nucleotide sequence> (from the ATG initiation codon to the DNA sequence encoding the carboxy terminal amino acid residues of the variable region) (SEQ ID NO: 13)

```
       10         20         30         40         50         60
ATGGACATGA GGGTCCCCGC TCAGCTCCTG GGGCTTCTGC TGCTCTGGCT CCCAGGTGCC

       70         80         90        100        110        120
AGATGTGCCA TCCAGTTGAC CCAGTCTCCA TCCTCCCTGT CTGGATCTGT AGGAGACAGA

      130        140        150        160        170        180
GTCACCATCA CTTGCCGGGC AAGTCAGGGC ATTAGCAGTG CTTTAGTCTG GTATCAGCAG

      190        200        210        220        230        240
AAACCAGGGA AAGCTCCTAA GCTCCTGATC TATGATGCCT CCAGTTTGGA AAGTGGGGTC

      250        260        270        280        290        300
CCATCAAGGT TCAGCGGCAG TGGATCTGGG ACAGATTTCA CTCTCACCAT CAGCAGCCTG

      310        320        330        340        350        360
CAGCCTGAAG ATTTTGCAAC TTATTACTGT CAACAGTTTA ATGATTACTT CACTTTCGGC

      370        380    384
CCTGGGACCA AAGTGGATAT CAAA
```

<C10 light chain amino acid sequence> (to the leader sequence and variable region) (SEQ ID NO: 14) (Underlined amino acid residues represent the leader sequence as a secretion signal)

```
       10         20         30         40         50         60
MDMRVPAQLL GLLLLWLPGA RCAIQLTQSP SSLSASVGDR VTITCRASQG ISSALVWYQQ

       70         80         90        100        110        120
KPGKAPKLLI YDASSLESGV PSRFSGSGSG TDFTLTISSL QPEDFATYYC QQFNDYFTFG

      128
PGTKVDIK
```

Further, in the gene sequence of C10 antibody subcloned in PCR 4 Blunt-TOPO vector, a part of the constant region of the human antibody sequence was cloned and the DNA nucleotide sequence of this region was also analyzed. The result indicated that the presence of the sequence encoding the amino acid residue 118 to 191 in the heavy chain constant

region which is shown by the EU index by Kabat et al., was confirmed and was in complete agreement with the amino acid sequence of human IgG1, and thus it was determined that the subclass of C10 antibody was IgG1. In addition, the antibody gene encoding C15 antibody was obtained and the sequence thereof was determined by using the same method.

Example 6

Construction of Recombinant C10 Antibody Expression Vector

Production of C10 expression vector (Process scheme is shown in FIG. **1**)

The DNA of LV (light chain leader sequence+variable region) of C10 antibody was amplified by PCR by KOD-Plus-DNA polymerase using obtained plasmid DNA containing LV[C] chain of C10 antibody as a template and primers C10_L5_Bg1 (SEQ ID NO: 15) and C10_L3_Bs1 (SEQ ID NO: 16) which were designed to add restriction enzyme sites (5' terminal BglII, 3' terminal BsiWI) for linkage to the ends. The reaction temperature condition was: after heating for 1 min at the starting temperature 94° C., a cycle of 94° C./5 sec and 68° C./45 sec was repeated 35 times and a final heating 72° C./7 min. The amplified DNA fragment was digested with restriction enzymes BglII and BsiWI and purified by recovering 400 bp DNA from agarose gel electrophoresis. While the vector DNA, N5KG1-Val Lark vector (IDEC Pharmaceuticals, a modified vector of N5KG1 (U.S. Pat. No. 6,001,358)) was similarly digested with restriction enzymes BglII and BsiWI sequentially, subjected to dephosphorylation treatment with Alkaline Phosphatase (*E. coli* C75) (Takara Shuzo Co., Ltd.) and then recovered as a little smaller than about 9 kb DNA after purification by agarose gel electrophoresis and subcloned in pCR4Blunt-TOPO vector as a template and the primers, C10_H5_Sal (SEQ ID NO: 17) and C10_H3_Nhe (SEQ ID NO: 18) designed to add restriction enzyme sites (SalI at the 5' terminal, NheI at 3' terminal) for linkage to the ends. The reaction temperature condition was: after heating for 1 min at the starting temperature 94° C., a cycle of 94° C./5 sec and 68° C./45 sec was repeated 35 times and a final heating 72° C./7 min. Purified HV amplified DNA fragment was subcloned in pCR4Blunt-TOPO vector, and the insert DNA of thus obtained clones of plasmid DNA analyzed by sequencing. The primers used for DNA sequencing were M13-20FW and M13RV described above. The inserted part of the subclones was analyzed by DNA sequencing, and the plasmid DNA (TOPO_C10_HV), which had no difference with the template HV and the primer parts were also the same sequence as designed, was selected. This DNA was digested with restriction enzymes, SalI and NheI, subjected to agarose gel electrophoresis, and the DNA fragment which was about 420 bp was recovered and purified, and was ligated using T4 DNA ligase to N5KG1_C10_Lv DNA (about 9 kb) which was similarly subjected to restriction enzyme treatment (SalI and NheI) and dephosphorylation. The ligation product was introduced into *E. coli* DH10B and the target plasmid DNA was selected from the transformants thus obtained. The antibody expressing plasmid DNA, N5KG1_C10_IH (clone #1) obtained in this way was mass produced and purified, and it was confirmed that no change was introduced during the cloning process in the DNA nucleotide sequence of the entire region of L chain and H chain and around the inserted site (FIGS. **2** and **3**). Confirmation of the DNA sequence was carried out by using primers of SEQ ID NO: 19-25. Simplified map of C10 antibody expression vector is shown in FIG. **4**. In addition, a recombinant C15 antibody expression vector was constructed by using the same method.

C10_L5_Bgl:	GAGAGAGAGATCTCTCACCATGGACATGAGGGTCCCCGCT	(SEQ ID NO: 15)
C10_L3_Bsi:	AGAGAGAGAGCGTACGTTTGATATCCACTTTGGTCCCAGGGC	(SEQ ID NO: 16)
C10_H5_Sal:	AGAGAGAGAGGTCGACCACCATGGACTGGACCTGGAGGGTCTTC	(SEQ ID NO: 17)
C10_H3_Nhe:	AGAGAGAGAGGCTAGCTGAAGAGACGGTGACCATTGTCCC	(SEQ ID NO: 18)
hh-4:	GGTGCCAGGGGGAAGACCGATGG	(SEQ ID NO: 19)
hh-1:	CCAAGGGCCCATCGGTCTTCCCCCTGGCAC	(SEQ ID NO: 20)
CMVH903F:	GACACCCTCATGATCTCCCGGACC	(SEQ ID NO: 21)
CMVHR1303:	TGTTCTCCGGCTGCCCATTGCTCT	(SEQ ID NO: 22)
SEQU4618:	TCTATATAAGCAGAGCTGGGTACGTCC	(SEQ ID NO: 23)
hk-1:	TGGCTGCACCATCTGTCTTCATCTTC	(SEQ ID NO: 24)
SEQU1783:	GGTACGTGAACCGTCAGATCGCCTGGA	(SEQ ID NO: 25)

DNA purification kit. These 2 fragments were ligated with T4 DNA ligase and transfected to *E. coli* DH10B to obtain transformants. Plasmid DNA of the transformants, which contained the insert DNA, was subjected to DNA nucleotide sequence analysis, and plasmid DNA, N5KG1_C10_LV, in which LV of C10 antibody was inserted in frame at 5' upstream of human antibody light chain constant region of N5KG1-Val Lark was obtained. Next, the HV (the leader sequence+variable region of heavy chain) of C10 antibody was inserted to the plasmid vector in which LV was inserted (N5KG1_C10-$_{13}$ Lv). The HV was amplified by PCR using the plasmid DNA containing the HV[C] of C10 antibody

Example 7

Preparation of Recombinant C10 Antibody

C10 antibody expressing cells were produced by introducing the constructed C10 antibody expression vector to host cells. A strain of dihydrofolate reductase (DHFR) deletion mutant CHO DG44 cells (hereinafter, referred to as CHO cells, IDEC Pharmaceuticals), conditioned to a serum-free medium, EX-CELL325 PF medium (JRH, containing 2 mM glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, hypoxanthine and thymidine (HT) supplement (1:100) (Invit-

rogen)) was used as host cells for expression. Introduction of the vector to the host cells was carried out by electroporation. The gene was introduced to 4×106 CHO cells by electroporation by linearizing about 2 μg of the C10 expression vector with a restriction enzyme AscI and using a BioRad Electroporator at 350 V, 500 μF, and then cells were seeded to 96 cell culture plates. After introducing the vector to the cells, G418 was added and the culture was continued. After confirming colonies, strains expressing antibody were selected. The selected CHO cell lines were cultured in EX-CELL-325 PF medium (containing 2 mM glutamine, 100 units/ml penicillin, 100 μg/ml streptomycin, hypoxanthine and thymidine (HT) supplement (1:100) (Invitrogen)) under 5% CO2. The culture supernatant was absorbed to a Mabselect Protein A column (GE Healthcare Bioscience), washed with PBS and eluted with 20 mM Na-citrate and 50 mM NaCl (pH 3.4) buffer. The eluate was neutralized to pH 7.0 with 50 mM sodium phosphate pH 7.0. The conductivity was adjusted to 4.0 ms/cm or below by diluting about 1.5 fold with deionized water. Next, the sample was applied to a linked column of Q-Sepharose (Hitrap Q HP, GE Healthcare Bioscience) and SP-Sepharose (Hitrap SP FF, GE Healthcare Bioscience) for absorption, washed with 20 mM sodium phosphate buffer (pH 5.0) and then eluted with PBS(−). The antibody solution thus prepared was filter sterilized through a 0.22 μm pore size membrane filter, MILLEX-GV (Millipore). The concentration of purified C10 antibody was calculated by measuring 280 nm absorption and by assuming 1 mg/mL as 1.4 OD. In addition, a recombinant C15 antibody was prepared by using the same method.

Example 8

Construction of Cynomolgus Monkey FGF23 Protein Expression Vector

(1) Construction of Cynomolgus Monkey FGF23 Protein Expression Vector

To EDTA treated venous blood of cynomolgus monkey, 5% Dextran T-2000 (GE Healthcare Bioscience) suspended in PBS (−) was mixed at the ratio of 2:1 to precipitate red blood cells. Then, the supernatant was layered on top of a lymphocyte separation solution (Ficoll-Plaque) (GE Healthcare Bioscience) and centrifuged to obtain the lymphocyte fraction. Lymphocytes thus obtained were suspended in ISOGEN-LS (Nippon Gene), and total lymphocyte RNA of cynomolgus monkey was obtained according to the attached protocol. From this total lymphocyte RNA of cynomolgus monkey, the lymphocyte cDNA library of cynomolgus monkey was prepared using First Strand cDNA Synthesis Kit (Invitrogen) according to the attached protocol. cDNA encoding cynomolgus monkey FGF23 was amplified using the lymphocyte cDNA library of cynomolgus monkey as a template, monkey FGF23FW primer (SEQ ID NO: 26) and monkey FGF23RV primer (SEQ ID NO: 27), and KOD plus DNA polymerase (Toyobo), and incubating at 94° C. for 5 min, then carrying out 45 cycles of a PCR step of heating at 94° C. for 20 sec, at 55° C. for 30 sec and at 72° C. for 50 sec. The monkey FGF23FW primer anneals to a sequence present in the 5' upstream region of the nucleotide sequence encoding human FGF23 and adds the EcoRI restriction site to the 5' side of the FGF23 coding region in the amplified fragment. The monkey FGF23RV primer contains a sequence which anneals to the sequence containing the stop codon of the human FGF23 coding region, and the Not I restriction site. This amplified fragment was digested with EcoRI and NotI, and cloned by inserting at the EcoRI and NotI restriction sites of pEAK8/IRES/EGFP vector, which is an expression vector pEAK8 (Edge Biosystem) to which internal ribosome entry site (IRES) and enhanced green fluorescent protein (EGFP) are linked. The nucleotide sequence of thus obtained plasmid was determined to confirm that it encodes a cynomolgus monkey FGF23 protein. This vector was called pEAK8/IRES/EGFP/monkeyFGF23. The nucleotide sequence and amino acid sequence of cynomolgus monkey FGF23 obtained in the present Example are shown in SEQ ID NO: 28 and 29, respectively.

monkeyFGF23FW:
GGAATTCCACCATGTTGGGGGCCCGCCTCAGGCT (SEQ ID NO: 26)

monkeyFGF23RV:
ATTTGCGGCCGCTAGATGAACTTGGCGAAGGGGC (SEQ ID NO: 27)

Nucleotide sequence of cynomolgus monkey FGF23 (SEQ ID NO: 28)

ATGTTGGGGGCCCGCCTCAGGCTCTGGGTCTGTGCCTTGTGCAGCGTCT
GCAGCATGAGCGTCATCAGAGCCTATCCCAATGCCTCCCCATTGCTCG
GCTCCAGCTGGGGTGGCCTGATCCACCTGTACACAGCCACAGCCAGGA
ACAGCTACCACCTGCAGATCCACAAGAATGGCCACGTGGATGGCGCAC
CCCATCAGACCATCTACAGTGCCCTGATGATCAGATCAGAGGATGCTG
GCTTTGTGGTGATTACAGGTGTGATGAGCAGAAGATACCTCTGCATGG
ATTTCGGAGGCAACATTTTTGGATCACACTATTTCAACCCGGAGAACTG
CAGGTTCCGACACTGGACGCTGGAGAACGGCTACGACGTCTACCACTC
TCCTCAGCATCACTTTCTGGTCAGTCTGGGCCGGGCGAAGAGGGCCTTC
CTGCCAGGCATGAACCCACCCCCCTACTCCCAGTTCCTGTCCCGGAGG
AACGAGATCCCCCTCATCCACTTCAACACCCCCAGACCACGGCGGCAC
ACCCGGAGCGCCGAGGACGACTCGGAGCGGGACCCCCTGAACGTGCT
GAAGCCCCGGGCCCGGATGACCCCGGCCCCGGCCTCCTGCTCACAGGA
GCTCCCGAGCGCCGAGGACAACAGCCCGGTGGCCAGCGACCCGTTAGG
GGTGGTCAGGGGCGGTCGGGTGAACACGCACGCTGGGGGAACGGGCC
CGGAAGCCTGCCGCCCCTTCGCCAAGTTCATCTAG

Amino acid sequence of cynomolgus monkey FGF23 (SEQ ID NO: 29)

MLGARLRLWV CALCSVCSMS VIRAYPNASP LLGSSWGGLI
HLYTATARNS YHLQIHKNGH VDGAPHQTIY SALMIRSEDA
GFVVITGVMS RRYLCMDFGG NIFGSHYFNP ENCRFRHWTL
ENGYDVYHSP QHHFLVSLGR AKRAFLPGMN PPPYSQFLSR
RNEIPLIHFN TPRPRRHTRS AEDDSERDPL NVLKPRARMT
PAPASCSQEL PSAEDNSPVA SDPLGVVRGG RVNTHAGGTG
PEACRPFAKF I

(2) Preparation of Supernatant of Cynomolgus Monkey FGF23 Expressing Cells

pEAK8/IRES/EGFP/monkey FGF23 was transiently transfected to PEAK rapid cells (Edge Biosystem) by the calcium phosphate method, and their culture supernatant was obtained.

Example 9

Investigation for Binding of C10 to Antibody Cynomolgus Monkey FGF23

The fact that C10 antibody binds not only to human FGF23 but also cynomolgus monkey FGF23 was investigated by the following method using sandwich ELISA. C10 antibody prepared in Example 4, 2C3B antibody and human IgG1 control antibody were diluted in 50 mM NaHCO3 solution to a concentration of 5 μg/ml and added to each well of 96 well microtiter plates for ELISA (Maxisorp (Registered Trade Name), Nunc), incubated at 4° C. for 12 hours. Thus, C10 antibody, 2C3B antibody and human IgG1 control antibody as a control were absorbed to microplates. Next, these solutions were removed, and a blocking reagent (SuperBlock (Registered Trade mark) Blocking buffer, PIERCE) was added to each well, incubated at room temperature for 30 min and then each well was washed twice with Tris-buffered saline (T-TBS) containing 0.1% Tween20. To each well of the microtiter plate to which anti-FGF23 antibodies were coated, full length human FGF23 protein purified in Example 2 or the expressing cell supernatant of cells expressing cynomolgus monkey FGF23 prepared in Example 8 was added after diluting to appropriate concentrations, reacted to antibody in solid phase for 2 hours, and then each well was washed twice with Tris-buffered saline (T-TBS) containing 0.1% Tween20. Next, biotin labeled 3C1E antibody at 3 μg/ml was added and incubated at room temperature for 1.5 hours to bind biotin labeled 3C1E antibody to human or cynomolgus monkey FGF23 bound to the antibody in solid phase. After washing with T-TBS, horseradish peroxidase labeled streptavidin (DAKO) diluted 5000 fold was reacted for 1 hour and washed 3 times with T-TBS. Next, a substrate buffer containing tetramethylbenzidine (DAKO) was added to each well and incubated at room temperature for 30 min. The reaction was stopped by addition of 0.5 M sulfuric acid to each well. Absorption at the wavelength of 450 nm with reference wavelength of 570 nm was measured using a microplate reader (MTP-300, Colona Electric Co.). Reactivity of human full length FGF23 protein and the culture supernatant of cynomolgus monkey FGF23 expressing cells were compared by diluting with factor of 3. The result is shown in FIGS. **5**A and B. As clearly shown in FIG. **5**A, the reactivity of C10 antibody or 2C3B antibody in solid phase to human full length FGF23 protein is about the same. To serially diluted culture supernatant of cynomolgus monkey FGF23 expressing cells under the conditions, not much difference is observed between the reactivity of C10 antibody and 2C3B antibody (FIG. **5**B). That is, C10 antibody, like 2C3B antibody, was proven to be able to bind to human and cynomolgus monkey FGF23.

Example 10

Comparison of the Effect of C10 Antibody and 2C3B Antibody on Normal Cynomolgus Monkey Blood Phosphorous Concentration and Blood 1α, 25 Dihydroxy Vitamin D Concentration

FGF23 has activities of excreting phosphorous from the kidney, reducing serum phosphorous concentration as well as inhibiting vitamin D activating enzyme and reducing blood 1α,25 dihydroxy vitamin D (hereinafter referred to as 1,25D) concentration (International Publication No. WO02/14504 Pamphlet). It has been demonstrated that administration of antibody, such as 2C3B antibody and the like, which has a suppressive effect, that is, neutralizing activity, on FGF23, to normal mice causes inhibition of endogenous FGF23 action and an increase of serum phosphorous concentration and serum 1,25D concentration (International Publication No. WO03/057733 Pamphlet). Thus, it has been strongly suggested that antibody having neutralizing activity on FGF23 has therapeutic effect on human diseases including tumor-induced osteomalachia, XLH and the like which are caused by excessive FGF23. Therefore, C10 antibody obtained in the present invention was investigated for FGF23 neutralizing activity in vivo. In particular, since its pharmacological effect on human is expected, the neutralizing effect was measured in monkeys, which are evolutionally more closely related to humans compared to species such as rodents, by using the suppression of the function of endogenous FGF23, increase of serum phosphorous concentration and increase of serum 1,25D concentration as indexes. Experiments were conducted using a mouse antibody, 2C3B antibody, as a comparative control for C10 antibody.

Effect of C10 antibody and 2C3B antibody on the increase of serum phosphorous concentration was compared in untreated normal cynomolgus monkeys by the following method. C10 antibody produced in Example 4 was used. Experimental animals used were female cynomolgus monkeys of 2-3 years old and body weight 2-4 kg. 3 animals were used in each group of the solvent administration and 2C3B antibody administration, and 4 animals were used in the C10 administration group. C10 and 2C3B antibodies were prepared in PBS (−) at a concentration of 3 mg/ml and used as an administration solution. The solvent, PBS (−), was used as a negative control. C10 and 2C3B antibodies were administered once from the brachial cephalic vein at a flow rate of 1 ml/min and amount of 3 mg/kg and 1 ml/kg. Serum phosphorous concentration was measured using L type Wako inorganic phosphorous reagent (Wako Pure Chemical Industries) and a Hitachi Clinical Analyzer Model 7180 (Hitachi, Ltd.). Serum 1,25D concentration was measured using 1, 25 $(OH)_2D$ RIA Kit [TFB] (Immunodiagnostic System). Measurements were carried out at day 0.5, 1, 2, 3, 5, 7, 10, 14, 21, 28, 35, 42, and 49 after the administration of antibody. Data were shown in average +/− standard error. FIG. **6** shows the transition of serum phosphorous concentration in periodically collected blood samples up to 10 days after the administration of each antibody. In the PBS (−) administered group, the serum phosphorous concentration was almost constant during the test period, while in the C10 antibody and 2C3B antibody administered groups a clear increase of the serum phosphorous concentration was observed when compared with before the administration and PBS (−) administered group. The day when the highest serum phosphorous concentration was observed in both C10 antibody administered group and 2C3B antibody administered group was 5 days after the administration of the antibodies. At this time point, the serum phosphorous concentration in PBS(−) group, 2C3B antibody group and C10 antibody group was 5.28 mg/dl, 8.10 mg/dl and 9.59 mg/dl, respectively. Comparing the serum phosphorous concentration of 2C3B antibody group and the C10 antibody group at 5 days after the administration of antibody with the serum phosphorous concentration of the PBS (−), the increase in the 2C3B antibody group was 2.82 mg/dl, while that of C10 antibody group was 4.31 mg, suggesting that C10 antibody induced about 1.5 times or higher increase in the serum phosphorous concentration compared to the 2C3B antibody (FIG. **7**). Thus the increase effect in the serum phosphorous concentration in C10 antibody adminis-

tered group is markedly higher compared to that in the 2C3B antibody administered group. Further, at 10 days after the administration the serum phosphorous concentration in the 2C3B antibody administered group was at the same level as that in PBS (−) group, while the serum phosphorous concentration in the C10 administered group (8.76 mg/dl) was still maintaining higher level than the highest level (8.10 mg/dl) in the 2C3B antibody administered group (FIG. **6**). Further, the increased serum phosphorous concentration by C10 antibody is sustained far longer than that by 2C3B antibody. The duration, in which the significant difference of the serum phosphate concentration from the PBS (−) group was observed, was 7 days for the 2C3B group, while it was surprisingly 35 days, about 5 times longer, in the C10 antibody group. Similarly, for 1,25D concentration, after the administration C10 antibody demonstrated a marked increase and elongation of the sustained increased duration compared to 2C3B antibody (FIG. **8**). These results demonstrate that in cynomolgus monkeys C10 antibody have more powerful increasing activity for serum phosphorous concentration and serum 1,25D concentration, that is, having more powerful FGF23 neutralizing activity. The current treatment for hypophosphatemic rickets in XLH at this time requires a large dose of multiple administrations of phosphorous and vitamin D formulations per day to barely maintain the normal range of the phosphorous concentration. There are reports of poor compliance of patients due to the plurality of administrations to take. The fact that in the single administration of C10 antibody in the present study, a sustained raising activity on serum phosphorous concentration and serum 1,25D concentration was observed suggests that C10 antibody has possibly a marked advantage as a therapeutic drug for hypophosphatemia over conventional therapy.

Example 11

Confirmation of Reactivity of C15 Antibody to Human and Cynomolgus Monkey FGF23

pEAK8/IRES/EGFP/hFGF23 prepared in Example 1 or pEAK8/IRES/EGFP/monkey FGF23 prepared in Example 8 was transiently transfected into PEAK rapid cells (Edge Biosystem) by the calcium phosphate method. Each culture supernatant was collected 3 days after introduction. Western blotting of the collected culture supernatant was performed using C15 antibody prepared in Example 13 as a primary antibody (FIG. **9**). As a result, C15 was shown to bind to cynomolgus monkey FGF23, similarly to human FGF23.

Example 12

Comparison of the Effect of C10 Antibody and C15 Antibody on Blood Phosphorous Concentration and Blood 1α,25 Dihydroxy Vitamin D Concentration in Normal Cynomolgus Monkeys

Example 11 demonstrated that C15 antibody has binding activity with human and cynomolgus monkey FGF23 recombinant proteins as does C10 antibody. Subsequently, FGF23 neutralizing activity of C10 antibody and C15 antibody in vivo was compared by administering the antibodies to normal cynomolgus monkeys. The neutralizing activity on cynomolgus monkey endogenous FGF23 was evaluated by using the increase in serum phosphorous concentration as an index. The C10 antibody and C15 antibody produced in Example 7 were used. Normal cynomolgus monkeys of 2-3 years old and body weight 2-3 kg were used as experimental animals. 2 male animals and 1 female animal, totaling 3, were used in each group. The dilution medium used was PBS (−). C10 antibody was prepared at a concentration of 1 mg/ml and 3 mg/ml, and C15 antibody was prepared at a concentration of 3 mg/ml. The antibodies were administered once from the saphenous vein in a volume of 1 mL/kg at a flow rate of about 1 ml/min to achieve a dose of 1 mg/kg and 3 mg/kg for C10 antibody and a dose of 3 mg/kg for C15 antibody. Serum phosphorous concentration was measured using L type Wako inorganic phosphorous reagent (Wako Pure Chemical Industries) and a Hitachi Clinical Analyzer Model 7180 (Hitachi, Ltd.). Blood samples were taken before the administration of antibody, and at day 1, 3, 5, 7, 10, 14, 21 and 28 after the administration of antibody. Measurements of serum phosphorous concentration were conducted for all the blood sampling points. In the C10 antibody 1 mg/kg group, the C10 antibody 3 mg/kg group and the C15 antibody 3 mg/kg group, serum phosphorous concentrations before dosing were 5.37, 5.70 and 5.58 mg/dL, respectively, and there was no difference between groups. In all cynomolgus monkeys, the increase in serum phosphorous concentration was observed after the administration. Thus, not only C10 antibody but also C15 antibody were shown to have neutralizing activity on cynomolgus monkey endogenous FGF23. In the C10 antibody 1 mg/kg group, the C10 antibody 3 mg/kg group and the C15 antibody 3 mg/kg group, the serum phosphorous concentration 3 days after the administration was 9.03, 9.10 and 8.64 mg/dL, respectively. At this time point, the serum phosphorous concentration in the C10 antibody 1 mg/kg group and the C15 antibody 3 mg/kg group reached highest level. On the other hand, the serum phosphorous concentration in the C10 antibody 3 mg/kg group further increased and reached the highest level 5 days after the administration, and the level was 9.75 mg/dL. In the C10 antibody 1 mg/kg group, the C10 antibody 3 mg/kg group and the C15 antibody 3 mg/kg group, the maximum differences of serum phosphorous concentration between before and after administration were 3.67, 4.65 and 3.06 mg/dL, respectively. From this result, the effect of C10 antibody on the increase in serum phosphorous concentration was shown to be higher compared to that of C15 antibody at the same dose of 3 mg/kg. In addition, surprisingly, C10 antibody at a dose of 1 mg/kg increased the serum phosphorous concentration more than C15 antibody at a dose of 3 mg/kg. Next, the duration of serum phosphorus increase over the pre-dosing level was compared. As a result, the duration of phosphorus increment in the C10 antibody 1 mg/kg group, the C10 antibody 3 mg/kg group and the C15 antibody 3 mg/kg group was 14, 28 and 7 days, respectively. From this result, C10 antibody was shown to have a sustained raising activity of serum phosphorous concentration compared to that of C15 antibody at the same dose of 3 mg/kg. In addition, surprisingly, serum phosphorous concentration increased higher at peak and sustained high level much longer by C10 antibody at a dose of 1 mg/kg than by C15 antibody at a dose of 3 mg/kg. The above results demonstrate that in cynomolgus monkeys C10 antibody has more powerful increasing activity for serum phosphorous concentration and sustaining activity for serum phosphorous concentration compared to those of C15 antibody simultaneously obtained with C10 antibody. That is, C10 antibody

has significantly powerful neutralizing activity on cynomolgus monkey FGF23 compared to C15 antibody.

Example 13

Preparation of Human FGF23 DNA Fragment (Signal Sequence-Free)

A reaction solution was prepared by KOD-plus-DNA polymerase (Toyobo), following the manufacturer's instruction. Fifty pmol of FGF23(−SP) FW primer (SEQ ID NO: 34) and FGF23(−SP) RV primer (SEQ ID NO: 35), and human FGF23-cDNA (756 bp from the initiation codon to the stop codon, SEQ ID NO: 36) as the template were added up to 50 μl of the reaction solution. After incubating the mixture at 94° C. for 3 min, it was subjected to 30 cycles of a PCR step of heating at 98° C. for 15 sec, at 63° C. for 15 sec and at 68° C. for 2 min 30 sec. The mixture was then incubated at 72° C. for 3 min. The obtained 684 bp amplified fragment was separated and collected on a 0.8% gel. The amplified fragment was recovered from the collected gel by QIAquick Gel Extraction Kit (Qiagen), following the manufacturer's instruction. The collected PCR amplified fragment was digested with FseI (New England Biolabs Japan), and the enzyme-treated fragment was recovered by QIAquick PCR Purification Kit (Qiagen), following the manufacturer's instruction. As a result, a partial DNA fragment corresponding to the mature form region without the signal sequence of human FGF23 was obtained.

FGF23(-SP) FW: TATCCCAATGCCTCCCCACTGCTCGGCTCCAGCTG (SEQ ID NO: 34)

FGF23(-SP) RV: TTGGCCGGCCCTAGATGAACTTGGCGAAGGGGCGGCAGCCTTCCG (SEQ ID NO: 35, including the FseI site)

The nucleotide sequence of human FGF23 (nucleotides in the signal sequence region are underlined, and nucleotides in the mature form region excluding the signal sequence region from the full length are surrounded by a rectangular line.) (SEQ ID NO: 36)

ATGTTGGGGGCCCGCCTCAGGCTCTGGGTCTGTGCCTTGTGCAGCGTCTGCAGCATGAGCGTCCTCAGAGC
CTATCCCAATGCCTCCCCACTGCTCGGCTCCAGCTGGGGTGGCCTGATCCACCTGTACACAGCCACAGCCA
GGAACAGCTACCACCTGCAGATCCACAAGAATGGCCATGTGGATGGCGCACCCCATCAGACCATCTACAGT
GCCCTGATGATCAGATCAGAGGATGCTGGCTTTGTGGTGATTACAGGTGTGATGAGCAGAAGATACCTCTG
CATGGATTTCAGAGGCAACATTTTTGGATCACACTATTTCGACCCGGAGAACTGCAGGTTCCAACACCAGA
CGCTGGAAAACGGGTACGACGTCTACCACTCTCCTCAGTATCACTTCCTGGTCAGTCTGGGCCGGGCGAAG
AGAGCCTTCCTGCCAGGCATGAACCCACCCCCGTACTCCCAGTTCCTGTCCCGGAGGAACGAGATCCCCCT
AATTCACTTCAACACCCCCATACCACGGCGGCACACCCGGAGCGCCGAGGACGACTCGGAGCGGGACCCCC
TGAACGTGCTGAAGCCCCGGGCCCGGATGACCCCGGCCCCGGCCTCCTGTTCACAGGAGCTCCCGAGCGCC
GAGGACAACAGCCCGATGGCCAGTGACCCATTAGGGGTGGTCAGGGGCGGTCGAGTGAACACGCACGCTGG
GGGAACGGGCCCGGAAGGCTGCCGCCCCTTCGCCAAGTTCATCTAG

The amino acid sequence of human FGF23 based on SEQ ID NO: 36 as the standard (amino acid residues in the signal sequence region are underlined, and amino acid residues in the mature form region excluding the signal sequence region from the full length are surrounded by a rectangular line.) (SEQ ID NO: 37)

MLGARLRLWVCALCSVCSMSVLRAYPNASPLLGSSWGGLIHLYTATARNSYHLQIHKNGHVDGAPHQTIYS
ALMIRSEDAGFVVITGVMSRRYLCMDFRGNIFGSHYFDPENCRFQHQTLENGYDVYHSPQYHFLVSLGRAK
RAFLPGMNPPPYSQFLSRRNEIPLIHFNTPIPRRHTRSAEDDSERDPLNVLKPRARMTPAPASCSQELPSA
EDNSPMASDPLGVVRGGRVNTIIAGGTGPEGCRPFAKFI

Example 14

Construction of pPSs FGF23 Vector

pPSs5.5 described in Example 1-8 of WO2006/78072 was digested with SfoI and FseI, and its terminals were subjected to dephosphorylation treatment with Alkaline Phosphatase derived from *E. coli*. A DNA fragment including human FGF23 prepared in Example 13 was inserted to the vector. The vector was then introduced into DH5α, and DNA was prepared from the obtained transformants. The nucleotide sequence of the ligated region was confirmed to obtain pPSs FGF23 vector (FIG. **10**).

Example 15

Construction of pUS FGF23 KI Vector

pCk loxPVΔP described in Example 43-1 of WO2006/78072 was digested with SalI and FseI, and the terminals were subjected to dephosphorylation treatment with Alkaline Phosphatase derived from *E. coli* C75. After inserting a fragment of about 1.5 kb, wherein the fragment was separated and collected on a 0.8% agarose gel after digesting pPSs FGF23 vector prepared in the above Example 14 with SalI and FseI, the vector was then introduced into *E. coli* XL10-Gold Ultracompetent Cells (STRATAGENE). DNA was prepared from the obtained transformants. The nucleotide sequence of the ligated region was confirmed to obtain pUS FGF23 KI vector (FIG. **11**).

The polynucleotide sequence from the initiation codon to the stop codon of pUS FGF23 KI vector human FGF23 expression unit (985 bp containing mouse Igκ signal sequence including an intron region substituted to FGF23 signal sequence (the underlined part in SEQ ID NO: 38) and FGF23 mature form sequence in its downstream, SEQ ID NO: 38) and the amino acid sequence encoded by the cDNA (247 amino acids, the underlined part represents mouse Igκ signal sequence, SEQ ID NO: 39) are shown in the following. Sequence information of mouse Igκ signal sequence including an intron region was based on MUSIGKVR1 obtained from GenBank (Accession No. K02159), and the upstream genome sequence thereof was obtained from the UCSC mouse genome database.

SEQ ID NO: 38:
ATGGAGACAGACACACTCCTGTTATGGGTACTGCTGCTCTGGGTTCCAGGTGAGAGTGCAGAGAAGTGTTG
GATGCAACCTCTGTGGCCATTATGATACTCCATGCCTCTCTGTTCTTGATCACTATAATTAGGGCATTTGT
CACTGGTTTTAAGTTTCCCCAGTCCCCTGAATTTTCCATTTTCTCAGAGTGATGTCCAAAATTATTCTTAA
AAATTTAAATAAAAAGGTCCTCTGCTGTGAAGGCTTTTATACATATATAACAATAATCTTTGTGTTTATCA
TTCCAGGTTCCACTGGCTATCCCAATGCCTCCCCACTGCTCGGCTCCAGCTGGGGTGGCCTGATCCACCTG
TACACAGCCACAGCCAGGAACAGCTACCACCTGCAGATCCACAAGAATGGCCATGTGGATGGCGCACCCCA
TCAGACCATCTACAGTGCCCTGATGATCAGATCAGAGGATGCTGGCTTTGTGGTGATTACAGGTGTGATGA
GCAGAAGATACCTCTGCATGGATTTCAGAGGCAACATTTTTGGATCACACTATTTCGACCCGGAGAACTGC
AGGTTCCAACACCAGACGCTGGAAAACGGGTACGACGTCTACCACTCTCCTCAGTATCACTTCCTGGTCAG
TCTGGGCCGGGCGAAGAGAGCCTTCCTGCCAGGCATGAACCCACCCCCGTACTCCCAGTTCCTGTCCCGGA
GGAACGAGATCCCCCTAATTCACTTCAACACCCCCATACCACGGCGGCACACCCGGAGCGCCGAGGACGAC
TCGGAGCGGGACCCCCTGAACGTGCTGAAGCCCCGGGCCCGGATGACCCCGGCCCCGGCCTCCTGTTCACA
GGAGCTCCCGAGCGCCGAGGACAACAGCCCGATGGCCAGTGACCCATTAGGGGTGGTCAGGGGCGGTCGAG
TGAACACGCACGCTGGGGGAACGGGCCCGGAAGGCTGCCGCCCCTTCGCCAAGTTCATCTAG

SEQ ID NO: 39
METDTLLLWVLLLWVPGSTGYPNASPLLGSSWGGLIHLYTATARNSYHLQIHKNGHVDGAPHQTIYSALMI
RSEDAGFVVITGVMSRRYLCMDFRGNIFGSHYFDPENCRFQHQTLENGYDVYHSPQYHFLVSLGRAKRAFL
PGMNPPPYSQFLSRRNEIPLIHFNTPIPRRHTRSAEDDSERDPLNVLKPRARMTPAPASCSQELPSAEDNS
PMASDPLGVVRGGRVNTHAGGTGPEGCRPFAKFI

Example 16

Preparation of pUS FGF23 KI Vector for Electroporation

60 μg of pUS FGF23 KI vector was digested at 37° C. for 5 hours using spermidine-added (1 mM pH7.0, Sigma Aldrich Japan) buffer (Roche Diagnostics, H buffer for restriction enzyme) and NotI (Takara Bio, Inc.). After phenol/chloroform extraction, 2.5 volumes of 100% ethanol and 0.1 volume of 3 M sodium acetate were added, and the mixture was kept at −20° C. for 16 hours. The vector linearized with NotI was collected by centrifugation and sterilized by adding 70% ethanol thereto. 70% ethanol was removed and air drying was performed for 1 hour in a clean bench. An HBS solution was added to form a 0.5 μg/μL DNA solution, and the solution was kept at room temperature for 1 hour to prepare pUS FGF23 KI vector for electroporation.

Example 17

Obtaining a PL FGF23 Mouse ES Cell Line Using pUS FGF23 KI Vector and an RS Element Targeting Mouse ES Cell Line

To obtain a PL FGF23 mouse ES cell line, wherein human FGF23-cDNA was inserted by homologous recombination into downstream of an immunoglobulin κ light chain gene, according to the method shown in Example 16, pUS FGF23 KI vector linearized with the restriction enzyme NotI was introduced to RS element targeting mouse ES cells according to the established method (Shinichi Aizawa, "Biotechnology Manual Series 8, Gene Targeting," Yodosha, 1995). RS element targeting mouse ES cells were obtained by the method described in Example 10 of WO2006/78072.

The method for culturing RS element targeting mouse ES cells was in accordance with the described method (Shinichi Aizawa, the aforementioned document), and G418 resistant primary cells in culture (purchased from Invitrogen) treated with mitomycin C (Sigma Aldrich Japan) were used as feeder cells. First, the RS element targeting mouse ES cells were grown and were treated by trypsin, and suspended in HBS to a density of 3×107 cells/ml. 0.5 ml of the cell suspension was mixed with 10 μg of vector DNA. Electroporation (Capacitance: 960 μF, voltage: 250 V, room temperature) was then performed using Gene Pulser Cuvette (electrode distance: 0.4 cm, Bio Rad Laboratories). The electroporated cells were suspended in 10 ml of ES culture medium (Shinichi Aizawa, the aforementioned document), and then the cells were seeded to a plastic Petri dish for 100 mm tissue culture (Falcon, Becton Dickinson), wherein feeder cells were previously seeded. After 36 hours, the culture medium was substituted with ES culture medium containing 0.8 μg/ml puromycin (Sigma Aldrich Japan). Colonies which appeared 7 days after were picked up, and each was grown to confluence in a 24 well plate. Two thirds thereof were suspended in 0.2 ml of a stock medium (FBS+10% DMSO, Sigma Aldrich Japan) and the resulting suspension was kept at −80° C. The remaining one third was seeded to a 12 well gelatin coated plate. The cells were cultured for 2 days, and genomic DNA was prepared from 106 to 107 cells using Puregene DNA Isolation Kits (Qiagen). The resulting genomic DNA of puromycin resistant RS element targeting mouse ES cells was digested with the restriction enzyme EcoRI (Takara Bio, Inc.) and separated by agarose gel electrophoresis. Subsequently, Southern blotting was performed to detect homologous recombinants by using as the probe Ck 3'probe which was the DNA fragment of the 3' terminal of Ig light chain Jκ-Cκ genomic DNA (XhoI to EcoRI, about 1.4 kb, WO00/10383, FIG. **5**) used in the invention described in WO00/10383 (see Example 48). A band (15.1 kb) was detected due to EcoRI digestion in the wild type RS element targeting mouse ES cells. A new band (12.8 kb) is expected to appear below the band in addition to the band (FIG. **12**) in a homologous recombinant, and the new band was detected in the puromycin resistant strain. That is, these clones were proven to be having human FGF23-cDNA inserted into downstream of the immunoglobulin K chain gene in one of the alleles.

Example 18

Obtaining a US FGF23 Mouse ES Cell Line by Deleting the Drug Resistance Genes from a PL FGF23 Mouse ES Cell Line

To obtain a US FGF23 gene introduced mouse ES cell line, wherein 2 kinds of drug resistance genes (Puror, Neor) were deleted, from a PL FGF23 mouse ES cell line, pCAGGS-Cre vector (Sunaga et al., Mol Reprod Dev., 46: 109-113, 1997) was introduced to PL FGF23 mouse ES cells according to the established method (Shinichi Aizawa, "Biotechnology Manual Series 8, Gene Targeting," Yodosha, 1995).

The method for culturing PL FGF23 mouse ES cells was in accordance with the described method (Shinichi Aizawa, the aforementioned document), and G418 resistant primary cells in culture (purchased from Invitrogen) treated with mitomycin C (Sigma Aldrich Japan) were used as feeder cells. First, PL FGF23 mouse ES cells were grown and were treated with trypsin, and suspended in HBS to a density of 3×107 cells/ml. 0.5 ml of the cell suspension was mixed with 10 μg of vector DNA. Electroporation (Capacitance: 960 μF, voltage: 250 V, room temperature) was then performed using a Gene Pulser Cuvette (electrode distance: 0.4 cm, Bio Rad Laboratories). The electroporated cells were suspended in 10 ml of ES culture medium (Shinichi Aizawa, the aforementioned document), and then 2.5 ml of the suspension was seeded to a plastic Petri dish for 60 mm tissue culture (Falcon, Becton Dickinson), wherein feeder cells were previously seeded. After 30 hours, 1000 cells of the ES cells were seeded to a plastic Petri dish for 100 mm tissue culture (Falcon, Becton Dickinson), wherein feeder cells were previously seeded. Colonies which appeared 6 days after were picked up, and each was grown to confluence in a 24 well plate. Two thirds thereof were suspended in 0.2 ml of a stock medium (FBS+10% DMSO, Sigma Aldrich Japan) and the resulting suspension was kept at −80° C. The remaining one third was seeded to a 12 well gelatin coated plate. The cells were cultured for 2 days, and genomic DNA was prepared from 106 to 107 cells using Puregene DNA Isolation Kits (Qiagen). The resulting genomic DNA of mouse ES cells was digested with the restriction enzyme EcoRI (Takara Bio, Inc.) and separated by agarose gel electrophoresis. Subsequently, Southern blotting was performed to detect an ES cell line, wherein only the Puror gene between loxPV sequences was deleted, by using as the probe Ck 3'probe which was the DNA fragment of the 3' terminal of Ig light chain Jκ-Cκ genomic DNA (XhoI to EcoRI, about 1.4 kb, WO00/10383, FIG. **5**) used in the invention described in WO00/10383 (see Example 48). Two bands (15.1 kb and 12.8 kb) were detected due to EcoRI digestion in the ES cells retaining the Puror gene, and two bands (15.1 kb and 10.9 kb) were detected due to EcoRI digestion in the ES cell line, wherein only the Puror gene was deleted (FIG. **12**). In addition, by using the Southern blotting membrane obtained in the procedure similar to the above, and 3'KO-

probe prepared by the method shown in Example 9 of WO2006/78072 as the probe, the ES cell line, wherein the only the Neor gene between loxP sequences was deleted, was detected. Two bands (7.4 K and 5.7 K) were detected due to EcoRI digestion in the ES cells retaining the Neor gene, and two bands (5.7 K and 4.6 K) were detected due to EcoRI digestion in the ES cell line, wherein only the Neor gene was deleted (FIG. **12**). From these results, the US FGF23 mouse ES cell line, wherein 2 kinds of the drug resistance genes (Puror, Neor) were deleted simultaneously, was obtained from the PL FGF23 mouse ES cell line.

Example 19

Preparation of a US FGF23 KI Chimeric Mouse Using a US FGF23 Mouse ES Cell Line and a Host Embryo Derived from a B Lymphocyte Deficient Mouse Strain

In a homozygous knockout for the immunoglobulin μ chain gene, functional B lymphocytes are deficient and antibodies are not produced (Kitamura et al., Nature, 350: 423-426, 1991). Embryos obtained by cross-breeding the above individual homozygous male and female grown in a clean environment were used as the hosts for preparing chimeric mice in the present Example. In such case, the majority of functional B lymphocytes in a chimeric mouse were derived from the injected ES cells. In the present Example, an individual immunoglobulin μ chain gene knockout mouse described in a report by Tomizuka et al. (Proc. Natl. Acad. Sci. USA, 97: 722-7, 2000), which was backcrossed to the MCH (ICR) strain (CLEA Japan, Inc.) 3 times or more, was used for host embryo preparation.

The US FGF23 mouse ES cell line obtained in the above Example 18, wherein the insertion of human FGF23-cDNA downstream of an immunoglobulin κ chain gene was confirmed, was started from a frozen stock, and the cells were injected to a 8-cell stage embryo obtained by cross-breeding individual male and female mice of the above immunoglobulin μ chain gene knockout homozygotes, with 8-10 cells per embryo. After overnight culture in ES culture medium (Shinichi Aizawa, "Biotechnology Manual Series 8, Gene Targeting," Yodosha, 1995), the embryos were developed into blastocysts. The injection embryos were then transplanted to the uterus in an adopted parent MCH (ICR) mouse (CLEA Japan, Inc.) 2.5 days after pseudopregnancy treatment, with about 10 injection embryos per one side of the uterus, respectively. As a result of transplanting the injection embryos prepared by using a US FGF23 mouse ES cell line prepared in Example 18, chimeric offspring mice were born. An individual chimera is determined by the coat color, in which whether or not the ES cell-derived wild type color (dark brown) can be recognized in the host embryo-derived white color. Among the chimeric offspring mice born, individual mice obviously having parts in the wild type color in the coat color, that is, having recognizable contribution of the ES cells, were obtained. From these results, the US FGF23 mouse ES cell line, wherein human FGF23-cDNA is inserted into downstream of an immunoglobulin κ chain gene, was shown to maintain chimeric forming ability. That is, the cell line has the ability to differentiate into normal tissues of an individual mouse. In addition, the US FGF23 KI chimeric mouse, as will be described later in Example 21, has a high blood FGF23 concentration, and could be used as an animal model of disease exhibiting findings similar to hypophosphatemic rickets.

Example 20

Preparation of Control Chimeric Mouse

A chimeric mouse, in which functional genes including the human FGF23-cDNA prepared according to the method described in Example 11 of WO2006/78072 are not inserted, was used as an individual control chimeric mouse (WT mouse) in the experiment administering C10 antibody to US FGF23 KI chimeric mouse in the following Example 21.

Example 21

Verification of the Effect of C10 Antibody on Improvement in Pathology Using a US FGF23 KI Chimeric Mouse

Examples 10 and 12 demonstrated that C10 antibody significantly suppresses the effect of endogenous FGF23 and elevates the serum phosphorous concentration and serum 1,25D concentration thereof compared to 2C3B antibody and C15 antibody in normal cynomolgus monkey. It has been strongly suggested that antibody having neutralizing activity on human FGF23 has therapeutic effect on human diseases such as tumor-induced osteomalacia, hypophosphatemic rickets including XLH and the like, and osteomalacia which are caused by excessive FGF23. Therefore, the C10 antibody obtained in the present invention was investigated for the effect on improvement in pathology caused by excessive human FGF23. For the trial of this therapeutic effect of C10 antibody, experiments were conducted using a US FGF23 KI chimeric mouse (referred to as an "hFGF23KI mouse" hereinafter) prepared in Example 19. 12 hFGF23 KI mice were used as disease-model animals and 6 normal control mice (WT mice, prepared in Example 20) of the same weeks of age were used as the comparative controls. At 7 weeks of age, serum of hFGF23 KI mice was collected to measure the serum concentration of FGF23 (FGF-23 ELISA KIT, Kainos Laboratories, Inc.) and phosphorus, respectively. Compared to the WT mice, serum FGF23 concentration was significantly increased in hFGF23 KI mice (WT mice; n=6, 163 pg/mL, hFGF23KI mice; n=12, 1467 pg/mL). From this result, it was suggested that the introduction of the human FGF23 gene to the hFGF23 KI mouse was precisely performed and that, in addition, excessive exogenous human FGF23 was present in the hFGF23 KI mouse blood. In addition, compared to the WT mice, in hFGF23 KI mice, a significant reduction in the serum phosphorous concentration was shown (WT mice; n=6, 5.82 mg/dL, hFGF23KI mice; n=12, 2.62 mg/dL). It was also suggested that hypophosphatemia was induced due to excessive human FGF23 action in hFGF23 KI mice. At this time point, 12 hFGF23 KI mice were divided into the following 2 groups of 6 mice each, having an equal FGF23 concentration: the C10 antibody administered group and the control IgG1 administered group (FIG. **13**). Next, since 8 weeks of age, repeated intravenous administration of C10 antibody or purified human IgG1 (control antibody) for isotype control was conducted at a dose of 30 mg/kg and frequency of once a week five times. Blood samples were taken before the first administration and 3 days after the administration, and the serum was obtained. Appendicular grip strength was measured 24 hours after the fourth administration using a Saitoh-GRIP STRENGTH METER (MK-380S, Muromachi Kikai Co., Ltd.). Appendicular grip

strength was evaluated by using as an index the maximum force (grip strength) exerted by a mouse, wherein the mouse was placed on a measurement grid, to let the mouse grip the grid, and then the mouse was pulled by the tail horizontally by our hand until the animal released the grid for being unable to bear the withdrawing force. Bones were evaluated 24 hours after the fifth administration. The collected femur and tibia from mice euthanized by blood drawing from the heart under anesthesia were fixed in 70% ethanol. Serum phosphorous concentration was measured at the before first administration, 3 days after the first administration and 24 hours after the fifth administration. Undecalcified femur was embedded in resin, and stained with Villanueva-Goldner for histological evaluation. Bone mineral content in tibia was measured through the ashing process.

As a result, significantly low serum phosphorus concentration was observed in the hFGF23KI mouse control antibody administered group at the time of grouping and 24 hours after fifth administration compared to the WT mouse control antibody administered group, which means continuous hypophosphatemic conditions (FIG. **14**). On the other hand, it was observed that the serum phosphorous concentration at 3 days after administration was increased in hFGF23KI mouse C10 antibody administered group to the same level as that in the WT mouse control antibody administered group (FIG. **14**). In addition, the serum phosphorous concentration after the fifth administration in the hFGF23KI mouse C10 antibody administered group was also the same level as that in the WT mouse control antibody administered group, which means the effect of C10 antibody for the increment of serum phosphorus concentration was maintained even after five times of administration (FIG. **15**).

As a case of hypophosphatemic patients, skeletal muscle weakness has been reported (Baker and Worthley, Crit Care Resusc., 4: 307-315, 2000). In the present study, hFGF23KI mice had been expected the muscle weakness because of the hypophosphatemia. Consequently, appendicular grip strength was measured by the above method as an index of muscle weakness, and compared among groups. As a result, the grip strength of the hFGF23KI mouse control antibody administered group was shown to be significantly low compared to that of the WT mouse control antibody administered group, and muscle weakness was observed in this disease model (FIG. **16**). In contrast, significant improvement of grip strength was observed in the hFGF23KI mouse C10 antibody administered group (FIG. **16**).

Next, under-calcified femoral tissues were stained by Villanueva-Goldner method for histological observation. As a result, a large amount of osteoid (shown in red in FIG. **17**) was observed in the bone in the hFGF23KI mouse control antibody administered group compared to that in WT mouse control antibody administered group, suggesting that calcification defect was induced in that group. This is widely known as a characteristic symptom of rickets. In contrast, in the hFGF23KI mice received C10 antibody treatment, reduction of the area occupied with osteoid was observed, and predicted that osteoid was replaced with calcified bones (shown in green in FIG. **17**). From this result, it was suggested that C10 antibody improves bone calcification reduced by excessive FGF23. Consequently, the amount of minerals contained in tibia was measured by calcification, and compared between each group. The amount of minerals contained in tibia in the hFGF23KI mouse control antibody administered group was significantly reduced compared to the WT mouse control antibody administered group (FIG. **18**). In contrast, in the hFGF23KI mouse C10 antibody administered group, improvement in the amount of minerals was confirmed (FIG. **18**). From the above results, it was confirmed that, in hFGF23KI mice, C10 antibody administration neutralizes the effect of excessively acting human FGF23 in vivo, and improves various symptoms of hypophosphatemic rickets such as hypophosphatemia, muscle weakness, bone calcification disorder and the like. That is, C10 antibody was shown to be an effective therapeutic agent for various human diseases involving FGF23.

INDUSTRIAL APPLICABILITY

The C10 antibody of the present invention which is an antibody against FGF23 has high activity to raise serum phosphate concentrations in vivo in a sustained manner and/or to raise serum 1,25D concentrations in a sustained manner as compared to known antibodies against FGF23. The present invention can be used with dramatic effects as an agent for prevention or treatment of diseases which are caused by excessive action of FGF23 or for diseases which may be improved in the pathology by controlling the action of FGF23.

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Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
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Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
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Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
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Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
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Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
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Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
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Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
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gagctgagca gcctgagatc tgaggacacg gccgtgtatt attgtgcgag agatattgtg 360

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Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Asn His Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Ile Ile Asn Pro Ile Ser Gly Ser Thr Ser Asn Ala
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Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
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Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
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Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
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Gln Gly Ile Ser Ser Ala Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys
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cacctgtaca cagccacagc caggaacagc taccacctgc agatccacaa gaatggccac 180

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Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
35 40 45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
50 55 60

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Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
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Asp Phe Gly Gly Asn Ile Phe Gly Ser His Tyr Phe Asn Pro Glu Asn
            100                 105                 110

Cys Arg Phe Arg His Trp Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln His His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Arg Pro Arg Arg
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His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Val Ala Ser Asp Pro Leu
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acaggcccct ggacaagggc ttgagtggat gggaataatc aaccctatta gtggtagcac    240

aagtaacgca cagaagttcc agggcagagt caccatgacc agggacacgt ccacgagcac    300

agtctacatg gagctgagca gcctgagatc tgaggacacg gccgtgtatt attgtgcgag    360

agatattgtg gatgcttttg atttctgggg ccaagggaca atggtcaccg tctcttcagc    420

tagcaccaag ggcccatcgg tcttcccccct ggcaccctcc tccaagagca cctctggggg    480

cacagcggcc ctgggctgcc tggtcaagga ctacttcccc gaaccggtga cggtgtcgtg    540

gaactcaggc gccctgacca gcggcgtgca caccttcccg gctgtcctac agtcctcagg    600

actctactcc ctcagcagcg tggtgaccgt gccctccagc agcttgggca cccagaccta    660

catctgcaac gtgaatcaca agcccagcaa caccaaggtg gacaagaaag ttgagcccaa    720

atcttgtgac aaaactcaca catgcccacc gtgcccagca cctgaactcc tgggggggacc    780

gtcagtcttc ctcttccccc caaaacccaa ggacaccctc atgatctccc ggacccctga    840

ggtcacatgc gtggtggtgg acgtgagcca cgaagaccct gaggtcaagt tcaactggta    900

cgtggacggc gtggaggtgc ataatgccaa gacaaagccg cgggaggagc agtacaacag    960

cacgtaccgt gtggtcagcg tcctcaccgt cctgcaccag gactggctga atggcaagga   1020
```

-continued

gtacaagtgc aaggtctcca acaaagccct cccagccccc atcgagaaaa ccatctccaa 1080

agccaaaggg cagccccgag aaccacaggt gtacaccctg cccccatccc gggatgagct 1140

gaccaagaac caggtcagcc tgacctgcct ggtcaaaggc ttctatccca gcgacatcgc 1200

cgtggagtgg gagagcaatg ggcagccgga gaacaactac aagaccacgc ctcccgtgct 1260

ggactccgac ggctccttct tcctctacag caagctcacc gtggacaaga gcaggtggca 1320

gcaggggaac gtcttctcat gctccgtgat gcatgaggct ctgcacaacc actacacgca 1380

gaagagcctc tccctgtctc cgggtaaatg aggatcc 1417

<210> SEQ ID NO 31
<211> LENGTH: 466
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 31

Met Asp Trp Thr Trp Arg Val Phe Cys Leu Leu Ala Val Ala Pro Gly
1 5 10 15

Ala His Ser Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys
20 25 30

Pro Gly Ala Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe
35 40 45

Thr Asn His Tyr Met His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu
50 55 60

Glu Trp Met Gly Ile Ile Asn Pro Ile Ser Gly Ser Thr Ser Asn Ala
65 70 75 80

Gln Lys Phe Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Thr Ser
85 90 95

Thr Val Tyr Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val
100 105 110

Tyr Tyr Cys Ala Arg Asp Ile Val Asp Ala Phe Asp Phe Trp Gly Gln
115 120 125

Gly Thr Met Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
130 135 140

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
145 150 155 160

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
165 170 175

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
180 185 190

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
195 200 205

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
210 215 220

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
225 230 235 240

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
245 250 255

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
260 265 270

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
275 280 285

-continued

```
Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
    290                 295                 300

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
305                 310                 315                 320

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
                325                 330                 335

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
            340                 345                 350

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
        355                 360                 365

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
    370                 375                 380

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
385                 390                 395                 400

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
                405                 410                 415

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
            420                 425                 430

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
        435                 440                 445

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
    450                 455                 460

Gly Lys
465
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<210> SEQ ID NO 32
<211> LENGTH: 724
<212> TYPE: DNA
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 32

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ctcccaggtg ccagatgtgc catccagttg acccagtctc catcctccct gtctgcatct    120

gtaggagaca gagtcaccat cacttgccgg gcaagtcagg gcattagcag tgctttagtc    180

tggtatcagc agaaaccagg gaaagctcct aagctcctga tctatgatgc ctccagtttg    240

gaaagtgggg tcccatcaag gttcagcggc agtggatctg ggacagattt cactctcacc    300

atcagcagcc tgcagcctga agattttgca acttattact gtcaacagtt taatgattac    360

ttcactttcg gccctgggac caaagtggat atcaaacgta cggtggctgc accatctgtc    420

ttcatcttcc cgccatctga tgagcagttg aaatctggaa ctgcctctgt tgtgtgcctg    480

ctgaataact tctatcccag agaggccaaa gtacagtgga aggtggataa cgccctccaa    540

tcgggtaact cccaggagag tgtcacagag caggacagca aggacagcac ctacagcctc    600

agcagcaccc tgacgctgag caaagcagac tacgagaaac acaaagtcta cgcctgcgaa    660

gtcacccatc agggcctgag ctcgcccgtc acaaagagct tcaacagggg agagtgttga    720

attc                                                                 724
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<210> SEQ ID NO 33
<211> LENGTH: 235
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 33

Met Asp Met Arg Val Pro Ala Gln Leu Leu Gly Leu Leu Leu Leu Trp
1 5 10 15

Leu Pro Gly Ala Arg Cys Ala Ile Gln Leu Thr Gln Ser Pro Ser Ser
20 25 30

Leu Ser Ala Ser Val Gly Asp Arg Val Thr Ile Thr Cys Arg Ala Ser
35 40 45

Gln Gly Ile Ser Ser Ala Leu Val Trp Tyr Gln Gln Lys Pro Gly Lys
50 55 60

Ala Pro Lys Leu Leu Ile Tyr Asp Ala Ser Ser Leu Glu Ser Gly Val
65 70 75 80

Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr
85 90 95

Ile Ser Ser Leu Gln Pro Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln
100 105 110

Phe Asn Asp Tyr Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
115 120 125

Arg Thr Val Ala Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu
130 135 140

Gln Leu Lys Ser Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe
145 150 155 160

Tyr Pro Arg Glu Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln
165 170 175

Ser Gly Asn Ser Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser
180 185 190

Thr Tyr Ser Leu Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu
195 200 205

Lys His Lys Val Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser
210 215 220

Pro Val Thr Lys Ser Phe Asn Arg Gly Glu Cys
225 230 235

<210> SEQ ID NO 34
<211> LENGTH: 35
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

tatcccaatg cctccccact gctcggctcc agctg 35

<210> SEQ ID NO 35
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

ttggccggcc ctagatgaac ttggcgaagg ggcggcagcc ttccg 45

<210> SEQ ID NO 36
<211> LENGTH: 756
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

atgttggggg cccgcctcag gctctgggtc tgtgccttgt gcagcgtctg cagcatgagc 60

gtcctcagag cctatcccaa tgcctcccca ctgctcggct ccagctgggg tggcctgatc 120

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cacctgtaca cagccacagc caggaacagc taccacctgc agatccacaa gaatggccat    180

gtggatggcg caccccatca gaccatctac agtgccctga tgatcagatc agaggatgct    240

ggctttgtgg tgattacagg tgtgatgagc agaagatacc tctgcatgga tttcagaggc    300

aacatttttg gatcacacta tttcgacccg gagaactgca ggttccaaca ccagacgctg    360

gaaaacgggt acgacgtcta ccactctcct cagtatcact tcctggtcag tctgggccgg    420

gcgaagagag ccttcctgcc aggcatgaac ccacccccgt actcccagtt cctgtcccgg    480

aggaacgaga tccccctaat tcacttcaac acccccatac cacggcggca cacccggagc    540

gccgaggacg actcggagcg ggacccccctg aacgtgctga agccccgggc ccggatgacc    600

ccggccccgg cctcctgttc acaggagctc ccgagcgccg aggacaacag cccgatggcc    660

agtgacccat taggggtggt caggggcggt cgagtgaaca cgcacgctgg gggaacgggc    720

ccggaaggct gccgcccctt cgccaagttc atctag                              756
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<210> SEQ ID NO 37
<211> LENGTH: 251
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

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Met Leu Gly Ala Arg Leu Arg Leu Trp Val Cys Ala Leu Cys Ser Val
1               5                   10                  15

Cys Ser Met Ser Val Leu Arg Ala Tyr Pro Asn Ala Ser Pro Leu Leu
            20                  25                  30

Gly Ser Ser Trp Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg
        35                  40                  45

Asn Ser Tyr His Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala
    50                  55                  60

Pro His Gln Thr Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala
65                  70                  75                  80

Gly Phe Val Val Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met
                85                  90                  95

Asp Phe Arg Gly Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn
            100                 105                 110

Cys Arg Phe Gln His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His
        115                 120                 125

Ser Pro Gln Tyr His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala
    130                 135                 140

Phe Leu Pro Gly Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg
145                 150                 155                 160

Arg Asn Glu Ile Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg
                165                 170                 175

His Thr Arg Ser Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val
            180                 185                 190

Leu Lys Pro Arg Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln
        195                 200                 205

Glu Leu Pro Ser Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu
    210                 215                 220

Gly Val Val Arg Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly
225                 230                 235                 240

Pro Glu Gly Cys Arg Pro Phe Ala Lys Phe Ile
                245                 250
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<210> SEQ ID NO 38
<211> LENGTH: 985
<212> TYPE: DNA
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 38

atggagacag acacactcct gttatgggta ctgctgctct gggttccagg tgagagtgca 60

gagaagtgtt ggatgcaacc tctgtggcca ttatgatact ccatgcctct ctgttcttga 120

tcactataat tagggcattt gtcactggtt ttaagtttcc ccagtcccct gaattttcca 180

ttttctcaga gtgatgtcca aaattattct taaaaattta aataaaaagg tcctctgctg 240

tgaaggcttt tatacatata taacaataat ctttgtgttt atcattccag gttccactgg 300

ctatcccaat gcctccccac tgctcggctc cagctggggt ggcctgatcc acctgtacac 360

agccacagcc aggaacagct accacctgca gatccacaag aatggccatg tggatggcgc 420

accccatcag accatctaca gtgccctgat gatcagatca gaggatgctg gctttgtggt 480

gattacaggt gtgatgagca gaagatacct ctgcatggat ttcagaggca acatttttgg 540

atcacactat ttcgacccgg agaactgcag gttccaacac cagacgctgg aaaacgggta 600

cgacgtctac cactctcctc agtatcactt cctggtcagt ctgggccggg cgaagagagc 660

cttcctgcca ggcatgaacc cacccccgta ctcccagttc ctgtcccgga ggaacgagat 720

ccccctaatt cacttcaaca cccccatacc acggcggcac acccggagcg ccgaggacga 780

ctcggagcgg gacccccctga acgtgctgaa gccccgggcc cggatgaccc cggccccggc 840

ctcctgttca caggagctcc cgagcgccga ggacaacagc ccgatggcca gtgacccatt 900

aggggtggtc aggggcggtc gagtgaacac gcacgctggg ggaacgggcc cggaaggctg 960

ccgccccttc gccaagttca tctag 985

<210> SEQ ID NO 39
<211> LENGTH: 247
<212> TYPE: PRT
<213> ORGANISM: Mus musculus

<400> SEQUENCE: 39

Met Glu Thr Asp Thr Leu Leu Leu Trp Val Leu Leu Leu Trp Val Pro
1 5 10 15

Gly Ser Thr Gly Tyr Pro Asn Ala Ser Pro Leu Leu Gly Ser Ser Trp
20 25 30

Gly Gly Leu Ile His Leu Tyr Thr Ala Thr Ala Arg Asn Ser Tyr His
35 40 45

Leu Gln Ile His Lys Asn Gly His Val Asp Gly Ala Pro His Gln Thr
50 55 60

Ile Tyr Ser Ala Leu Met Ile Arg Ser Glu Asp Ala Gly Phe Val Val
65 70 75 80

Ile Thr Gly Val Met Ser Arg Arg Tyr Leu Cys Met Asp Phe Arg Gly
85 90 95

Asn Ile Phe Gly Ser His Tyr Phe Asp Pro Glu Asn Cys Arg Phe Gln
100 105 110

His Gln Thr Leu Glu Asn Gly Tyr Asp Val Tyr His Ser Pro Gln Tyr
115 120 125

His Phe Leu Val Ser Leu Gly Arg Ala Lys Arg Ala Phe Leu Pro Gly
130 135 140

Met Asn Pro Pro Pro Tyr Ser Gln Phe Leu Ser Arg Arg Asn Glu Ile
145 150 155 160

-continued

```
Pro Leu Ile His Phe Asn Thr Pro Ile Pro Arg Arg His Thr Arg Ser
                165                 170                 175

Ala Glu Asp Asp Ser Glu Arg Asp Pro Leu Asn Val Leu Lys Pro Arg
            180                 185                 190

Ala Arg Met Thr Pro Ala Pro Ala Ser Cys Ser Gln Glu Leu Pro Ser
        195                 200                 205

Ala Glu Asp Asn Ser Pro Met Ala Ser Asp Pro Leu Gly Val Val Arg
    210                 215                 220

Gly Gly Arg Val Asn Thr His Ala Gly Gly Thr Gly Pro Glu Gly Cys
225                 230                 235                 240

Arg Pro Phe Ala Lys Phe Ile
                245


<210> SEQ ID NO 40
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 40

Asn His Tyr Met His
1               5


<210> SEQ ID NO 41
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 41

Ile Ile Asn Pro Ile Ser Gly Ser Thr Ser Asn Ala Gln Lys Phe Gln
1               5                   10                  15

Gly


<210> SEQ ID NO 42
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

Asp Ile Val Asp Ala Phe Asp Phe
1               5


<210> SEQ ID NO 43
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

Arg Ala Ser Gln Gly Ile Ser Ser Ala Leu Val
1               5                   10


<210> SEQ ID NO 44
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

Asp Ala Ser Ser Leu Glu Ser
1 5

<210> SEQ ID NO 45
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 45

Gln Gln Phe Asn Asp Tyr Phe Thr
1 5

What is claimed is:

1. An isolated antibody against human FGF23, comprising a heavy chain variable region or a light chain variable region having the same amino acid sequence as an antibody produced by hybridoma C10 (Accession No. FERM BP-10772).

2. An isolated antibody against human FGF23, comprising a heavy chain variable region comprising an amino acid sequence from the amino acid at position 20 of SEQ ID NO: 12 to the amino acid at position 136 of SEQ ID NO: 12 or a light chain variable region comprising an amino acid sequence from the amino acid at position 23 of SEQ ID NO: 14 to the amino acid at position 128 of SEQ ID NO: 14.

3. The antibody of claim **2**, wherein (A) the antibody against human FGF23 comprises a heavy chain variable region and a light chain variable region and (B) the heavy chain variable region comprises an amino acid sequence from the amino acid at position 20 of SEQ ID NO: 12 to the amino acid at position 136 of SEQ ID NO: 12 and the light chain variable region comprises an amino acid sequence from the amino acid at position 23 of SEQ ID NO: 14 to the amino acid at position 128 of SEQ ID NO: 14.

4. An isolated antibody against human FGF23 produced by hybridoma C10 (Accession No. FERM BP-10772).

5. The isolated antibody against human FGF23 of claim **1**, wherein the class of the antibody is selected from the group consisting of IgG, IgA, IgE, and IgM.

6. The isolated antibody against human FGF23 of claim **5**, wherein the subclass of the IgG antibody is selected from the group consisting of IgG1, IgG2, IgG3, and IgG4.

7. A pharmaceutical composition, comprising as an active ingredient, the isolated antibody against human FGF23 of claim **1**.

8. A hybridoma C10 (Accession No. FERM BP-10772).

9. An isolated antibody against human FGF23, comprising a heavy chain variable region and a light chain variable region having the same amino acid sequence as an antibody produced by hybridoma C10 (Accession No. FERM BP-10772), wherein the subclass of said antibody is IgG1.

10. An isolated antibody against human FGF23, comprising a heavy chain variable region comprising an amino acid sequence from the amino acid sequence at position 20 of SEQ ID NO:12 to the amino acid at position 136 of SEQ ID NO:12 and a light chain variable region comprising an amino acid sequence from the amino acid at position 23 of SEQ ID NO:14 to the amino acid at position 128 of SEQ ID NO:14, wherein the subclass of said antibody is IgG1.

* * * * *

US008722033B2

(12) **United States Patent**
Towne et al.

(10) **Patent No.: US 8,722,033 B2**
(45) **Date of Patent: May 13, 2014**

(54) **HUMAN IL-23 ANTIGEN BINDING PROTEINS**

(75) Inventors: **Jennifer E. Towne**, Seattle, WA (US); **Janet D. Cheng**, Seattle, WA (US); **Jason C. O'Neill**, Brier, WA (US); **Yu Zhang**, Shoreline, WA (US); **Yu Sun**, Seattle, WA (US); **Heather Cerne**, Seattle, WA (US); **Derek E. Piper**, Santa Clara, CA (US); **Randal R. Ketchem**, Snohomish, WA (US)

(73) Assignee: **Amgen Inc.**, Thousand Oaks, CA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **13/504,449**

(22) PCT Filed: **Oct. 26, 2010**

(86) PCT No.: **PCT/US2010/054148**

§ 371 (c)(1),
(2), (4) Date: **Aug. 31, 2012**

(87) PCT Pub. No.: **WO2011/056600**

PCT Pub. Date: **May 12, 2011**

(65) **Prior Publication Data**

US 2013/0004501 A1 Jan. 3, 2013

Related U.S. Application Data

(60) Provisional application No. 61/381,287, filed on Sep. 9, 2010, provisional application No. 61/254,982, filed on Oct. 26, 2009.

(51) **Int. Cl.**
C07K 16/24 (2006.01)
A61K 39/395 (2006.01)

(52) **U.S. Cl.**
CPC ***A61K 39/395*** (2013.01); ***C07K 16/24*** (2013.01)
USPC **424/85.2**; 530/387.1; 530/388.1; 530/388.23

(58) **Field of Classification Search**
None
See application file for complete search history.

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Primary Examiner — Prema Mertz
(74) *Attorney, Agent, or Firm* — Marshall, Gerstein & Borun LLP

(57) **ABSTRACT**

Antigen binding proteins that bind to human IL-23 protein are provided. Nucleic acids encoding the antigen binding protein, vectors, and cells encoding the same as well as use of IL-23 antigen binding proteins for diagnostic and therapeutic purposes are also provided.

6 Claims, 2 Drawing Sheets

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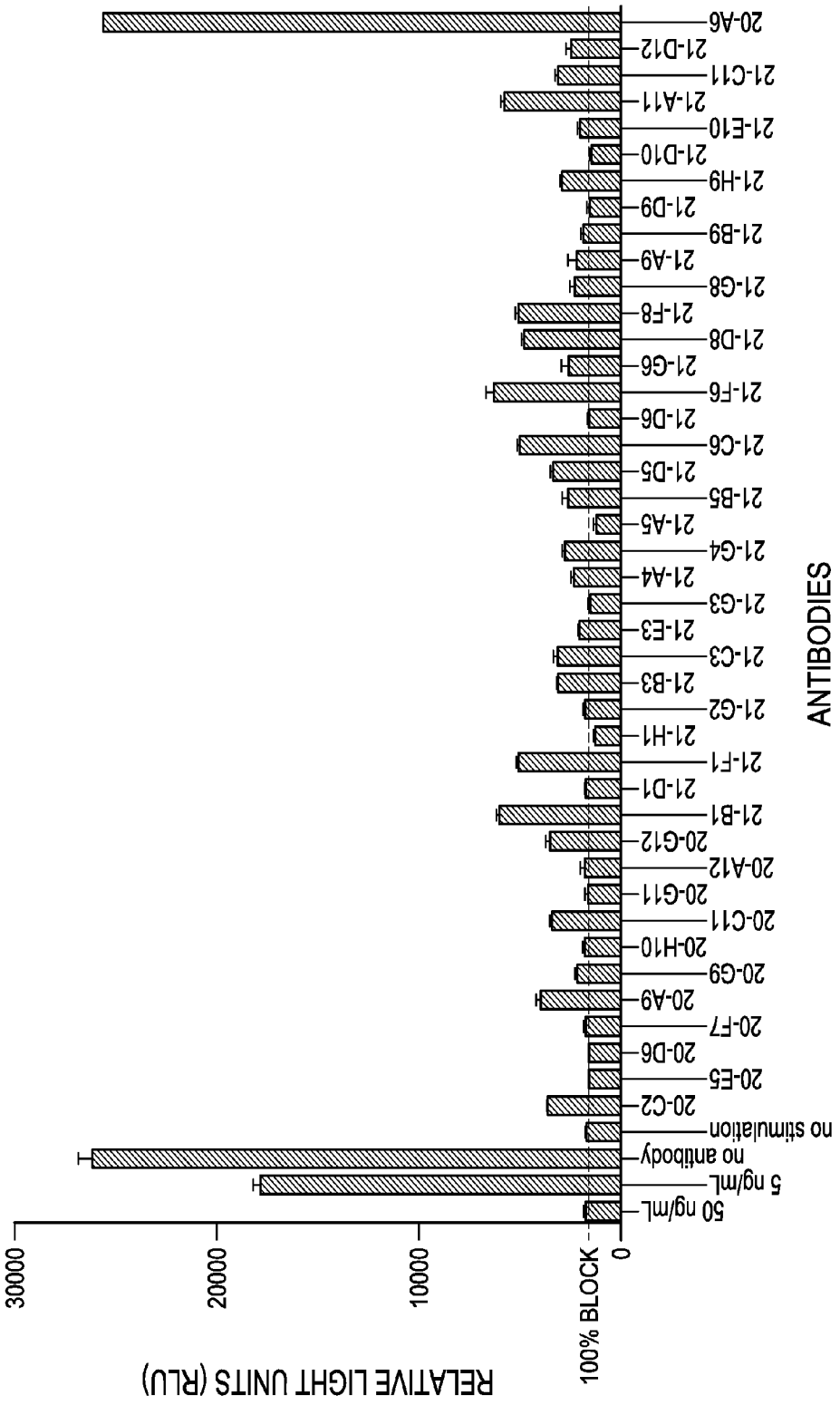
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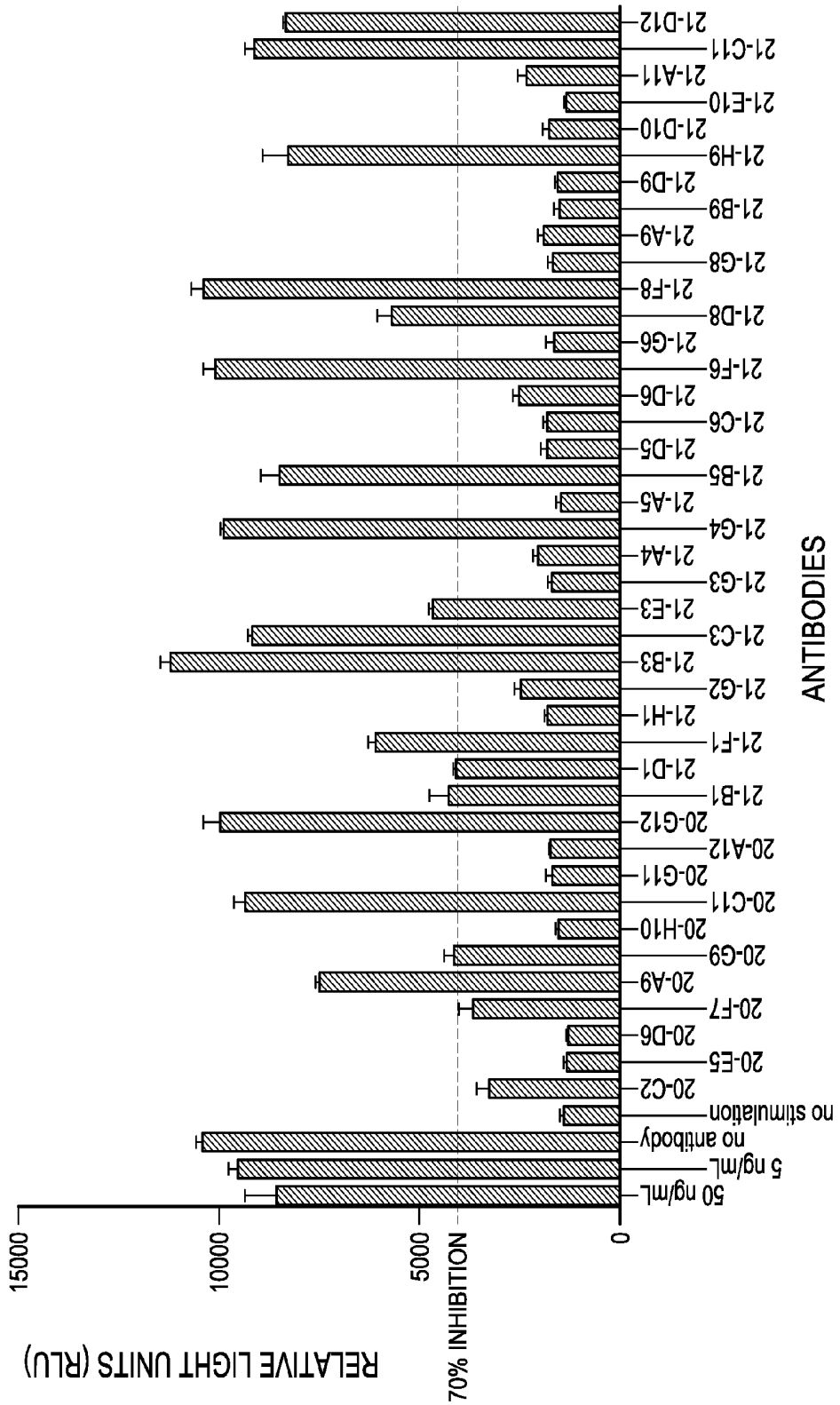
Fig. 1A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ANTIBODIES

Fig. 1B

HUMAN IL-23 ANTIGEN BINDING PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national stage application under 35 U.S.C. §371 of international Application No. PCT/US2010/054148, having an international filing date of Oct. 26, 2010; which claims priority to U.S. provisional patent application Ser. No. 61/254,982, filed Oct. 26, 2009 and U.S. provisional patent application Ser. No. 61/381,287, filed Sep. 9, 2010, which are incorporated herein by reference.

REFERENCE TO THE SEQUENCE LISTING

The present application is being filed along with a Sequence Listing in electronic format. The Sequence Listing is provided as a file entitled A-1529-US-PCI_Sequence_as_filed__04__25__2012, created Apr. 24, 2012, which is 101 KB in size. The information in the electronic format of the Sequence Listing is incorporated herein by reference in its entirety.

BACKGROUND

Interleukin 23 (IL-23), a heterodimeric cytokine, is a potent inducer of pro-inflammatory cytokines. IL-23 is related to the heterodimeric cytokine Interleukin 12 (IL-12) both sharing a common p40 subunit. In IL-23, a unique p19 subunit is covalently bound to the p40 subunit. In IL-12, the unique subunit is p35 (Oppmann et al., Immunity, 2000, 13: 713-715). The IL-23 heterodimeric protein is secreted. Like IL-12, IL-23 is expressed by antigen presenting cells (such as dendritic cells and macrophages) in response to activation stimuli such as CD40 ligation, Toll-like receptor agonists and pathogens. IL-23 binds a heterodimeric receptor comprising an IL-12Rβ1 subunit (which is shared with the IL-12 receptor) and a unique receptor subunit, IL-23R. The IL-12 receptor consists of IL-12Rβ1 and IL-12Rβ2. IL-23 binds its heterodimeric receptor and signals through JAK2 and Tyk2 to activate STAT1, 3, 4 and 5 (Parham et al., J. Immunol. 2002, 168:5699-708). The subunits of the receptor are predominantly co-expressed on activated or memory T cells and natural killer cells and also at lower levels on dendritic cells, monocytes, macrophages, microglia, keratinocytes and synovial fibroblasts. IL-23 and IL-12 act on different T cell subsets and play substantially different roles in vivo.

IL-23 acts on activated and memory T cells and promotes survival and expansion of the T cell subset, Th17. Th17 cells produce proinflammatory cytokines including IL-6, IL-17, TNFα, IL-22 and GM-CSF. IL-23 also acts on natural killer cells, dendritic cells and macrophages to induce pro-inflammatory cytokine expression. Unlike IL-23, IL-12 induces the differentiation of naïve CD4+ T cells into mature Th1 IFNγ-producing effector cells, and induces NK and cytotoxic T cell function by stimulating IFNγ production. Th1 cells driven by IL-12 were previously thought to be the pathogenic T cell subset in many autoimmune diseases, however, more recent animal studies in models of inflammatory bowel disease, psoriasis, inflammatory arthritis and multiple sclerosis, in which the individual contributions of IL-12 versus IL-23 were evaluated have firmly established that IL-23, not IL-12, is the key driver in autoimmune/inflammatory disease (Ahern et al., Immun. Rev. 2008 226:147-159; Cua et al., Nature 2003 421:744-748; Yago et al., Arthritis Res and Ther. 2007 9(5): R96). It is believed that IL-12 plays a critical role in the development of protective innate and adaptive immune responses to many intracellular pathogens and viruses and in tumor immune surveillance. See Kastelein, et al., Annual Review of Immunology, 2007, 25: 221-42; Liu, et al., Rheumatology, 2007, 46(8): 1266-73; Bowman et al., Current Opinion in Infectious Diseases, 2006 19:245-52; Fieschi and Casanova, Eur. J. Immunol. 2003 33:1461-4; Meeran et al., Mol. Cancer. Ther. 2006 5: 825-32; Langowski et al., Nature 2006 442: 461-5. As such, IL-23 specific inhibition (sparing IL-12 or the shared p40 subunit) should have a potentially superior safety profile compared to dual inhibition of IL-12 and IL-23.

Therefore, use of IL-23 specific antagonists that inhibit human IL-23 (such as antibodies that bind at least the unique p19 subunit or bind both the p19 and p40 subunits of IL-23) that spare IL-12 should provide efficacy equal to or greater than IL-12 antagonists or p40 antagonists without the potential risks associated with inhibition of IL-12. Murine, humanized and phage display antibodies selected for inhibition of recombinant IL-23 have been described; see for example U.S. Pat. No. 7,491,391, WIPO Publications WO1999/05280, WO2007/0244846, WO2007/027714, WO 2007/076524, WO2007/147019, WO2008/103473, WO 2008/103432, WO2009/043933 and WO2009/082624. However, there is a need for fully human therapeutic agents that are able to inhibit native human IL-23. Such therapeutics are highly specific for the target, particularly in vivo. Complete inhibition of the in vivo target can result in lower dose formulations, less frequent and/or more effective dosing which in turn results in reduced cost and increased efficiency. The present invention provides such IL-23 antagonists.

SUMMARY

Antigen binding proteins that bind IL-23, particularly native human IL-23, are provided. The human IL-23 antigen binding proteins can reduce, inhibit, interfere with, and/or modulate at least one of the biological responses related to IL-23, and as such, are useful for ameliorating the effects of IL-23 related diseases or disorders. IL-23 antigen binding proteins can be used, for example, to reduce, inhibit, interfere with and/or modulate IL-23 signaling, IL-23 activation of Th17 cells, IL-23 activation of NK cells, or inducing production of proinflammatory cytokines.

Also provided are expression systems, including cell lines, for the production of IL-23 antigen binding proteins and methods of diagnosing and treating diseases related to human IL-23.

Some of the antigen binding proteins that bind IL-23 that are provided comprise at least one heavy chain variable region comprising a CDRH1, a CDRH2 and a CDRH3 selected from the group consisting of: a CDRH1 that differs by no more than one amino acid substitution, insertion or deletion from a CDRH1 as shown in TABLE 3; a CDRH2 that differs by no more than three, two or one amino acid substitutions, insertions and/or deletions from a CDRH2 as shown in TABLE 3; a CDRH3 that differs by no more than three, two or one amino acid substitutions, insertions and/or deletions from a CDRH3 as shown in TABLE 3; and comprising at least one light chain variable region comprising a CDRL1, a CDRL2 and a CDRL3 selected from the group consisting of: a CDRL1 that differs by no more than three, two or one amino acid substitutions, insertions and/or deletions from a CDRL1 as shown in TABLE 3; a CDRL2 that differs by no more than one amino acid substitution, insertion or deletion from a CDRL2 as shown in TABLE 3; a CDRL3 that differs by no more than one amino acid substitution, insertion or deletion from a CDRL3 as shown in TABLE 3. In one embodiment is

provided isolated antigen binding proteins comprising: a CDRH1 selected from the group consisting of SEQ ID NO: 91, 94, 97, 100, and 103; a CDRH2 selected from the group consisting of SEQ ID NO:92, 95, 98, 101, 104, 107, and 110; a CDRH3 selected from the group consisting of SEQ ID NO: 93, 96, 99, 102, and 105; a CDRL1 selected from the group consisting of SEQ ID NO: 62, 65, 68, 71, and 74; a CDRL2 selected from the group consisting of SEQ ID NO:63, 66, 69, 72, 75, and 78; and a CDRL3 selected from the group consisting of SEQ ID NO:64, 67, 70 and 73. In another embodiment is provided isolated antigen bindings protein of comprising: a CDRH1 selected from the group consisting of SEQ ID NO: 91, 106, 109, 112, and 115; a CDRH2 selected from the group consisting of SEQ ID NO: 113, 116, 118, 120, 121, and 122; a CDRH3 selected from the group consisting of SEQ ID NO: 108, 111, 114, 117, and 119; a CDRL1 selected from the group consisting of SEQ ID NO: 77, 80, 83, 85, 86, 87, 88, 89 and 90; a CDRL2 is SEQ ID NO: 81; and a CDRL3 selected from the group consisting of SEQ ID NO: 76, 79, 82 and 84. In another embodiment is provided an isolated antigen-binding protein of that comprises at least one heavy chain variable region and at least one light chain variable region. In yet another embodiment is provided an isolated antigen-binding protein as described above that comprise at least two heavy chain variable regions and at least two light chain variable regions. In yet another embodiment is provided an isolated antigen binding protein wherein the antigen binding protein is coupled to a labeling group.

Also provided are isolated antigen binding proteins that bind IL-23 selected from the group consisting of a) an antigen binding protein having CDRH1 of SEQ ID NO:129, CDRH2 of SEQ ID NO:132, CDRH3 of SEQ ID NO:136, and CDRL1 of SEQ ID NO:123, CDRL2 of SEQ ID NO:81, and CDRL3 of SEQ ID NO: 76; b) an antigen binding protein having CDRH1 of SEQ ID NO:131, CDRH2 of SEQ ID NO: 134, CDRH3 of SEQ ID NO:137 and CDRL1 of SEQ ID NO:124, CDRL2 of SEQ ID N0126 and CDRL3 of SEQ ID NO:128; c) a) an antigen binding protein having CDRH1 of SEQ ID NO:130, CDRH2 of SEQ ID NO:133, CDRH3 of SEQ ID NO:99 and CDRL1 of SEQ ID NO:68, CDRL2 of SEQ ID NO:69, and CDRL3 of SEQ ID NO:67; and d) an antigen binding protein having CDRH1 SEQ ID NO:91, CDRH2 SEQ ID NO: 135, CDRH3 SEQ ID NO:138 and CDRL1 SEQ ID NO:125, CDRL2 SEQ ID NO:127, and CDRL3 SEQ ID NO:64.

Also provided are isolated antigen binding proteins that bind IL-23 comprising at least one heavy chain variable region and at least one light chain variable region, selected from the group consisting of: a heavy chain variable region comprising amino acid residues 31-35, 50-65 and 99-113 of SEQ ID NO:31; and a light chain variable region comprising amino acid residues 23-36, 52-58 and 91-101 of SEQ ID NO:1; a heavy chain variable region comprising amino acid residues 31-35, 50-65 and 99-110 of SEQ ID NO:34 and heavy chain variable region comprising amino acid residues 31-35, 50-66 and 99-110 of SEQ ID NO:36; and a light chain variable region comprising amino acid residues 23-36, 52-62 and 97-105 of SEQ ID NO:4; a heavy chain variable region comprising amino acid residues 31-35, 50-66 and 99-114 of SEQ ID NO:38; and a light chain variable region comprising amino acid residues 23-34, 50-61 and 94-106 of SEQ ID NO:7; a heavy chain variable region comprising amino acid residues 31-35, 50-66 and 99-114 of SEQ ID NO:40; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 94-106 of SEQ ID NO:9; a heavy chain variable region comprising amino acid residues 31-35, 50-66 and 99-114 of SEQ ID NO:42; and a light chain variable region comprising amino acid residues 23-34, 50-61 and 94-106 of SEQ ID NO:11; a heavy chain variable region comprising amino acid residues 31-35, 50-65 and 98-107 of SEQ ID NO:44; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID NO:13; a heavy chain variable region comprising amino acid residues 31-37, 52-67 and 100-109 of SEQ ID NO:46 or SEQ ID NO:153; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID N015; a heavy chain variable region comprising amino acid residues 31-37, 52-67 and 100-109 of SEQ ID NO:48; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID NO:17; a heavy chain variable region comprising amino acid residues 31-37, 52-67 and 101-109 of SEQ ID NO:50; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID NO:19; a heavy chain variable region comprising amino acid residues 31-35, 50-65 and 98-107 of SEQ ID NO: 52; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 98-107 of SEQ ID NO:21; a heavy chain variable region comprising amino acid residues 31-37, 52-67 and 100-109 of SEQ ID NO:54; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID NO:23; a heavy chain variable region comprising amino acid residues 31-37, 52-67 and 100-109 of SEQ ID NO:56; and a light chain variable region comprising amino acid residues 24-34, 50-56 and 89-97 of SEQ ID NO:25; and a heavy chain variable region comprising amino acid residues 31-37, 52-57 and 100-109 of SEQ ID NO:58; and a light chain variable region comprising amino acid residues 24-34, 500-56 and 89-97 of SEQ ID NO:27.

Provided herein is an isolated antigen binding protein that binds IL-23 comprising a heavy chain variable region and a light chain variable region, wherein the heavy chain variable region sequence differs by no more than 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, additions and/or deletions from a heavy chain variable region sequence as shown in TABLE 2; and wherein the light chain variable region sequence differs by no more than 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions, additions and/or deletions from a light chain variable region sequence as shown in TABLE 1.

Also provided is an isolated antigen binding protein that binds IL-23 selected from the group consisting of a) a heavy chain variable region of SEQ ID NO:140 and a light chain variable region of SEQ ID NO: 30; b) a heavy chain variable region of SEQ ID NO:141 and a light chain variable region of SEQ ID NO:61; c) a heavy chain variable region of SEQ ID NO:142 and a light chain variable region of SEQ ID NO:4; and d) a heavy chain variable region of SEQ ID NO:143 and a light chain variable region of SEQ ID NO:139.

Also provided is an isolated antigen binding protein comprising a heavy chain variable region comprising of an amino acid sequence having at least 90%, 95%, 96%, 97%, 98% or 99% sequence identity to SEQ ID NO:31, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56 and 58; and a light chain variable region comprising an amino acid sequence having at least 90% sequence identity to SEQ ID NO: 1, 4, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25 and 27. In another embodiment is an isolated antigen binding protein comprising a heavy chain variable region selected from the group consisting of SEQ ID NO: 44, 46, 48, 50, 52, 54, 56, 58 and 153, and a light chain variable region selected from the group consisting of SEQ ID NO:13, 15, 17, 19, 21, 23, 25, and 27. In yet another embodiment is an isolated antigen binding protein comprising a heavy chain variable region selected from the group consist-

ing of SEQ ID NO: 31, 34, 36, 38, 40 and 42, and a light chain variable region selected from the group consisting of SEQ ID NO: 1, 4, 7, 9 and 11.

Also provided is an isolated antigen binding protein that binds IL-23 comprising a heavy chain variable region and a light chain variable region selected from the group consisting of: a) a heavy chain variable region of SEQ ID NO:31 and a light chain variable region of SEQ ID NO:1; b) a heavy chain variable region of SEQ ID NO:34 or 36 and a light chain variable region of SEQ ID NO:4; c) a heavy chain variable region of SEQ ID NO:38 and a light chain variable region of SEQ ID NO: 7; d) a heavy chain variable region of SEQ ID NO:40 and a light chain variable region of SEQ ID NO:9; e) a heavy chain variable region of SEQ ID NO:42 and a light chain variable region of SEQ ID NO: 11; f) a heavy chain variable region of SEQ ID NO:44 and a light chain variable region of SEQ ID NO:13; g) a heavy chain variable region of SEQ ID NO:46 or SEQ ID NO:153 and a light chain variable region of SEQ ID NO:15; h) a heavy chain variable region of SEQ ID NO:48 and a light chain variable region of SEQ ID NO:17; i) a heavy chain variable region of SEQ ID NO:50 and a light chain variable region of SEQ ID NO: 19; j) a heavy chain variable region of SEQ ID NO:52 and a light chain variable region of SEQ ID NO:21; k) a heavy chain variable region of SEQ ID NO:54 and a light chain variable region of SEQ ID NO:23; l) a heavy chain variable region of SEQ ID NO:56 and a light chain variable region of SEQ ID NO:25; and m) a heavy chain variable region of SEQ ID NO:58 and a light chain variable region of SEQ ID NO:27.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contacts 30, 31, 32, 49, 50, 52, 53, 56, 92 and 94 of SEQ ID NO:15, wherein the residue contacts have a difference value of greater than or equal to 10 $Å^2$ as determined by solvent exposed surface area. Within one embodiment the residue contacts comprise residues 31-35, 54, 58-60, 66, and 101-105 of SEQ ID NO:46.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contacts 31-34, 51, 52, 55, 68, 93 and 98 of SEQ ID NO:1, wherein the residue contacts have a difference value of greater than or equal to 10 $Å^2$ as determined by solvent exposed surface area. Within one embodiment the residue contacts comprise residues 1, 26, 28, 31, 32, 52, 53, 59, 76, 101, 102 and 104-108 of SEQ ID NO:31.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 32-35, 54, 58-60, 66 and 101-105 of SEQ ID NO:46, as determined by X-ray crystallography. In one embodiment the antigen binding protein is 5 Å or less from residues 31-35, 54, 56, 58-60, 66 and 101-105 of SEQ ID NO:46.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 30-32, 49, 52, 53, 91-94 and 96 of SEQ ID NO:15, as determined by X-ray crystallography. In one embodiment the antigen binding protein is 5 Å or less from residues 30-32, 49, 50, 52, 53, 56, 91-94 and 96 of SEQ ID NO:15.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 26-28, 31, 53, 59, 102 and 104-108 of SEQ ID NO:31, as determined by X-ray crystallography. In one embodiment the antigen binding protein is 5 Å or less from residues 1, 26-28, 30-32, 52, 53, 59, 100, and 102-108 of SEQ ID NO:31.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein when said antigen binding protein is bound to human IL-23, said antigen binding protein is 5 Å or less from residues 31-34, 51, 52, 55, 68 and 93 of SEQ ID NO:1 as determined by X-ray crystallography. In one embodiment the antigen binding protein is 5 Å or less from residues 29, 31-34, 51, 52, 55, 68, 93 and 100 of SEQ ID NO:1.

Also provided is an isolated antigen binding protein as described above, wherein the antigen binding protein is an antibody. In one embodiment is provided an isolated antigen binding protein wherein the antibody is a monoclonal antibody, a recombinant antibody, a human antibody, a humanized antibody, a chimeric antibody, a multispecific antibody, or an antibody fragment thereof. In another embodiment is provided an isolated antigen binding protein wherein the antibody fragment is a Fab fragment, a Fab' fragment, a F(ab')2 fragment, a Fv fragment, a diabody, or a single chain antibody molecule. In yet another embodiment is provided an isolated antigen binding protein wherein the antigen binding protein is a human antibody. In still another embodiment is provided an isolated antigen binding protein wherein the antigen binding protein is a monoclonal antibody. In another embodiment is provided an isolated antigen binding protein wherein the antigen binding protein is of the IgG1-, IgG2-IgG3- or IgG4-type. In yet another embodiment is provided an isolated antigen binding protein wherein the antigen binding protein is of the IgG1- or IgG2-type.

An isolated nucleic acid molecule encoding an antigen binding protein as described above, is also provided. In one embodiment is provided an isolated nucleic acid molecule wherein at least one heavy chain variable region is encoded by an isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs:32, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59 and 152 and at least one light chain variable region is encoded by an isolated nucleic acid molecule selected from the group consisting of SEQ ID NOs:2, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28. In another embodiment is provided a nucleic acid molecule wherein the nucleic acid molecule is operably linked to a control sequence. In another embodiment is provided a vector comprising a nucleic acid molecule as described above. In yet another embodiment is provided a host cell comprising the nucleic acid molecule as described above. In another embodiment is provided a host cell comprising the vector described above. In yet another embodiment is provided an isolated polynucleotide sufficient for use as a hybridization probe, PCR primer or sequencing primer that is a fragment of the nucleic acid molecule as described above or its complement.

Also provided is a method of making the antigen binding protein as described above, comprising the step of preparing said antigen binding protein from a host cell that secretes said antigen binding protein.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises a residue contact within residues 46-58, a residue contact within residues 112-120, and a residue contact within residues 155-163 of the human IL-23p19 subunit as described in SEQ ID NO:145, wherein the residue contact has a difference value greater than or equal to 10 $Å^2$ as determined by solvent exposed surface area. In one embodiment is provided wherein the covered patch formed when the antigen binding

protein is bound to human IL-23 comprises one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve or thirteen residue contacts within residues 46-58, one, two, three, four, five, six, seven, eight, nine or ten residue contacts within residues 112-120, and one, two, three, four, five, six, seven, eight or nine residue contacts within residues 155-163 of the human IL-23p19 subunit as described in SEQ ID NO:145. In another embodiment is provided wherein the covered patch formed when the antigen binding protein binds to human IL-23 comprises a residue contact within residues 121-125 of the human IL-23p40 subunit as described in SEQ ID NO:147. In a related embodiment is wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises one, two, three, four or five residue contacts within residues 121-125 of the human IL-23p40 subunit as described in SEQ ID NO:147. Within another embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contacts 46, 47, 49, 50, 53, 112-116, 118, 120, 155, 156, 159, 160, and 163 of SEQ ID NO:145. In another embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contacts 46, 47, 49, 50, 53, 112-118, 120, 155, 156, 159, 160, and 163 of SEQ ID NO:145. Within another embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residues 46, 47, 49, 50, 53-55, 57, 58, 112-116, 118-120, 155, 156, 159, 160, 162 and 163 of SEQ ID NO:145. In a related embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contact 122 of the human IL-23p40 subunit as described in SEQ ID NO:147. In another related embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contacts 122 and 124 of the human IL-23p40 subunit as described in SEQ ID NO:147. In yet another related embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contact 121-123 and 125 of the human IL-23p40 subunit as described in SEQ ID NO:147. In a further related embodiment is provided wherein the covered patch formed when the antigen binding protein is bound to human IL-23 comprises residue contact 121-123, 125 and 283 of the human IL-23p40 subunit as described in SEQ ID NO:147.

Also provided is an isolated antigen binding protein that binds human IL-23, wherein when said antigen binding protein is bound to human IL-23 said antigen binding protein is 5 Å or less from a residue within residues 46-58, from a residue within residues 112-123, and from a residue within residues 155-163 of the human IL-23p19 subunit as described in SEQ ID NO:145, as determined by X-ray crystallography. In one embodiment, when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve or thirteen residues within residues 46-58, from one, two, three, four, five, six, seven, eight, nine or ten, residues within residues 112-123, and from one, two, three, four, five, six, seven, eight or nine residues within residues 155-163 of the human IL-23p19 subunit as described in SEQ ID NO:145. Within another embodiment when the antigen binding protein is bound to human IL-23 the antigen binding protein is 5 Å or less from residues 46-50, 113-116, 120, 156, 159, 160 and 163 of SEQ ID NO:145. Within another embodiment when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 46-50, 112-120, 156, 159, 160 and 163 of SEQ ID NO:145. Within a related embodiment when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 46-50, 53, 112-120, 156, 159, 160 and 163 of SEQ ID NO:145. Within another embodiment when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 46-50, 53-55, 58, 113-116, 120, 121, 156, 159, 160, 162 and 163 of SEQ ID NO:145. Within a related embodiment when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 46-51, 53-55, 57, 58, 112-116, 118-121, 123, 155, 156, 159, 160, 162 and 163 of SEQ ID NO:145. Within a further embodiment when the antigen binding protein is bound to human IL-23 the antigen binding protein is 5 Å or less from a residue within residues 121-125, of the human IL-23p40 subunit as described in SEQ ID NO:147, as determined by X-ray crystallography. With a related embodiment when the antigen binding protein is bound to human IL-23, said antigen binding protein is 5 Å or less from residues 122 and 124 of SEQ ID NO:147. Within another embodiment when the antigen binding protein is bound to human IL-23, the antigen binding protein is 5 Å or less from residues 121-123 and 125 of SEQ ID NO:147.

Also provided is an isolated antigen binding protein as described above, wherein the antigen binding protein has at least one property selected from the group consisting of: a) reducing human IL-23 activity; b) reducing production of a proinflammatory cytokine; c) binding to human IL-23 with a KD of ≤5×10-8 M; d) having a Koff rate of ≤5×10-6 1/s; and d) having an IC50 of ≤400 pM.

A pharmaceutical composition comprising at least one antigen binding protein as described above and pharmaceutically acceptable excipient is provided. In one embodiment is provided a pharmaceutical composition further comprises a labeling group or an effector group. In yet another embodiment is provided a pharmaceutical composition wherein the labeling group is selected from the group consisting of isotopic labels, magnetic labels, redox active moieties, optical dyes, biotinylated groups and predetermined polypeptide epitopes recognized by a secondary reporter. In yet another embodiment is provided a pharmaceutical composition wherein the effector group is selected from the group consisting of a radioisotope, radionuclide, a toxin, a therapeutic group and a chemotherapeutic group.

Also provided is a method for treating or preventing a condition associated with IL-23 in a patient, comprising administering to a patient in need thereof an effective amount of at least one isolated antigen binding protein as described above. In one embodiment is provided a method of wherein the condition is selected from the group consisting of an inflammatory disorder, a rheumatic disorder, an autoimmune disorder, an oncological disorder and a gastrointestinal disorder. In yet another embodiment is provided a method wherein the condition is selected from the group consisting of multiple sclerosis, rheumatoid arthritis, cancer, psoriasis, inflammatory bowel disease, Crohn's disease, ulcerative colitis, systemic lupus erythematosus, psoriatic arthritis, autoimmune myocarditis; type 1 diabetes and ankylosing spondylitis. In still another embodiment is provided a method wherein the isolated antigen-binding protein is administered alone or as a combination therapy.

Also provided is a method of reducing IL-23 activity in a patient comprising administering an effective amount of at least one antigen binding protein as described above. In one embodiment is provided a method of reducing IL-23 activity, wherein said IL-23 activity is inducing production of a proinflammatory cytokine.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1A: Results of STAT-luciferase reporter assay using recombinant human IL-23. All antibodies completely inhibited recombinant human IL-23

FIG. 1B: Results from STAT-luciferase reporter assay using native human IL-23. Only half of those antibodies that completely inhibited recombinant human IL-23 were able to completely inhibit native human IL-23

DETAILED DESCRIPTION

The present invention provides compositions, kits, and methods relating to IL-23 antigen binding proteins, including molecules that antagonize IL-23, such as anti-IL-23 antibodies, antibody fragments, and antibody derivatives, e.g., antagonistic anti-IL-23 antibodies, antibody fragments, or antibody derivatives. Also provided are polynucleotides, and derivatives and fragments thereof, comprising a sequence of nucleic acids that encodes all or a portion of a polypeptide that binds to IL-23, e.g., a polynucleotide encoding all or part of an anti-IL-23 antibody, antibody fragment, or antibody derivative, plasmids and vectors comprising such nucleic acids, and cells or cell lines comprising such polynucleotides and/or vectors and plasmids. The provided methods include, for example, methods of making, identifying, or isolating IL-23 antigen binding proteins, such as anti-IL-23 antibodies, methods of determining whether a molecule binds to IL-23, methods of determining whether a molecule antagonizes IL-23, methods of making compositions, such as pharmaceutical compositions, comprising an IL-23 antigen binding protein, and methods for administering an IL-23 antigen binding protein to a subject, for example, methods for treating a condition mediated by IL-23, and for antagonizing a biological activity of IL-23, in vivo or in vitro.

Unless otherwise defined herein, scientific and technical terms used in connection with the present invention shall have the meanings that are commonly understood by those of ordinary skill in the art. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures used in connection with, and techniques of, cell and tissue culture, molecular biology, immunology, microbiology, genetics and protein and nucleic acid chemistry and hybridization described herein are those well known and commonly used in the art. The methods and techniques of the present invention are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification unless otherwise indicated. See, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001) and Ausubel et al., Current Protocols in Molecular Biology, Greene Publishing Associates (1992), and Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications, as commonly accomplished in the art or as described herein. The terminology used in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described herein are those well known and commonly used in the art. Standard techniques can be used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

All patents and other publications identified are expressly incorporated herein by reference in their entirety for the purpose of describing and disclosing, for example, the methodologies described in such publications that might be used in connection with information described herein.

The polynucleotide and protein sequences of the p19 subunit of human IL-23 (SEQ ID NOs: 144 and 145), the shared p40 subunit (SEQ ID NOs:146 and 147), the human IL-23 receptor hererodimeric subunits IL-12Rβ1 (SEQ ID NOs: 150 and 151) and IL-23R (SEQ ID NOs: 148 and 149), are known in the art, see for example, GenBank Accession Nos. AB030000; M65272, NM_005535, NM_144701, as are those from other mammalian species. Recombinant IL-23 and IL-23 receptor proteins including single chain and Fc proteins as well as cells expressing the IL-23 receptor have been described or are available from commercial sources. (see for example, Oppmann et al., Immunity, 2000, 13: 713-715; R&D Systems, Minneapolis. Minn.; United States Biological, Swampscott, Mass.; WIPO Publication No. WO 2007/076524). Native human IL-23 can be obtained from human cells such as dendritic cells using methods known in the art including those described herein.

IL-23 is a heterodimeric cytokine comprised of a unique p19 subunit that is covalently bound to a shared p40 subunit. The p19 subunit comprises four α-helices, "A", "B", "C" and "D" in an up-up-down-down motif joined by three intra-helix loops between the A and B helices, between the B and C helices and between the C and D helices, see Oppmann et al., Immunity, 2000, 13: 713-715 and Beyer, et al., J Mol Biol, 2008. 382(4): 942-55. The A and D helices of 4 helical bundle cytokines are believed to be involved with receptor binding. The p40 subunit comprises three beta-sheet sandwich domains, D1, D2 and D3 (Lupardus and Garcia, J. Mol. Biol., 2008, 382:931-941.

The term "polynucleotide" includes both single-stranded and double-stranded nucleic acids and includes genomic DNA, RNA, mRNA, cDNA, or synthetic origin or some combination thereof which is not associated with sequences normally found in nature. Isolated polynucleotides comprising specified sequences may include, in addition to the specified sequences, coding sequences for up to ten or even up to twenty other proteins or portions thereof, or may include operably linked regulatory sequences that control expression of the coding region of the recited nucleic acid sequences, and/or may include vector sequences. The nucleotides comprising the polynucleotide can be ribonucleotides or deoxyribonucleotides or a modified form of either type of nucleotide. The modifications include base modifications such as bromouridine and inosine derivatives, ribose modifications such as 2',3'-dideoxyribose, and internucleotide linkage modifications such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoroanilothioate, phoshoraniladate and phosphoroamidate.

The term "oligonucleotide" means a polynucleotide comprising 100 or fewer nucleotides. In some embodiments, oligonucleotides are 10 to 60 bases in length. In other embodiments, oligonucleotides are 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 nucleotides in length. Oligonucleotides may be single stranded or double stranded, e.g., for use in the construction of a mutant gene. Oligonucleotides may be sense or antisense oligonucleotides. An oligonucleotide can include a detectable label, such as a radiolabel, a fluorescent label, a hapten or an antigenic label, for detection assays. Oligonucleotides may be used, for example, as PCR primers, cloning primers or hybridization probes.

The terms "polypeptide" or "protein" means a macromolecule having the amino acid sequence of a native protein, that

is, a protein produced by a naturally-occurring and non-recombinant cell; or it is produced by a genetically-engineered or recombinant cell, and comprise molecules having the amino acid sequence of the native protein, or molecules having one or more deletions from, insertions to, and/or substitutions of the amino acid residues of the native sequence. The term also includes amino acid polymers in which one or more amino acids are chemical analogs of a corresponding naturally-occurring amino acid and polymers. The terms "polypeptide" and "protein" encompass IL-23 antigen binding proteins (such as antibodies) and sequences that have one or more deletions from, additions to, and/or substitutions of the amino acid residues of the antigen binding protein sequence. The term "polypeptide fragment" refers to a polypeptide that has an amino-terminal deletion, a carboxyl-terminal deletion, and/or an internal deletion as compared with the full-length native protein. Such fragments may also contain modified amino acids as compared with the native protein. In certain embodiments, fragments are about five to 500 amino acids long. For example, fragments may be at least 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 50, 70, 100, 110, 150, 200, 250, 300, 350, 400, or 450 amino acids long. Useful polypeptide fragments include immunologically functional fragments of antibodies, including binding domains. In the case of an IL-23 antigen binding protein, such as an antibody, useful fragments include but are not limited to one or more CDR regions, a variable domain of a heavy or light chain, a portion of an antibody chain, a portion of a variable region including less than three CDRs, and the like.

"Amino acid" includes its normal meaning in the art. The twenty naturally-occurring amino acids and their abbreviations follow conventional usage. See, Immunology—A Synthesis, 2nd Edition, (E. S. Golub and D. R. Gren, eds.), Sinauer Associates: Sunderland, Mass. (1991). Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as [alpha]-, [alpha]-disubstituted amino acids, N-alkyl amino acids, and other unconventional amino acids may also be suitable components for polypeptides. Examples of unconventional amino acids include: 4-hydroxyproline, [gamma]-carboxyglutamate, [epsilon]-N,N,N-trimethyllysine, [epsilon]-N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, [sigma]-N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxyl-terminal direction, in accordance with standard usage and convention.

The term "isolated protein" refers to a protein, such as an antigen binding protein (an example of which could be an antibody), that is purified from proteins or polypeptides or other contaminants that would interfere with its therapeutic, diagnostic, prophylactic, research or other use. As used herein, "substantially pure" means that the described species of molecule is the predominant species present, that is, on a molar basis it is more abundant than any other individual species in the same mixture. In certain embodiments, a substantially pure molecule is a composition wherein the object species comprises at least 50% (on a molar basis) of all macromolecular species present. In other embodiments, a substantially pure composition will comprise at least 80%, 85%, 90%, 95%, or 99% of all macromolecular species present in the composition. In certain embodiments, an essentially homogeneous substance has been purified to such a degree that contaminating species cannot be detected in the composition by conventional detection methods and thus the composition consists of a single detectable macromolecular species.

A "variant" of a polypeptide (e.g., an antigen binding protein such as an antibody) comprises an amino acid sequence wherein one or more amino acid residues are inserted into, deleted from and/or substituted into the amino acid sequence relative to another polypeptide sequence. Variants include fusion proteins. A "derivative" of a polypeptide is a polypeptide that has been chemically modified in some manner distinct from insertion, deletion, or substitution variants, e.g., via conjugation to another chemical moiety.

The terms "naturally occurring" or "native" as used throughout the specification in connection with biological materials such as polypeptides, nucleic acids, host cells, and the like, refers to materials which are found in nature, such as native human IL-23. In certain aspects, recombinant antigen binding proteins that bind native IL-23 are provided. In this context, a "recombinant protein" is a protein made using recombinant techniques, i.e., through the expression of a recombinant nucleic acid as described herein. Methods and techniques for the production of recombinant proteins are well known in the art.

The term "antibody" refers to an intact immunoglobulin of any isotype, or a fragment thereof that can compete with the intact antibody for specific binding to the target antigen, and includes, for instance, chimeric, humanized, fully human, and bispecific antibodies. An antibody as such is a species of an antigen binding protein. Unless otherwise indicated, the term "antibody" includes, in addition to antibodies comprising two full-length heavy chains and two full-length light chains, derivatives, variants, fragments, and muteins thereof, examples of which are described below. An intact antibody generally will comprise at least two full-length heavy chains and two full-length light chains, but in some instances may include fewer chains such as antibodies naturally occurring in camelids which may comprise only heavy chains. Antibodies may be derived solely from a single source, or may be "chimeric," that is, different portions of the antibody may be derived from two different antibodies as described further below. The antigen binding proteins, antibodies, or binding fragments may be produced in hybridomas, by recombinant DNA techniques, or by enzymatic or chemical cleavage of intact antibodies.

The term "functional fragment" (or simply "fragment") of an antibody or immunoglobulin chain (heavy or light chain), as used herein, is an antigen binding protein comprising a portion (regardless of how that portion is obtained or synthesized) of an antibody that lacks at least some of the amino acids present in a full-length chain but which is capable of specifically binding to an antigen. Such fragments are biologically active in that they bind specifically to the target antigen and can compete with other antigen binding proteins, including intact antibodies, for specific binding to a given epitope. In one aspect, such a fragment will retain at least one CDR present in the full-length light or heavy chain, and in some embodiments will comprise a single heavy chain and/or light chain or portion thereof. These biologically active fragments may be produced by recombinant DNA techniques, or may be produced by enzymatic or chemical cleavage of antigen binding proteins, including intact antibodies. Fragments include, but are not limited to, immunologically functional fragments such as Fab, Fab', F(ab')2, Fv, domain antibodies and single-chain antibodies, and may be derived from any mammalian source, including but not limited to human, mouse, rat, camelid or rabbit. It is contemplated further that a functional portion of the antigen binding proteins disclosed

herein, for example, one or more CDRs, could be covalently bound to a second protein or to a small molecule to create a therapeutic agent directed to a particular target in the body, possessing bifunctional therapeutic properties, or having a prolonged serum half-life.

The term "compete" when used in the context of antigen binding proteins (e.g., neutralizing antigen binding proteins or neutralizing antibodies) means competition between antigen binding proteins as determined by an assay in which the antigen binding protein (e.g., antibody or immunologically functional fragment thereof) under test prevents or inhibits specific binding of a reference antigen binding protein (e.g., a ligand, or a reference antibody) to a common antigen (e.g., an IL-23 protein or a fragment thereof). Numerous types of competitive binding assays can be used, for example: solid phase direct or indirect radioimmunoassay (RIA), solid phase direct or indirect enzyme immunoassay (EIA), sandwich competition assay (see, e.g., Stahli et al., 1983, Methods in Enzymology 92:242-253); solid phase direct biotin-avidin EIA (see, e.g., Kirkland et al., 1986, J. Immunol. 137:3614-3619) solid phase direct labeled assay, solid phase direct labeled sandwich assay (see, e.g., Harlow and Lane, 1988, Antibodies, A Laboratory Manual, Cold Spring Harbor Press); solid phase direct label RIA using 1-125 label (see, e.g., Morel et al., 1988, Molec. Immunol. 25:7-15); solid phase direct biotin-avidin EIA (see, e.g., Cheung, et al., 1990, Virology 176:546-552); and direct labeled RIA (Moldenhauer et al., 1990, Scand. J. Immunol. 32:77-82). Typically, such an assay involves the use of purified antigen bound to a solid surface or cells bearing either of these, an unlabelled test antigen binding protein and a labeled reference antigen binding protein.

Competitive inhibition is measured by determining the amount of label bound to the solid surface or cells in the presence of the test antigen binding protein. Usually the test antigen binding protein is present in excess. Antigen binding proteins identified by competition assay (competing antigen binding proteins) include antigen binding proteins binding to the same epitope as the reference antigen binding proteins and antigen binding proteins binding to an adjacent epitope sufficiently proximal to the epitope bound by the reference antigen binding protein for steric hindrance to occur. Usually, when a competing antigen binding protein is present in excess, it will inhibit specific binding of a reference antigen binding protein to a common antigen by at least 40%, 45%, 50%, 55%, 60%, 65%, 70% or 75%. In some instance, binding is inhibited by at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% 98%, 99% or more.

The term "epitope" or "antigenic determinant" refers to a site on an antigen to which an antigen binding protein binds. Epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with denaturing solvents. Epitope determinants may include chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl or sulfonyl groups, and may have specific three dimensional structural characteristics, and/or specific charge characteristics. An epitope typically includes at least 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35 amino acids in a unique spatial conformation. Epitopes can be determined using methods known in the art.

IL-23 Antigen Binding Proteins

An "antigen binding protein" as used herein means a protein that specifically binds a specified target antigen; the antigen as provided herein is IL-23, particularly human IL-23, including native human IL-23. Antigen binding proteins as provided herein interact with at least a portion of the unique p19 subunit of IL-23, detectably binding IL-23; but do not bind with any significance to IL-12 (e.g., the p40 and/or the p35 subunits of IL-12), thus "sparing IL-12". As a consequence, the antigen binding proteins provided herein are capable of impacting IL-23 activity without the potential risks that inhibition of IL-12 or the shared p40 subunit might incur. The antigen binding proteins may impact the ability of IL-23 to interact with its receptor, for example by impacting binding to the receptor, such as by interfering with receptor association. In particular, such antigen binding proteins totally or partially reduce, inhibit, interfere with or modulate one or more biological activities of IL-23. Such inhibition or neutralization disrupts a biological response in the presence of the antigen binding protein compared to the response in the absence of the antigen binding protein and can be determined using assays known in the art and described herein. Antigen binding proteins provided herein inhibit IL-23-induced proinflammatory cytokine production, for example IL-23-induced IL-22 production in whole blood cells and IL-23-induced IFNγ expression in NK and whole blood cells. Reduction of biological activity can be about 20%, 30%, 40%, 50%, 60%, 70%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97% 98%, 99% or more.

An antigen binding protein may comprise a portion that binds to an antigen and, optionally, a scaffold or framework portion that allows the antigen binding portion to adopt a conformation that promotes binding of the antigen binding protein to the antigen. Examples of antigen binding proteins include antibodies, antibody fragments (e.g., an antigen binding portion of an antibody), antibody derivatives, and antibody analogs. The antigen binding protein can comprise an alternative protein scaffold or artificial scaffold with grafted CDRs or CDR derivatives. Such scaffolds include, but are not limited to, antibody-derived scaffolds comprising mutations introduced to, for example, stabilize the three-dimensional structure of the antigen binding protein as well as wholly synthetic scaffolds comprising, for example, a biocompatible polymer. See, for example, Korndorfer et al., Proteins: Structure, Function, and Bioinformatics, (2003) Volume 53, Issue 1:121-129; Roque et al., Biotechnol. Prog., 2004, 20:639-654. In addition, peptide antibody mimetics ("PAMs") can be used, as well as scaffolds based on antibody mimetics utilizing fibronection components as a scaffold.

Certain antigen binding proteins described herein are antibodies or are derived from antibodies. Such antigen binding proteins include, but are not limited to, monoclonal antibodies, bispecific antibodies, minibodies, domain antibodies, synthetic antibodies, antibody mimetics, chimeric antibodies, humanized antibodies, human antibodies, antibody fusions, antibody conjugates, single chain antibodies, and fragments thereof, respectively. In some instances, the antigen binding protein is an immunological fragment of an antibody (e.g., a Fab, a Fab', a F(ab')2, or a scFv). The various structures are further described and defined herein.

Certain antigen binding proteins that are provided may comprise one or more CDRs as described herein (e.g., 1, 2, 3, 4, 5, 6 or more CDRs). In some instances, the antigen binding protein comprises (a) a polypeptide structure and (b) one or more CDRs that are inserted into and/or joined to the polypeptide structure. The polypeptide structure can take a variety of different forms. For example, it can be, or comprise, the framework of a naturally occurring antibody, or fragment

or variant thereof, or may be completely synthetic in nature. Examples of various polypeptide structures are further described below.

An antigen binding protein of the invention is said to "specifically bind" its target antigen when the dissociation equilibrium constant (KD) is ≤10-8 M. The antigen binding protein specifically binds antigen with "high affinity" when the KD is ≤5×10-9 M, and with "very high affinity" when the KD is ≤5×10-10 M. In one embodiment the antigen binding protein will bind to human IL-23 with a KD of ≤5×10-12 M, and in yet another embodiment it will bind with a KD≤5×10-13 M. In another embodiment of the invention, the antigen binding protein has a KD of ≤5×10-12 M and an Koff of about 5×10-6 1/s. In another embodiment, the Koff is ≤5×10-71/s.

Another aspect provides an antigen binding protein having a half-life of at least one day in vitro or in vivo (e.g., when administered to a human subject). In one embodiment, the antigen binding protein has a half-life of at least three days. In another embodiment, the antibody or portion thereof has a half-life of four days or longer. In another embodiment, the antibody or portion thereof has a half-life of eight days or longer. In another embodiment, the antibody or antigen binding portion thereof is derivatized or modified such that it has a longer half-life as compared to the underivatized or unmodified antibody. In another embodiment, the antigen binding protein contains point mutations to increase serum half life, such as described in WIPO Publication No. WO 00/09560.

In embodiments where the antigen binding protein is used for therapeutic applications, an antigen binding protein can reduce, inhibit, interfere with or modulate one or more biological activities of IL-23, such inducing production of proinflammatory cytokines. IL-23 has many distinct biological effects, which can be measured in many different assays in different cell types; examples of such assays and known and are provided herein.

Some of the antigen binding proteins that are provided have the structure typically associated with naturally occurring antibodies. The structural units of these antibodies typically comprise one or more tetramers, each composed of two identical couplets of polypeptide chains, though some species of mammals also produce antibodies having only a single heavy chain. In a typical antibody, each pair or couplet includes one full-length "light" chain (in certain embodiments, about 25 kDa) and one full-length "heavy" chain (in certain embodiments, about 50-70 kDa). Each individual immunoglobulin chain is composed of several "immunoglobulin domains", each consisting of roughly 90 to 110 amino acids and expressing a characteristic folding pattern. These domains are the basic units of which antibody polypeptides are composed. The amino-terminal portion of each chain typically includes a variable region that is responsible for antigen recognition. The carboxy-terminal portion is more conserved evolutionarily than the other end of the chain and is referred to as the "constant region" or "C region". Human light chains generally are classified as kappa and lambda light chains, and each of these contains one variable region and one constant domain (CL1).z Heavy chains are typically classified as mu, delta, gamma, alpha, or epsilon chains, and these define the antibody's isotype as IgM, IgD, IgG, IgA, and IgE, respectively. IgG has several subtypes, including, but not limited to, IgG1, IgG2, IgG3, and IgG4. IgM subtypes include IgM, and IgM2. IgA subtypes include IgA1 and IgA2. In humans, the IgA and IgD isotypes contain four heavy chains and four light chains; the IgG and IgE isotypes contain two heavy chains and two light chains; and the IgM isotype contains five heavy chains and five light chains. The heavy chain constant region (CH) typically comprises one or more domains that may be responsible for effector function. The number of heavy chain constant region domains will depend on the isotype. IgG heavy chains, for example, each contains three CH region domains known as CH1, CH2 and CH3. The antibodies that are provided can have any of these isotypes and subtypes, for example, the IL-23 antigen binding protein is of the IgG1, IgG2, or IgG4 subtype. If an IgG4 is desired, it may also be desired to introduce a point mutation (CPSCP->CPPCP) in the hinge region as described in Bloom et al., 1997, Protein Science 6:407) to alleviate a tendency to form intra-H chain disulfide bonds that can lead to heterogeneity in the IgG4 antibodies. Antibodies provided herein that are of one type can be changed to a different type using subclass switching methods. See, e.g., Lantto et al., 2002, Methods Mol. Biol. 178:303-316.

In full-length light and heavy chains, the variable and constant regions are joined by a "J" region of about twelve or more amino acids, with the heavy chain also including a "D" region of about ten more amino acids. See, e.g., Fundamental Immunology, 2nd ed., Ch. 7 (Paul, W., ed.) 1989, New York: Raven Press. The variable regions of each light/heavy chain pair typically form the antigen binding site.

Variable Regions

Various heavy chain and light chain variable regions (or domains) provided herein are depicted in TABLES 1 and 2. Each of these variable regions may be attached, for example, to heavy and light chain constant regions described above. Further, each of the so generated heavy and light chain sequences may be combined to form a complete antigen binding protein structure.

Provided are antigen binding proteins that contain at least one heavy chain variable region (VH) selected from the group consisting of VH1, VH2, VH3, VH4, VH5, VH6, VH7, VH8, VH9, VH10, VH11, VH12, VH13, VH14, VH15 and VH16 and/or at least one light chain variable region (VL) selected from the group consisting of VL1, VL2, VL3, VL4, VL5, VL6, VL7, VL8, VL9, VL10, VL11, VL12, VL13, VL14, VL15, and VL16 as shown in TABLES 1 and 2 below.

Each of the heavy chain variable regions listed in TABLE 2 may be combined with any of the light chain variable regions shown in TABLE 1 to form an antigen binding protein. In some instances, the antigen binding protein includes at least one heavy chain variable region and/or one light chain variable region from those listed in TABLES 1 and 2. In some instances, the antigen binding protein includes at least two different heavy chain variable regions and/or light chain variable regions from those listed in TABLES 1 and 2. The various combinations of heavy chain variable regions may be combined with any of the various combinations of light chain variable regions.

In other instances, the antigen binding protein contains two identical light chain variable regions and/or two identical heavy chain variable regions. As an example, the antigen binding protein may be an antibody or immunologically functional fragment that comprises two light chain variable regions and two heavy chain variable regions in combinations of pairs of light chain variable regions and pairs of heavy chain variable regions as listed in TABLES 1 and 2. Examples of such antigen binding proteins comprising two identical heavy chain and light chain variable regions include: Antibody A VH14/VL14; Antibody B VH9/VL9; Antibody C VH10/VL10; Antibody D VH15/VL15; Antibody E VH1/VL1, Antibody F VH11/VL11; Antibody G VH12/VL12; Antibody H VH13/VL13; Antibody I VH8/VL8; Antibody J VH3/VL3; Antibody K VH7/VL7; Antibody L VH4/VL4; Antibody M VH5/VL5 and Antibody N VH6/VL6.

Some antigen binding proteins that are provided comprise a heavy chain variable region and/or a light chain variable region comprising a sequence of amino acids that differs from the sequence of a heavy chain variable region and/or a light chain variable region selected from TABLES 1 and 2 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid. The light and heavy chain variable regions, in some antigen binding proteins, comprise sequences of amino acids that have at least 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98% or 99% sequence identity to the amino acid sequences provided in TABLES 1 and 2. Still other antigen binding proteins, e.g., antibodies or immunologically functional fragments, also include variant heavy chain region forms and/or variant light chain region forms as described herein.

The term "identity" refers to a relationship between the sequences of two or more polypeptide molecules or two or more polynucleotides, as determined by aligning and comparing the sequences. "Percent identity" means the percent of identical residues between the amino acids or nucleotides in the compared molecules and is calculated based on the size of the smallest of the molecules being compared.

TABLE 1

Exemplary Variant Light Chain Region Sequences

	FR1	CDRL1	FR2	CDRL2
V_L1	QSVLTQPPSVSGAPGQRVTISC	***TGSSSNTGAGYDVH***	WYQQVPGTAPKLLIY	***GSGNRPS***
	SEQ ID NO: 1			
V_L2	QSVLTQPPSVSGAPGQRVTISC	***TGSSSNIGAGYDVH***	WYQQLPGTAPKLLIY	***GSNNRPS***
	SEQ ID NO: 3			
V_L3	QAVLTQPSSLSASPGASASLTC	***TLRSGINVGTYRIY***	WYQQKPGSPPQYLLR	***YKSDSDKQQGS***
	SEQ ID NO: 4			
V_L4	QAVLTQPSSLSASPGASASLTC	***TLRSGINVGTYRIY***	WYQQKPGSPPQYLLR	***YKSDSDKQQGS***
	SEQ ID NO: 4			
V_L5	QPVLTQPPSASASLGASVTLTC	***TLNSGYSDYKVD***	WYQQRPGKGPRFVMR	***VGTGGIVGSKGD***
	SEQ ID NO 7			
V_L6	QPVLTQPPSASASLGASVTLTC	***TLSSGYSDYKVD***	WYQQRPGKGPRFVMR	***VGTGGIVGSKGE***
	SEQ ID NO: 9			
V_L7	QPELTQPPSASASLGASVTLTC	***TLSSGYSDYKVD***	WYQLRPGKGPRFVMR	***VGTGGTVGSKGE***
	SEQ ID NO: 11			
V_L8	DIQLTPSPSSVSASVGDRVTITC	***RASQGIAGWLA***	WYQQKPGKAPKLLIY	***AASSLQS***
	SEQ ID NO: 13			
V_L9	DIQMTQSPSSVSASVGDRVTITC	***RASQVISSWLA***	WYQQKPGKAPSLLIY	***AASSLQS***
	SEQ ID NO: 15			
V_L10	DIQMTQSPSSVSASVGDRVTITC	***RASQGSSSWFA***	WYQQKPGKAPKLLIY	***AASSLQS***
	SEQ ID NO: 17			
V_L11	DSQMTQSPSSVSASVGDRVTITC	***RASQGISSWFA***	WYQQKPGQAPNLLIY	***AASSLQS***
	SEQ ID NO: 19			
V_L12	DIQMTQSPSSVSASVGDRVTITC	***RAGQVISSWLA***	WYQQKPGKAPKLLIY	***AASSLQS***
	SEQ ID NO: 21			
V_L13	DIQMTQSPSSVSASVGDRVTITC	***RASQGFSGWLA***	WYQQKPGKAPKLLIY	***AASSLQS***
	SEQ ID NO: 23			
V_L14	DIQLTQSPSSVSASVGDRVTITC	***RASQVISSWFA***	WYQQKPGKAPNLLIY	***AASSLQS***
	SEQ ID NO: 25			
V_L15	DIQMTQSPSSVSASVGDRVTITC	***RASQGSSSWFA***	WYQQKPGKAPKLLIY	***AASSLQS***
	SEQ ID NO: 27			
V_L16	DIQMTQSPSSLSASVGDRVTITC	***RASQGIRNDLG***	WYQQKPGKAPKRLIY	***AASSLQS***
	SEQ ID NO: 29			

	FR3	CDRL3	FR4
V_L1	RFSGSKSGTSASLAITGLQAEDEADYYC	***QSYDSSLSGWV***	FGGGTRLTVL
	SEQ ID NO: 1		
V_L2	RFSGSKSGTSASLAITGLQAEDEADYYC	***QSYDSSLSGWV***	FGGGTKLTVL
	SEQ ID NO: 3		
V_L3	GVPSRFSGSKDASANAGILLISGLQSEDEADYYC	***MIWHSSASV***	FGGGTKLTVL
	SEQ ID NO: 4		

TABLE 1-continued

Exemplary Variant Light Chain Region Sequences

V_L4 GVPSRFSGSKDASANAGILLISGLQSEDEADYYC***MIWHSSASV***FGGGTKLTVL
SEQ ID NO: 4

V_L5 GIPDRFSVLGSGLNRYLTIKNIQEEDESDYHC***GADHGSGSNFVYV***FGTGTKVTVL
SEQ ID NO 7

V_L6 GIPDRFSVLGSGLNRYLTIKNIQEEDESDYHC***GADHGSGSNFVYV***FGTGTKVTVL
SEQ ID NO: 9

V_L7 GIPDRFSVLGSGLNRSLTIKNIQEEDESDYHC***GADHGSGSNFVYV***FGTGTKVTVL
SEQ ID NO: 11

V_L8 FSGSGSGTDFTLTISSLQPEDFATYYC***QQADSFPPT***FGGGTKVEIK
SEQ ID NO: 13

V_L9 FSGSVSGTDFTLTISSLQPEDFATYYC***QQANSFPFT***FGPGTKVDFK
SEQ ID NO: 15

V_L10 FSGSGSGTDFTLTISSLQPEDFATYYC***QQANSFPFT***FGPGTKVDIK
SEQ ID NO: 17

V_L11 FSGSGSGTEFTLTISSLQPEDFATYYC***QQANSFPFT***FGPGTKVDIK
SEQ ID NO: 19

V_L12 FSGSGSGTDFTLTISSLQPDDFATYYC***QQATSFPLT***FGGGTKVEIK
SEQ ID NO: 21

V_L13 FSGSGSGTDFTLTISSLQPEDFATYYC***QQATSFPLT***FGPGTKVDIK
SEQ ID NO: 23

V_L14 FSGSGSGTDFTLTISSLQPADFATYFC***QQATSFPLT***FGPGTKVDVK
SEQ ID NO: 25

V_L15 FSGSGSGTDFTLTISSLQPEDFATYYC***QQANSFPFT***FGPGTKVDIK
SEQ ID NO: 27

V_L16 FSGSGSGTEFTLTISSLQPEDFATYYC***LQHNSYPPT***FGQGTKVEIE
SEQ ID NO: 29

TABLE 2

Exemplary Variant Heavy Chain Region Sequences

	FR1	CDRH1	FR2	CDRH2
V_H1	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	***SYGMH***	WVRQAPGKGLEWVA	***VIWYDGSNEYYADSVKG***
	SEQ ID NO: 31			
V_H2	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	***SYGMH***	WVRQAPGKGLEWVA	***VIWYDGSNKYYADSVKG***
	SEQ ID NO: 33			
V_H3	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	***SYGMH***	WVRQAPGKGLEWVA	***VISFDGSLKYYADSVKG***
	SEQ ID NO: 34			
V_H4	QVQLVESGGGVVQPGRSLRLSCAASGFTFS	***SYAMH***	WVRQAPGKGLEWLS	***VISHDGSIKYYADSVKG***
	SEQ ID NO: 36			
V_H5	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	***SYSMN***	WVRQAPGKGLEWVS	***YISSRSSTIYIADSVKG***
	SEQ ID NO: 38			
V_H6	EVQLVESGGGLVQPGGSLRLSCAASGFTFS	***TYSMN***	WVRQAPGKGLEWVS	***YISSSSSTRYHADSVKG***
	SEQ ID NO: 40			
V_H7	EVQLVESGGGLVQPGGSLRLSCVVSGFTFS	***SFSMN***	WVRQAPGKGLEWVS	***YISSRSSTIYYADSVKG***
	SEQ ID NO: 42			
V_H8	QVQLQESGPGLVKPSETLSLTCTVSGGSIS	***TYYWS***	WIRQPAGKGLEWIG	***LIYTSGSTNYNPSLKS***
	SEQ ID NO: 44			
V_H9	QVQLQESGPGLVKPSQTLSLTCTVSGGSIS	***SGGYYWS***	WIRQHPGKGLEWIG	***HIHYSGNTYYNPSLKS***
	SEQ ID NO: 46			
V_H10	QVQLQESGPGLVKPSQTLSLTCTVSGGSIN	***SGGYYWS***	WIRQHPGKGLEWIG	***YIYYSGSSYYNPSLKS***
	SEQ ID NO: 48			

TABLE 2-continued

Exemplary Variant Heavy Chain Region Sequences

V_H11 QVQLQESGPGLVKPSQTLSLTCTVSGGSIS***SGGYYWS***WIRQHPGKGLEWIG***YIYYSGSTYYNPSLKS***
SEQ ID NO: 50

V_H12 QVQLQESGPRLVKPSETLSLTCTVSGDSIS***SYFWS***WIRQPPGKGLEWLG***YIYYSGSTNYNPSLKS***
SEQ ID NO: 52

V_H13 QVQLQESGPGLVKPSQTLSLTCTVSGGSIS***SGGYYWI***WIRQHPGKGLEWIG***YIYYSGNTYYNPSLKS***
SEQ ID NO: 54

V_H14 QVQLQESGPGLVKPSQTLSLTCTVSGGSIS***SGGYYWS***WIRQHPGKGLEWIG***YIYYSGSTYYNPSLKS***
SEQ ID NO: 56

V_H15 QVQLQESGPGLVKPSQTLSLTCTVSGGSIN***SGGYYWS***WIRQHPGKGLEWIG***YIYYSGSSYYNPSLKS***
SEQ ID NO: 58

V_H16 QVQLVESGGGVVQPGRSLRLSCAASGFTFS***SYGMH***WVRQAPGKGLEWVA***LIWYDGSNKYYADSVKG***
SEQ ID NO: 60

	FR3	CDRH3	FR4

V_H1 RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***DRGYTSSWYPDAFDI***WGQGTMVTVSS
SEQ ID NO: 31

V_H2 RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***DRGYSSSWYPDAFDI***WGQGTMVTVSS
SEQ ID NO: 33

V_H3 RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***ERTTLSGSYFDY***WGQGTLVTVSS
SEQ ID NO: 34

V_H4 RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***ERTTLSGSYFDY***WGQGTLVTVSS
SEQ ID NO: 36

V_H5 RFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR***RIAAAGGFHYYYALDV***WGQGTTVTVSS
SEQ ID NO: 38

V_H6 RFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR***RIAAAGPWGYYYAMDV***WGQGTTVTVSS
SEQ ID NO: 40

V_H7 RFTISRDNAKNSLYLQMNSLRDEDTAVYYCAR***RIAAAGPWGYYYAMDV***WGQGTTVTVSS
SEQ ID NO: 42

V_H8 RVTMSLDTSKNQFSLRLTSVTAADTAVYYCAR***DRGYYYGVDV***WGQGTTVTVSS
SEQ ID NO: 44

V_H9 RVTISVDTSKNQFSLKLSSVTAADTAVYYCAK***NRGFYYGMDV***WGQGTTVTVSS
SEQ ID NO: 46

V_H10 RVTISVDTSQNQFSLKLSSVTAADTAVYYCAR***DRGHYYGMDV***WGQGTTVTVSS
SEQ ID NO: 48

V_H11 RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***DRGHYYGMDV***WGQGTTVTVSS
SEQ ID NO: 50

V_H12 RVTISIDTSKNQFSLKLSSVTAADTAVYYCTR***DRGSYYGSDY***WGQGTLVTVSS
SEQ ID NO: 52

V_H13 RITISVDTSKNQFSLSLSSVTAADTAVYYCAR***NRGYYYGMDV***WGQGTTVTVSS
SEQ ID NO: 54

V_H14 RVTMSVDTSKNQFSLKLSSVTAADTAVYYCAK***NRGFYYGMDV***WGQGTTVTVSS
SEQ ID NO: 56

V_H15 RVTISVDTSKNQFSLKLSSVTAADTAVYYCAR***DRGHYYGMDV***WGQGTTVTVSS
SEQ ID NO: 58

V_H16 RFTISRDNSKNTLYLQMNSLRAEDTAVYYCAR***ENTVTIYYNYGMDV***WGQGTTVTVSS
SEQ ID NO: 60

For these calculations, gaps in alignments (if any) must be addressed by a particular mathematical model or computer program (i.e., an "algorithm"). Methods that can be used to calculate the identity of the aligned nucleic acids or polypeptides include those described in *Computational Molecular Biology*, (Lesk, A. M., ed.), 1988, New York: Oxford University Press; Biocomputing Informatics and Genome Projects, (Smith, D. W., ed.), 1993, New York: Academic Press; Computer Analysis of Sequence Data, Part I, (Griffin, A. M., and Griffin, H. G., eds.), 1994, New Jersey: Humana Press; von Heinje, G., 1987, Sequence Analysis in Molecular Biology, New York: Academic Press; Sequence Analysis Primer, (Gribskov, M. and Devereux, J., eds.), 1991, New York: M. Stockton Press; and Carillo et al., 1988, *SIAM J. Applied Math.* 48:1073.

In calculating percent identity, the sequences being compared are aligned in a way that gives the largest match between the sequences. The computer program used to determine percent identity is the GCG program package, which includes GAP (Devereux et al., 1984, *Nucl. Acid Res.* 12:387; Genetics Computer Group, University of Wisconsin, Madison, Wis.). The computer algorithm GAP is used to align the two polypeptides or polynucleotides for which the percent sequence identity is to be determined. The sequences are aligned for optimal matching of their respective amino acid or nucleotide (the "matched span", as determined by the algorithm). A gap opening penalty (which is calculated as 3× the average diagonal, wherein the "average diagonal" is the average of the diagonal of the comparison matrix being used; the "diagonal" is the score or number assigned to each perfect amino acid match by the particular comparison matrix) and a gap extension penalty (which is usually 1/10 times the gap opening penalty), as well as a comparison matrix such as PAM 250 or BLOSUM 62 are used in conjunction with the algorithm. In certain embodiments, a standard comparison matrix (see, Dayhoff et al., 1978, *Atlas of Protein Sequence and Structure* 5:345-352 for the PAM 250 comparison matrix; Henikoff et al., 1992, *Proc. Natl. Acad. Sci. U.S.A.* 89:10915-10919 for the BLOSUM 62 comparison matrix) is also used by the algorithm.

Recommended parameters for determining percent identity for polypeptides or nucleotide sequences using the GAP program are the following: Algorithm: Needleman et al., 1970, *J. Mol. Biol.* 48:443-453; Comparison matrix: BLOSUM 62 from Henikoff et al., 1992, supra; Gap Penalty: 12 (but with no penalty for end gaps), Gap Length Penalty: 4, Threshold of Similarity: 0. Certain alignment schemes for aligning two amino acid sequences may result in matching of only a short region of the two sequences and this small aligned region may have very high sequence identity even though there is no significant relationship between the two full-length sequences. Accordingly, the selected alignment method (GAP program) can be adjusted if so desired to result in an alignment that spans at least 50 contiguous amino acids of the target polypeptide.

The heavy and light chain variable regions disclosed herein include consensus sequences derived from groups of related antigen binding proteins. The amino acid sequences of the heavy and light chain variable regions were analyzed for similarities. Four groups emerged, one group having kappa light chain variable regions, (V_H9/V_L9, V_H10/V_L10, V_H11/V_L11, V_H13/V_L13, V_H14/V_L14 and V_H15/V_L15) and three groups having lambda light chain variable regions: lambda group 1 (V_H5/V_A5, V_H6/V_L6 and V_H7/V_L7), lambda group 2 (V_H3/V_L3 and V_H4/V_L4), and lambda group 3 (V_H1/V_L1 and V_H2/V_L2). Light chain germlines represented include VK1/A30 and VK1/L19. Light chain lambda germlines represented include VL1/1e, VL3/3p, VL5/5c and VL9/9a. Heavy chain germlines represented include VH3/3-30, VH3/3-30.3, VH3/3-33, VH3/3-48, VH4/4-31 and VH4/4-59. As used herein, a "consensus sequence" refers to amino acid sequences having conserved amino acids common among a number of sequences and variable amino acids that vary within given amino acid sequences. Consensus sequences may be determined using standard phylogenic analyses of the light and heavy chain variable regions corresponding to the IL-23 antigen binding proteins disclosed herein.

The light chain variable region consensus sequence for the kappa group is $DX_1QX_2TQSPSSVSASVGDRVTITCRASQGX_3X_4SX_5WX_6AWYQQKPGX_7APX_8LLIYAASSLQSGVPSR FS GSX_9SGTX_{10}FTLTISSLQPX_{11}DFATYX_{12}CQQANSFPFTFGPGTKVDX_{13}K$ (SEQ ID NO:30) where X_1 is selected from I or S; X_2 is selected from M or L; X_3 is selected from G or V and X_4 is selected from S, F or I; X_5 is selected from S or G; X_6 is selected from F or L; X_7 is selected from K or Q; X_8 is selected from K, N or S; X_9 is selected from G or V; X_{10} is selected from D or E, X_{11} is selected from E or A; X_{12} is selected from Y or F; and X_{13} is selected from I, V or F.

The light chain variable region consensus sequence for lambda group 1 is QPX_1 LTQPPSASASLGASVTLTCTLX$_2$SGYSDYKVDWYQX$_3$RPGKGPRFVMRVGTGGX$_4$VGSKGX$_5$GI PDRFSVLGSGLNRX$_6$LTIKNIQEEDESDYHCGADHGSGX$_7$NFVYVFGTGTKVTVL (SEQ ID NO:61) where X_1 is selected from V or E; X_2 is selected from N or S; X_3 is selected from Q or L and X_4 is selected from I or T; X_5 is selected from D or E; X_6 is selected from Y or S; and X_7 is selected from S or N.

The light chain variable region consensus sequence for lambda group 3 is QSVLTQPPSVSGAPGQRVTISCTGSSSNX$_1$GAGYDVHWYQQX$_2$PGTAPKLLIYGSX$_3$NRPSGVPDRF SG SKSGTSASLAITGLQAEDEADYYCQSYDSSLSGWVFGGGTX$_4$RLTVL (SEQ ID NO:139) where X_1 is selected from T or I; X_2 is selected from V or L; X_3 is selected from G or N and X_4 is selected from R or K.

The heavy chain variable region consensus sequence for the kappa group is QVQLQESGPGLVKPSQTLSLTCTVSGGSIX$_1$SGGYYWX$_2$WIRQHPGKGLEWIGX$_3$IX$_4$YSGX$_5$X$_6$YYNP SLK SRX$_7$TX$_8$SVDTSX$_9$NQFSLX$_{10}$LSSVTAADTAVYYCAX$_{11}$X$_{12}$RGX$_{13}$YYGMDVWGQGTTVTVSS (SEQ ID NO:140) where X_1 is selected from N or S; X_2 is selected from S or T; X_3 is selected from Y or H and X_4 is selected from Y or H; X_5 is selected from S or N; X_6 is selected from S or T; X_7 is selected from V or I; X_8 is selected from I or M; X_9 is selected from K or Q; X_{10} is selected from K or S, X_{11} is selected from R or K; X_{12} is selected from D or N; and X_{13} is selected from H, F or Y.

The heavy chain variable region consensus sequence for lambda group 1 is EVQLVESGGGLVQPGGSLRLSCX$_1$X$_2$SGFTFSX$_3$X$_4$SMNWVRQAPGKGLEWVSYISSX$_5$SSTX$_6$YX$_7$AD SV KGRFTISRDNAKNSLYLQMNSLRDEDTAVYYCARRIAAAGX$_8$X$_9$X$_{10}$YYYAX$_{11}$DVWGQGTTVTVSS (SEQ ID NO:141) where X_1 is selected from A or V; X_2 is selected from A or V; X_3 is selected from T or S and X_4 is selected from Y or F; X_5 is selected from S or R; X_6 is selected from R or I; X_7 is selected from H, Y or I; X_8 is selected from P or G; X_9 is selected from W or F; X_{10} is selected from G or H and X_{11} is selected from M or L.

The heavy chain variable region consensus sequence for lambda group 2 is QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYX$_1$MHWVRQAPGKGLEWX$_2$X$_3$VISX$_4$DGSX$_5$KYYAD SV KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCARERTTLSGSYFDYWGQGTLVTVSS (SEQ ID NO:142) where X$_1$ is selected from G or A; X$_2$ is selected from V or L; X$_3$ is selected from A or S and X$_4$ is selected from F or H and X$_5$ is selected from L or I.

The heavy chain variable region consensus sequence for lambda group 3 is QVQLVESGGGVVQPGRSLRLSCAASGFTFSSYGMHWVRQAPGKGLEWVAVIWYDGSNX$_1$YYADSV KG RFTISRDNSKNTLYLQMNSLRAEDTAVYYCARDRGYX$_2$SSWYPDAFDIWGQGTMVTVSS (SEQ ID NO: 143) where X$_1$ is selected from E or K and X$_2$ is selected from T or S.

Complementarity Determining Regions

Complementarity determining regions or "CDRs" are embedded within a framework in the heavy and light chain variable regions where they constitute the regions responsible for antigen binding and recognition. Variable domains of immunoglobulin chains of the same species, for example, generally exhibit a similar overall structure; comprising relatively conserved framework regions (FR) joined by hypervariable CDR regions. An antigen binding protein can have 1, 2, 3, 4, 5, 6 or more CDRs. The variable regions discussed above, for example, typically comprise three CDRs. The CDRs from heavy chain variable regions and light chain variable regions are typically aligned by the framework regions to form a structure that binds specifically on a target antigen (e.g., IL-23). From N-terminal to C-terminal, naturally-occurring light and heavy chain variable regions both typically conform to the following order of these elements: FR1, CDR1, FR2, CDR2, FR3, CDR3 and FR4. The CDR and FR regions of exemplary light chain variable domains and heavy chain variable domains are highlighted in TABLES 1 and 2. It is recognized that the boundaries of the CDR and FR regions can vary from those highlighted. Numbering systems have been devised for assigning numbers to amino acids that occupy positions in each of these domains. Complementarity determining regions and framework regions of a given antigen binding protein may be identified using these systems. Numbering systems are defined in Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed., US Dept. of Health and Human Services, PHS, NIH, NIH Publication No. 91-3242, 1991, or Chothia & Lesk, 1987, *J. Mol. Biol.* 196: 901-917; Chothia et al., 1989, *Nature* 342:878-883. Other numbering systems for the amino acids in immunoglobulin chains include IMGT® (the international ImMunoGeneTics information system; Lefranc et al, *Dev. Comp. Immunol.* 2005, 29:185-203); and AHo (Honegger and Pluckthun, *J. Mol. Biol.* 2001, 309(3):657-670). The CDRs provided herein may not only be used to define the antigen binding domain of a traditional antibody structure, but may be embedded in a variety of other polypeptide structures, as described herein.

The antigen binding proteins disclosed herein are polypeptides into which one or more CDRs may be grafted, inserted, embedded and/or joined. An antigen binding protein can have, for example, one heavy chain CDR1 ("CDRH1"), and/or one heavy chain CDR2 ("CDRH2"), and/or one heavy chain CDR3 ("CDRH3"), and/or one light chain CDR1 ("CDRL1"), and/or one light chain CDR2 ("CDRL2"), and/or one light chain CDR3 ("CDRL3"). Some antigen binding proteins include both a CDRH3 and a CDRL3. Specific embodiments generally utilize combinations of CDRs that are non-repetitive, e.g., antigen binding proteins are generally not made with two CDRH2 regions in one variable heavy chain region, etc. Antigen binding proteins may comprise one or more amino acid sequences that are identical to or that differ from to the amino acid sequences of one or more of the CDRs presented in TABLE 3 at only 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid residues, wherein each such sequence difference is independently either a deletion, insertion or substitution of one amino acid. The CDRs in some antigen binding proteins comprise sequences of amino acids that have at least 80%, 85%, 90%, 91%, 92, 93%, 94%, 95%, 96%, 97%, 98%, or 99% sequence identity to CDRs sequence listed in TABLE 3. In some antigen binding proteins, the CDRs are embedded into a "framework" region, which orients the CDR(s) such that the proper antigen binding properties of the CDR(s) is achieved.

TABLE 3

Exemplary CDRH and CDRL Sequences

Exemplary CDRL Sequences		
CDRL1	CDRL2	CDRL3
TGSSSNTGAGYDVH SEQ ID NO: 62	GSNNRPS SEQ ID NO: 63	QSYDSSLSGWV SEQ ID NO: 64
TGSSSNIGAGYDVH SEQ ID NO: 65	GSNNRPS SEQ ID NO: 66	MIWHSSASV SEQ ID NO: 67
TLRSGINVGTYRIY SEQ ID NO: 68	YKSDSDKQQGS SEQ ID NO: 69	GADHGSGSNFVYV SEQ ID NO: 70
TLNSGYSDYKV SEQ ID NO: 71	VGTGGIVGSKGD SEQ ID NO: 72	GADHGSGNNFVYV SEQ ID NO: 73
TLSSGYSDYKV SEQ ID NO: 74	VGTGGIVGSKGE SEQ ID NO: 75	QQANSFPFT SEQ ID NO: 76
RASQGFSGWLA SEQ ID NO: 77	VGTGGTVGSKGE SEQ ID NO: 78	QQATSFPLT SEQ ID NO: 79
RASQVISSWLA SEQ ID NO: 80	AASSLQS SEQ ID NO: 81	QQADSFPPT SEQ ID NO: 82

TABLE 3-continued

Exemplary CDRH and CDRL Sequences

RASQVISSWFA SEQ ID NO: 83	LQHNSYPPT SEQ ID NO: 84
RASQGSSSWFA SEQ ID NO: 85	
RASQGISSWFA SEQ ID NO: 86	
RAGQVISSWLA SEQ ID NO: 87	
RASQGIAGWLA SEQ ID NO: 88	
RASQGIRNDLG SEQ ID NO: 89	

Exemplary CDRH Sequences

CDRH1	CDRH2	CDRH3
SYGMH SEQ ID NO: 91	VIWYDGSNEYYADSVKG SEQ ID NO: 92	DRGYTSSWYPDAFDI SEQ ID NO: 93
SYAMH SEQ ID NO: 94	VIWYDGSNKYYADSVKG SEQ ID NO: 95	DRGYSSSWYPDAFDI SEQ ID NO: 96
TYSMN SEQ ID NO: 97	VISFDGSLKYYADSVKG SEQ ID NO: 98	ERTTLSGSYFDY SEQ ID NO: 99
SYSMN SEQ ID NO: 100	VISHDGSIKYYADSVKG SEQ ID NO: 101	RIAAAGGFHYYYALDV SEQ ID NO: 102
SFSMN SEQ ID NO: 103	YISSRSSTIYIADSVKG SEQ ID NO: 104	RIAAAGPWGYYYAMDV SEQ ID NO: 105
SGGYYWT SEQ ID NO: 106	YISSSSSTRYHADSVKG SEQ ID NO: 107	NRGYYYGMDV SEQ ID NO: 108
SGGYYWS SEQ ID NO: 109	YISSRSSTIYYADSVKG SEQ ID NO: 110	NRGFYYGMDV SEQ ID NO: 111
SYFWS SEQ ID NO: 112	YIYYSGNTYYNPSLKS SEQ ID NO: 113	DRGHYYGMDV SEQ ID NO: 114
TYYWS SEQ ID NO: 115	HIHYSGNTYYNPSLKS SEQ ID NO: 116	DRGSYYGSDY SEQ ID NO: 117
	YIYYSGSTYYNPSLKS SEQ ID NO: 118	DRGYYYGVDV SEQ ID NO: 119
	YIYYSGSSYYNPSLKS SEQ ID NO: 120	ENTVTIYYNYGMDV SEQ ID NO: 6
	YIYYSGSTNYNPSLKS SEQ ID NO: 121	
	LIYTSGSTNYNPSLKS SEQ ID NO: 122	
	LIWYDGSNKYYADSVKG SEQ ID NO: 90	

Provided herein are CDR1 regions comprising amino acid residues 23-34 of SEQ ID NOs: 7 and 11; amino acid residues 24-34 of SEQ ID NOs: 9, 13, 15, 17, 19 21, 23, 25, 27 and 29; amino acid residues 23-36 of SEQ ID NOs: 1, 3 and 4; amino acid residues 31-35 of SEQ ID NOs:31, 33, 34, 38, 40, 44, 52 and 60 and amino acid residues 31-37 or SEQ ID NOs: 46, 48, 50, 54, 56 and 58.

CDR2 regions are provided comprising amino acid residues 50-56 of SEQ ID NOs: 9, 13, 15, 17, 19, 21, 23, 25, 27 and 29; amino acid residues 50-61 of SEQ ID NOs: 7 and 11; amino acid residues 52-62 of SEQ ID NO:4; amino acid residues 50-65 of SEQ ID NOs: 31, 33, 44 and 52; amino acid residues 50-66 of SEQ ID NOs: 36, 38, 40, 42 and 60; amino acid residues 52-58 of SEQ ID NOs: 1 and 3 and amino acid residues 52-67 of SEQ ID NOs: 46, 48, 50, 54, 56 and 58.

CDR3 regions comprising amino acid residues 89-97 of SEQ ID NOs: 13, 15, 17, 19, 21, 23, 25, 27 and 29; amino acid residues 91-101 of SEQ ID NOs: 1 and 3; amino acid residues 94-106 of SEQ ID NOs: 7, 9 and 11; amino acid residues 98-107 of SEQ ID NOs: 44 and 52; amino acid residues 97-105 of SEQ ID NO: 4; amino acid residues 99-110 of SEQ ID NOs: 34 and 36; amino acid residues 99-112 of SEQ ID

NO: 112; amino acid residues 99-113 of SEQ ID NOs: 31 and 33; amino acid residues 99-114 of SEQ ID NOs: 38, 40 and 42; amino acid residues 100-109 of SEQ ID NOs: 46, 48, 54, 56 and 58; and amino acid residues 101-019 of SEQ ID NO; 50; are also provided.

The CDRs disclosed herein include consensus sequences derived from groups of related sequences. As described previously, four groups of variable region sequences were identified, a kappa group and three lambda groups. The CDRL1 consensus sequence from the kappa group consists of $RASQX_1X_2SX_3WX_4A$ (SEQ ID NO:123) where X_1 is selected from G or V; X_2 is selected from I, F or 5; X_3 is selected from S or G and X_4 is selected from F or L. The CDRL1 consensus sequence from lambda group 1 consists of $TLX_1SGYSDYKVD$ (SEQ ID NO:124) wherein X_1 is selected from N or S. The CDRL1 consensus sequences from lambda group 3 consists of $TGSSSNX_1GAGYDVH$ (SEQ ID NO:125) wherein X_1 is selected from I or T.

The CDRL2 consensus sequence from lambda group 1 consists of $VGTGGX_1VGSKGX_2$ (SEQ ID NO: 126) wherein X_1 is selected from I or T and X_2 is selected from D or E. The CDRL2 consensus sequence from lambda group 3 consists of GSX_1NRPS (SEQ ID NO:127) wherein X_1 is selected from N or G.

The CDRL3 consensus sequences include $GADHGSGX_1NFVYV$ (SEQ IDN NO:128) wherein X_1 is S or N.

The CDRH1 consensus sequence from the kappa group consists of $SGGYYWX_1$ (SEQ ID NO:129) wherein X_1 is selected from S or T. The CDRH1 consensus sequence from lambda group 1 consists of X_1X_2SMN (SEQ ID NO:131) wherein X_1 is selected from S or T and X_2 is selected from Y or F. The CDRH1 consensus sequence from lambda group 2 consists of SYX_1 MH (SEQ ID NO:130), wherein X_1 is selected from G or A.

The CDRH2 consensus sequence from the kappa group consists of X_1 $IX_2YSGX_3X_4YYNPSLKS$ (SEQ ID NO:132) wherein X_1 is selected from Y or H; X_2 is selected from Y or H; X_3 is selected from S or N and X_4 is selected from T or S. The consensus sequence from lambda group 1 consists of $YISSX_1SSTX_2YX_3ADSVKG$ (SEQ ID NO:134) wherein X_1 is selected from R or S, X_2 is selected from I or R, X_3 is selected from I, H or Y. The consensus sequence from lambda group 2 consists of $VISX_1DGSX_2KYYADSVKG$ (SEQ ID NO:133) wherein X_1 is F or H and X_2 is L or T. The CDRH2 consensus sequence from lambda group 3 consists of $VIWYDGSNX_1YYADSVKG$ (SEQ ID NO:135) wherein X_1 is selected from K or E.

The CDRH3 consensus sequence from the kappa group consists of $X_1RGX_2YYGMDV$ (SEQ ID NO:136) wherein X_1 is selected from N or D and X_2 is selected from H, Y or F. The CDRH3 consensus sequence from lambda group 1 consists of $RIAAAGX_1X_2X_3YYYAX_4DV$ (SEQ ID NO:137) wherein X_1 is selected from G or P; X_2 is selected from F or W; X_3 is selected from H or G and X_4 is selected from L and M. The CDRH3 consensus sequence from lambda group 3 consists of $DRGYX_1SSWYPDAFDI$ (SEQ ID NO:138) wherein X_1 is selected from S or T.

Monoclonal Antibodies

The antigen binding proteins that are provided include monoclonal antibodies that bind to IL-23. Monoclonal antibodies may be produced using any technique known in the art, e.g., by immortalizing spleen cells harvested from the transgenic animal after completion of the immunization schedule. The spleen cells can be immortalized using any technique known in the art, e.g., by fusing them with myeloma cells to produce hybridomas. Myeloma cells for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency, and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the desired fused cells (hybridomas). Examples of suitable cell lines for use in mouse fusions include Sp-20, P3-X63/Ag8, P3-X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XXO Bul; examples of cell lines used in rat fusions include R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210. Other cell lines useful for cell fusions are U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6.

In some instances, a hybridoma cell line is produced by immunizing an animal (e.g., a transgenic animal having human immunoglobulin sequences) with an IL-23 immunogen; harvesting spleen cells from the immunized animal; fusing the harvested spleen cells to a myeloma cell line, thereby generating hybridoma cells; establishing hybridoma cell lines from the hybridoma cells, and identifying a hybridoma cell line that produces an antibody that binds an IL-23 polypeptide while sparing IL-12. Such hybridoma cell lines, and anti-IL-23 monoclonal antibodies produced by them, are aspects of the present application.

Monoclonal antibodies secreted by a hybridoma cell line can be purified using any technique known in the art. Hybridomas or mAbs may be further screened to identify mAbs with particular properties, such as the ability to inhibit IL-23-induced activity.

Chimeric and Humanized Antibodies

Chimeric and humanized antibodies based upon the foregoing sequences are also provided. Monoclonal antibodies for use as therapeutic agents may be modified in various ways prior to use. One example is a chimeric antibody, which is an antibody composed of protein segments from different antibodies that are covalently joined to produce functional immunoglobulin light or heavy chains or immunologically functional portions thereof. Generally, a portion of the heavy chain and/or light chain is identical with or homologous to a corresponding sequence in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is/are identical with or homologous to a corresponding sequence in antibodies derived from another species or belonging to another antibody class or subclass. For methods relating to chimeric antibodies, see, for example, U.S. Pat. No. 4,816,567; and Morrison et al., 1985, *Proc. Natl. Acad. Sci. USA* 81:6851-6855. CDR grafting is described, for example, in U.S. Pat. Nos. 6,180,370, 5,693,762, 5,693,761, 5,585,089, and 5,530,101.

One useful type of chimeric antibody is a "humanized" antibody. Generally, a humanized antibody is produced from a monoclonal antibody raised initially in a non-human animal. Certain amino acid residues in this monoclonal antibody, typically from non-antigen recognizing portions of the antibody, are modified to be homologous to corresponding residues in a human antibody of corresponding isotype. Humanization can be performed, for example, using various methods by substituting at least a portion of a rodent variable region for the corresponding regions of a human antibody (see, e.g., U.S. Pat. No. 5,585,089, and No. 5,693,762; Jones et al., 1986, *Nature* 321:522-525; Riechmann et al., 1988, *Nature* 332:323-27; Verhoeyen et al., 1988, *Science* 239:1534-1536),

In certain embodiments, constant regions from species other than human can be used along with the human variable region(s) to produce hybrid antibodies.

Fully Human Antibodies

Fully human antibodies are also provided. Methods are available for making fully human antibodies specific for a given antigen without exposing human beings to the antigen ("fully human antibodies"). One specific means provided for implementing the production of fully human antibodies is the "humanization" of the mouse humoral immune system. Introduction of human immunoglobulin (Ig) loci into mice in which the endogenous Ig genes have been inactivated is one means of producing fully human monoclonal antibodies (mAbs) in mouse, an animal that can be immunized with any desirable antigen. Using fully human antibodies can minimize the immunogenic and allergic responses that can sometimes be caused by administering mouse or mouse-derivatized mAbs to humans as therapeutic agents.

Fully human antibodies can be produced by immunizing transgenic animals (usually mice) that are capable of producing a repertoire of human antibodies in the absence of endogenous immunoglobulin production. Antigens for this purpose typically have six or more contiguous amino acids, and optionally are conjugated to a carrier, such as a hapten. See, e.g., Jakobovits et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:2551-2555; Jakobovits et al., 1993, *Nature* 362:255-258; and Bruggermann et al., 1993, *Year in Immunol.* 7:33. In one example of such a method, transgenic animals are produced by incapacitating the endogenous mouse immunoglobulin loci encoding the mouse heavy and light immunoglobulin chains therein, and inserting into the mouse genome large fragments of human genome DNA containing loci that encode human heavy and light chain proteins. Partially modified animals, which have less than the full complement of human immunoglobulin loci, are then cross-bred to obtain an animal having all of the desired immune system modifications. When administered an immunogen, these transgenic animals produce antibodies that are immunospecific for the immunogen but have human rather than murine amino acid sequences, including the variable regions. For further details of such methods, see, for example, WIPO patent publications WO96/33735 and WO94/02602. Additional methods relating to transgenic mice for making human antibodies are described in U.S. Pat. Nos. 5,545,807; 6,713,610; 6,673,986; 6,162,963; 5,545,807; 6,300,129; 6,255,458; 5,877,397; 5,874,299 and 5,545,806; in WIPO patent publications WO91/10741, WO90/04036, and in EP 546073B1 and EP 546073A1.

The transgenic mice described above contain a human immunoglobulin gene minilocus that encodes unrearranged human heavy ([mu] and [gamma]) and [kappa] light chain immunoglobulin sequences, together with targeted mutations that inactivate the endogenous [mu] and [kappa] chain loci (Lonberg et al., 1994, *Nature* 368:856-859). Accordingly, the mice exhibit reduced expression of mouse IgM or [kappa] and in response to immunization, and the introduced human heavy and light chain transgenes undergo class switching and somatic mutation to generate high affinity human IgG [kappa] monoclonal antibodies (Lonberg et al., supra.; Lonberg and Huszar, 1995, *Intern. Rev. Immunol.* 13: 65-93; Harding and Lonberg, 1995, *Ann. N.Y Acad. Sci.* 764:536-546). The preparation of such mice is described in detail in Taylor et al., 1992, *Nucleic Acids Research* 20:6287-6295; Chen et al., 1993, *International Immunology* 5:647-656; Tuaillon et al., 1994, *J. Immunol.* 152:2912-2920; Lonberg et al., 1994, *Nature* 368: 856-859; Lonberg, 199, *Handbook of Exp. Pharmacology* 113:49-101; Taylor et al., 1994, *International Immunology* 6:579-591; Lonberg and Huszar, 1995, *Intern. Rev. Immunol.* 13:65-93; Harding and Lonberg, 1995, *Ann. N.Y. Acad. Sci.* 764:536-546; Fishwild et al., 1996, *Nature Biotechnology* 14:845-85. See, further U.S. Pat. No. 5,545,806; No. 5,569, 825; No. 5,625,126; No. 5,633,425; No. 5,789,650; No. 5,877,397; No. 5,661,016; No. 5,814,318; No. 5,874,299; and No. 5,770,429; as well as U.S. Pat. No. 5,545,807; WIPO Publication Nos. WO 93/1227; WO 92/22646; and WO 92/03918. Technologies utilized for producing human antibodies in these transgenic mice are disclosed also in WIPO Publication No. WO 98/24893, and Mendez et al., 1997, *Nature Genetics* 15:146-156. For example, the HCo7 and HCo12 transgenic mice strains can be used to generate anti-IL-23 antibodies.

Using hybridoma technology, antigen-specific human mAbs with the desired specificity can be produced and selected from the transgenic mice such as those described above. Such antibodies may be cloned and expressed using a suitable vector and host cell, or the antibodies can be harvested from cultured hybridoma cells.

Fully human antibodies can also be derived from phage-display libraries (such as disclosed in Hoogenboom et al., 1991, *J. Mol. Biol.* 227:381; Marks et al., 1991, *J. Mol. Biol.* 222:581; WIPO Publication No. WO 99/10494). Phage display techniques mimic immune selection through the display of antibody repertoires on the surface of filamentous bacteriophage, and subsequent selection of phage by their binding to an antigen of choice.

Bispecific or Bifunctional Antigen Binding Proteins

A "bispecific," "dual-specific" or "bifunctional" antigen binding protein or antibody is a hybrid antigen binding protein or antibody, respectively, having two different antigen binding sites, such as one or more CDRs or one or more variable regions as described above. In some instances they are an artificial hybrid antibody having two different heavy/light chain pairs and two different binding sites. Multispecific antigen binding protein or "multispecific antibody" is one that targets more than one antigen or epitope. Bispecific antigen binding proteins and antibodies are a species of multispecific antigen binding protein antibody and may be produced by a variety of methods including, but not limited to, fusion of hybridomas or linking of Fab' fragments. See, e.g., Songsivilai and Lachmann, 1990, *Clin. Exp. Immunol.* 79:315-321; Kostelny et al., 1992, *J. Immunol.* 148:1547-1553.

Immunological Fragments

Antigen binding proteins also include immunological fragments of an antibody (e.g., a Fab, a Fab', a $F(ab')_2$, or a scFv). A "Fab fragment" is comprised one light chain (the light chain variable region (V_L) and its corresponding constant domain (C_L)) and one heavy chain (the heavy chain variable region (V_H) and first constant domain (C_H1)). The heavy chain of a Fab molecule cannot form a disulfide bond with another heavy chain molecule. A "Fab' fragment" contains one light chain and a portion of one heavy chain that also contains the region between the C_H1 and C_H2 domains, such that an interchain disulfide bond can be formed between the two heavy chains of two Fab' fragments to form an $F(ab')_2$ molecule. A "$F(ab')_2$ fragment" thus is composed of two Fab' fragments that are held together by a disulfide bond between the two heavy chains. A "Fv fragment" consists of the variable light chain region and variable heavy chain region of a single arm of an antibody. Single-chain antibodies "scFv" are Fv molecules in which the heavy and light chain variable regions have been connected by a flexible linker to form a single polypeptide chain, which forms an antigen binding region. Single chain antibodies are discussed in detail in WIPO Publication No. WO 88/01649, U.S. Pat. No. 4,946, 778 and No. 5,260,203; Bird, 1988, *Science* 242:423; Huston et al., 1988, *Proc. Natl. Acad. Sci. U.S.A.* 85:5879; Ward et al.,

1989, *Nature* 334:544, de Graaf et al., 2002, *Methods Mol. Biol.* 178:379-387; Kortt et al., 1997, *Prot. Eng.* 10:423; Kortt et al., 2001, *Biomol. Eng.* 18:95-108 and Kriangkum et al., 2001, *Biomol. Eng.* 18:31-40. A "Fc" region contains two heavy chain fragments comprising the C_H1 and C_H2 domains of an antibody. The two heavy chain fragments are held together by two or more disulfide bonds and by hydrophobic interactions of the C_H3 domains.

Also included are domain antibodies, immunologically functional immunoglobulin fragments containing only the variable region of a heavy chain or the variable region of a light chain. In some instances, two or more V_H regions are covalently joined with a peptide linker to create a bivalent domain antibody. The two V_H regions of a bivalent domain antibody may target the same or different antigens. Diabodies are bivalent antibodies comprising two polypeptide chains, wherein each polypeptide chain comprises V_H and V_L domains joined by a linker that is too short to allow for pairing between two domains on the same chain, thus allowing each domain to pair with a complementary domain on another polypeptide chain (see, e.g., Holliger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-48, 1993 and Poljak et al., *Structure* 2:1121-23, 1994). Similarly, tribodies and tetrabodies are antibodies comprising three and four polypeptide chains, respectively, and forming three and four antigen binding sites, respectively, which can be the same or different. Maxibodies comprise bivalent scFvs covalently attached to the Fc region of IgG1, (see, e.g., Fredericks et al, 2004, *Protein Engineering, Design & Selection,* 17:95-106; Powers et al., 2001, *Journal of Immunological Methods,* 251:123-135; Shu et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:7995-7999; Hayden et al., 1994, *Therapeutic Immunology* 1:3-15).

Various Other Forms

Also provided are variant forms of the antigen binding proteins disclosed above, some of the antigen binding proteins having, for example, one or more conservative amino acid substitutions in one or more of the heavy or light chains, variable regions or CDRs listed in TABLES 1 and 2.

Naturally-occurring amino acids may be divided into classes based on common side chain properties: hydrophobic (norleucine, Met, Ala, Val, Leu, Ile); neutral hydrophilic (Cys, Ser, Thr, Asn, Gln); acidic (Asp, Glu); basic (His, Lys, Arg); residues that influence chain orientation (Gly, Pro); and aromatic (Trp, Tyr, Phe).

Conservative amino acid substitutions may involve exchange of a member of one of these classes with another member of the same class. Conservative amino acid substitutions may encompass non-naturally occurring amino acid residues, which are typically incorporated by chemical peptide synthesis rather than by synthesis in biological systems. These include peptidomimetics and other reversed or inverted forms of amino acid moieties. Such substantial modifications in the functional and/or biochemical characteristics of the antigen binding proteins described herein may be achieved by creating substitutions in the amino acid sequence of the heavy and light chains that differ significantly in their effect on maintaining (a) the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulkiness of the side chain.

Non-conservative substitutions may involve the exchange of a member of one of the above classes for a member from another class. Such substituted residues may be introduced into regions of the antibody that are homologous with human antibodies, or into the non-homologous regions of the molecule.

In making such changes, according to certain embodiments, the hydropathic index of amino acids may be considered. The hydropathic profile of a protein is calculated by assigning each amino acid a numerical value ("hydropathy index") and then repetitively averaging these values along the peptide chain. Each amino acid has been assigned a hydropathic index on the basis of its hydrophobicity and charge characteristics. They are: isoleucine (+4.5); valine (+4.2); leucine (+3.8); phenylalanine (+2.8); cysteine/cystine (+2.5); methionine (+1.9); alanine (+1.8); glycine (−0.4); threonine (−0.7); serine (−0.8); tryptophan (−0.9); tyrosine (−1.3); proline (−1.6); histidine (−3.2); glutamate (−3.5); glutamine (−3.5); aspartate (−3.5); asparagine (−3.5); lysine (−3.9); and arginine (−4.5).

The importance of the hydropathic profile in conferring interactive biological function on a protein is understood in the art (see, e.g., Kyte et al., 1982, *J. Mol. Biol.* 157:105-131). It is known that certain amino acids may be substituted for other amino acids having a similar hydropathic index or score and still retain a similar biological activity. In making changes based upon the hydropathic index, in certain embodiments, the substitution of amino acids whose hydropathic indices are within ±2 is included. In some aspects, those which are within ±1 are included, and in other aspects, those within ±0.5 are included.

It is also understood in the art that the substitution of like amino acids can be made effectively on the basis of hydrophilicity, particularly where the biologically functional protein or peptide thereby created is intended for use in immunological embodiments, as in the present case. In certain embodiments, the greatest local average hydrophilicity of a protein, as governed by the hydrophilicity of its adjacent amino acids, correlates with its immunogenicity and antigen binding or immunogenicity, that is, with a biological property of the protein.

The following hydrophilicity values have been assigned to these amino acid residues: arginine (+3.0); lysine (+3.0); aspartate (+3.0±1); glutamate (+3.0±1); serine (+0.3); asparagine (+0.2); glutamine (+0.2); glycine (0); threonine (−0.4); proline (−0.5±1); alanine (−0.5); histidine (−0.5); cysteine (−1.0); methionine (−1.3); valine (−1.5); leucine (−1.8); isoleucine (−1.8); tyrosine (−2.3); phenylalanine (−2.5) and tryptophan (−3.4). In making changes based upon similar hydrophilicity values, in certain embodiments, the substitution of amino acids whose hydrophilicity values are within ±2 is included, in other embodiments, those which are within ±1 are included, and in still other embodiments, those within ±0.5 are included. In some instances, one may also identify epitopes from primary amino acid sequences on the basis of hydrophilicity. These regions are also referred to as "epitopic core regions."

Exemplary conservative amino acid substitutions are set forth in TABLE 4.

TABLE 4

Conservative Amino Acid Substitutions

Residue	Sub	Residue	Sub	Residue	Sub	Residue	Sub
Ala	Ser	Gln	Asn	Leu	Ile, Val	Thr	Ser
Arg	Lys	Glu	Asp	Lys	Arg, Gln, Glu	Trp	Tyr
Asn	Gln, His	Gly	Pro	Met	Leu, Ile	Tyr	Trp, Phe

TABLE 4-continued

Conservative Amino Acid Substitutions

Residue	Sub	Residue	Sub	Residue	Sub	Residue	Sub
Asp	Glu	His	Asn, Gln	Phe	Met, Leu, Tyr	Val	Ile, Leu
Cys	Ser	Ile	Leu, Val	Ser	Thr	Thr	Ser

Residue = Original Residue
Sub = Exemplary Substitution

A skilled artisan will be able to determine suitable variants of polypeptides as set forth herein using well-known techniques. One skilled in the art may identify suitable areas of the molecule that may be changed without destroying activity by targeting regions not believed to be important for activity. The skilled artisan also will be able to identify residues and portions of the molecules that are conserved among similar polypeptides. In further embodiments, even areas that may be important for biological activity or for structure may be subject to conservative amino acid substitutions without destroying the biological activity or without adversely affecting the polypeptide structure.

Additionally, one skilled in the art can review structure-function studies identifying residues in similar polypeptides that are important for activity or structure. In view of such a comparison, one can predict the importance of amino acid residues in a protein that correspond to amino acid residues important for activity or structure in similar proteins. One skilled in the art may opt for chemically similar amino acid substitutions for such predicted important amino acid residues.

One skilled in the art can also analyze the 3-dimensional structure and amino acid sequence in relation to that structure in similar polypeptides. In view of such information, one skilled in the art may predict the alignment of amino acid residues of an antibody with respect to its three dimensional structure. One skilled in the art may choose not to make radical changes to amino acid residues predicted to be on the surface of the protein, since such residues may be involved in important interactions with other molecules. Moreover, one skilled in the art may generate test variants containing a single amino acid substitution at each desired amino acid residue. These variants can then be screened using assays for IL-23 activity, (see examples below) thus yielding information regarding which amino acids can be changed and which must not be changed. In other words, based on information gathered from such routine experiments, one skilled in the art can readily determine the amino acid positions where further substitutions should be avoided either alone or in combination with other mutations.

A number of scientific publications have been devoted to the prediction of secondary structure. See, Moult, 1996, *Curr. Op. in Biotech.* 7:422-427; Chou et al., 1974, *Biochem.* 13:222-245; Chou et al., 1974, Biochemistry 113:211-222; Chou et al., 1978, *Adv. Enzymol. Relat. Areas Mol. Biol.* 47:45-148; Chou et al., 1979, *Ann. Rev. Biochem.* 47:251-276; and Chou et al., 1979, *Biophys. J.* 26:367-384. Moreover, computer programs are currently available to assist with predicting secondary structure. One method of predicting secondary structure is based upon homology modeling. For example, two polypeptides or proteins that have a sequence identity of greater than 30%, or similarity greater than 40% often have similar structural topologies. The recent growth of the protein structural database (PDB) has provided enhanced predictability of secondary structure, including the potential number of folds within a polypeptide's or protein's structure. See, Holm et al., 1999, *Nucl. Acid. Res.* 27:244-247. It has been suggested (Brenner et al., 1997, *Curr. Op. Struct. Biol.* 7:369-376) that there are a limited number of folds in a given polypeptide or protein and that once a critical number of structures have been resolved, structural prediction will become dramatically more accurate.

Additional methods of predicting secondary structure include "threading" (Jones, 1997, *Curr. Opin. Struct. Biol.* 7:377-387; Sippl et al., 1996, *Structure* 4:15-19), "profile analysis" (Bowie et al., 1991, *Science* 253:164-170; Gribskov et al., 1990, *Meth. Enzym.* 183:146-159; Gribskov et al., 1987, *Proc. Nat. Acad. Sci.* 84:4355-4358), and "evolutionary linkage" (See, Holm, 1999, supra; and Brenner, 1997, supra).

In some embodiments, amino acid substitutions are made that: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter ligand or antigen binding affinities, and/or (4) confer or modify other physicochemical or functional properties on such polypeptides, such as maintaining the structure of the molecular backbone in the area of the substitution, for example, as a sheet or helical conformation; maintaining or altering the charge or hydrophobicity of the molecule at the target site, or maintaining or altering the bulkiness of a side chain.

For example, single or multiple amino acid substitutions (in certain embodiments, conservative amino acid substitutions) may be made in the naturally-occurring sequence. Substitutions can be made in that portion of the antibody that lies outside the domain(s) forming intermolecular contacts). In such embodiments, conservative amino acid substitutions can be used that do not substantially change the structural characteristics of the parent sequence (e.g., one or more replacement amino acids that do not disrupt the secondary structure that characterizes the parent or native antigen binding protein). Examples of art-recognized polypeptide secondary and tertiary structures are described in Proteins, Structures and Molecular Principles (Creighton, Ed.), 1984, W. H. New York: Freeman and Company; Introduction to Protein Structure (Branden and Tooze, eds.), 1991, New York: Garland Publishing; and Thornton et al., 1991, *Nature* 354:105.

Additional variants include cysteine variants wherein one or more cysteine residues in the parent or native amino acid sequence are deleted from or substituted with another amino acid (e.g., serine). Cysteine variants are useful, inter alia when antibodies (for example) must be refolded into a biologically active conformation. Cysteine variants may have fewer cysteine residues than the native protein, and typically have an even number to minimize interactions resulting from unpaired cysteines.

The heavy and light chain variable region and CDRs that are disclosed can be used to prepare antigen binding proteins that contain an antigen binding region that can specifically bind to an IL-23 polypeptide. "Antigen binding region" means a protein, or a portion of a protein, that specifically binds a specified antigen, such as the region that contains the amino acid residues that interact with an antigen and confer on the antigen binding protein its specificity and affinity for the target antigen. An antigen binding region may include one or more CDRs and certain antigen binding regions also include one or more "framework" regions. For example, one or more of the CDRs listed in TABLE 3 can be incorporated into a molecule (e.g., a polypeptide) covalently or noncovalently to make an immunoadhesion. An immunoadhesion may incorporate the CDR(s) as part of a larger polypeptide chain, may covalently link the CDR(s) to another polypeptide

chain, or may incorporate the CDR(s) noncovalently. The CDR(s) enable the immunoadhesion to bind specifically to a particular antigen of interest (e.g., an IL-23 polypeptide).

Other antigen binding proteins include mimetics (e.g., "peptide mimetics" or "peptidomimetics") based upon the variable regions and CDRs that are described herein. These analogs can be peptides, non-peptides or combinations of peptide and non-peptide regions. Fauchere, 1986, *Adv. Drug Res.* 15:29; Veber and Freidinger, 1985, *TINS* p. 392; and Evans et al., 1987, *J. Med. Chem.* 30:1229. Peptide mimetics that are structurally similar to therapeutically useful peptides may be used to produce a similar therapeutic or prophylactic effect. Such compounds are often developed with the aid of computerized molecular modeling. Generally, peptidomimetics are proteins that are structurally similar to an antigen binding protein displaying a desired biological activity, such as the ability to bind IL-23, but peptidomimetics have one or more peptide linkages optionally replaced by a linkage selected from, for example: $—CH_2NH—$, $—CH_2S—$, $—CH_2—CH_2—$, —CH—CH-(cis and trans), $—COCH_2—$, $—CH(OH)CH_2—$, and $—CH_2SO—$, by methods well known in the art. Systematic substitution of one or more amino acids of a consensus sequence with a D-amino acid of the same type (e.g., D-lysine in place of L-lysine) may be used in certain embodiments to generate more stable proteins. In addition, constrained peptides comprising a consensus sequence or a substantially identical consensus sequence variation may be generated by methods known in the art (Rizo and Gierasch, 1992, *Ann. Rev. Biochem.* 61:387), for example, by adding internal cysteine residues capable of forming intramolecular disulfide bridges which cyclize the peptide.

Derivatives of the antigen binding proteins that are described herein are also provided. The derivatized antigen binding proteins can comprise any molecule or substance that imparts a desired property to the antigen binding protein or fragment, such as increased half-life in a particular use. The derivatized antigen binding protein can comprise, for example, a detectable (or labeling) moiety (e.g., a radioactive, colorimetric, antigenic or enzymatic molecule, a detectable bead (such as a magnetic or electrodense (e.g., gold) bead), or a molecule that binds to another molecule (e.g., biotin or Streptavidin)), a therapeutic or diagnostic moiety (e.g., a radioactive, cytotoxic, or pharmaceutically active moiety), or a molecule that increases the suitability of the antigen binding protein for a particular use (e.g., administration to a subject, such as a human subject, or other in vivo or in vitro uses). Examples of molecules that can be used to derivatize an antigen binding protein include albumin (e.g., human serum albumin) and polyethylene glycol (PEG). Albumin-linked and PEGylated derivatives of antigen binding proteins can be prepared using techniques well known in the art. In one embodiment, the antigen binding protein is conjugated or otherwise linked to transthyretin (TTR) or a TTR variant. The TTR or TTR variant can be chemically modified with, for example, a chemical selected from the group consisting of dextran, poly(n-vinyl pyrrolidone), polyethylene glycols, propropylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohols.

Other derivatives include covalent or aggregative conjugates of IL-23 antigen binding proteins with other proteins or polypeptides, such as by expression of recombinant fusion proteins comprising heterologous polypeptides fused to the N-terminus or C-terminus of an IL-23 antigen binding protein. For example, the conjugated peptide may be a heterologous signal (or leader) polypeptide, e.g., the yeast alpha-factor leader, or a peptide such as an epitope tag. IL-23 antigen binding protein-containing fusion proteins can comprise peptides added to facilitate purification or identification of the IL-23 antigen binding protein (e.g., poly-His). An IL-23 antigen binding protein also can be linked to the FLAG peptide as described in Hopp et al., 1988, *Bio/Technology* 6:1204; and U.S. Pat. No. 5,011,912. The FLAG peptide is highly antigenic and provides an epitope reversibly bound by a specific monoclonal antibody (mAb), enabling rapid assay and facile purification of expressed recombinant protein. Reagents useful for preparing fusion proteins in which the FLAG peptide is fused to a given polypeptide are commercially available (Sigma, St. Louis, Mo.).

Oligomers that contain one or more IL-23 antigen binding proteins may be employed as IL-23 antagonists. Oligomers may be in the form of covalently-linked or non-covalently-linked dimers, trimers, or higher oligomers. Oligomers comprising two or more IL-23 antigen binding proteins are contemplated for use, with one example being a homodimer. Other oligomers include heterodimers, homotrimers, heterotrimers, homotetramers, heterotetramers, etc. Oligomers comprising multiple IL-23-binding proteins joined via covalent or non-covalent interactions between peptide moieties fused to the IL-23 antigen binding proteins, are also included. Such peptides may be peptide linkers (spacers), or peptides that have the property of promoting oligomerization. Among the suitable peptide linkers are those described in U.S. Pat. Nos. 4,751,180 and 4,935,233. Leucine zippers and certain polypeptides derived from antibodies are among the peptides that can promote oligomerization of IL-23 antigen binding proteins attached thereto. Examples of leucine zipper domains suitable for producing soluble oligomeric proteins are described in WIPO Publication No. WO 94/10308; Hoppe et al., 1994, *FEBS Letters* 344:191; and Fanslow et al., 1994, *Semin. Immunol.* 6:267-278. In one approach, recombinant fusion proteins comprising an IL-23 antigen binding protein fragment or derivative fused to a leucine zipper peptide are expressed in suitable host cells, and the soluble oligomeric IL-23 antigen binding protein fragments or derivatives that form are recovered from the culture supernatant.

Such oligomers may comprise from two to four IL-23 antigen binding proteins. The IL-23 antigen binding protein moieties of the oligomer may be in any of the forms described above, e.g., variants or fragments. Preferably, the oligomers comprise IL-23 antigen binding proteins that have IL-23 binding activity. Oligomers may be prepared using polypeptides derived from immunoglobulins. Preparation of fusion proteins comprising certain heterologous polypeptides fused to various portions of antibody-derived polypeptides (including the Fc domain) has been described, e.g., by Ashkenazi et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:10535; Byrn et al., 1990, *Nature* 344:677; and Hollenbaugh et al., 1992 "Construction of Immunoglobulin Fusion Proteins", in Current Protocols in Immunology, Suppl. 4, pages 10.19.1-10.19.11.

Also included are dimers comprising two fusion proteins created by fusing an IL-23 antigen binding protein to the Fc region of an antibody. The dimer can be made by, for example, inserting a gene fusion encoding the fusion protein into an appropriate expression vector, expressing the gene fusion in host cells transformed with the recombinant expression vector, and allowing the expressed fusion protein to assemble much like antibody molecules, whereupon interchain disulfide bonds form between the Fc moieties to yield the dimer. Such Fc polypeptides include native and mutein forms of polypeptides derived from the Fc region of an antibody. Truncated forms of such polypeptides containing the hinge region that promotes dimerization also are included. Fusion proteins comprising Fc moieties (and oligomers formed therefrom)

offer the advantage of facile purification by affinity chromatography over Protein A or Protein G columns. One suitable Fc polypeptide, described in WIPO Publication No. WO 93/10151 and U.S. Pat. Nos. 5,426,048 and 5,262,522, is a single chain polypeptide extending from the N-terminal hinge region to the native C-terminus of the Fc region of a human IgG1 antibody. Another useful Fc polypeptide is the Fc mutein described in U.S. Pat. No. 5,457,035, and in Baum et al., 1994, *EMBO J.* 13:3992-4001. The amino acid sequence of this mutein is identical to that of the native Fc sequence presented in WIPO Publication No. WO 93/10151, except that amino acid 19 has been changed from Leu to Ala, amino acid 20 has been changed from Leu to Glu, and amino acid 22 has been changed from Gly to Ala. The mutein exhibits reduced affinity for Fc receptors.

Glycosylation

The antigen binding protein may have a glycosylation pattern that is different or altered from that found in the native species. As is known in the art, glycosylation patterns can depend on both the sequence of the protein (e.g., the presence or absence of particular glycosylation amino acid residues, discussed below), or the host cell or organism in which the protein is produced. Particular expression systems are discussed below.

Glycosylation of polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tri-peptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tri-peptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylgalactosamine, galactose, or xylose, to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the antigen binding protein is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tri-peptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the starting sequence (for O-linked glycosylation sites). For ease, the antigen binding protein amino acid sequence may be altered through changes at the DNA level, particularly by mutating the DNA encoding the target polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the antigen binding protein is by chemical or enzymatic coupling of glycosides to the protein. These procedures are advantageous in that they do not require production of the protein in a host cell that has glycosylation capabilities for N- and O-linked glycosylation. Depending on the coupling mode used, the sugar(s) may be attached to (a) arginine and histidine, (b) free carboxyl groups, (c) free sulfhydryl groups such as those of cysteine, (d) free hydroxyl groups such as those of serine, threonine, or hydroxyproline, (e) aromatic residues such as those of phenylalanine, tyrosine, or tryptophan, or (f) the amide group of glutamine. These methods are described in PCT Publication No. WO 87/05330, and in Aplin and Wriston, 1981, *CRC Crit. Rev, Biochem.*, pp. 259-306.

Removal of carbohydrate moieties present on the starting antigen binding protein may be accomplished chemically or enzymatically. Chemical deglycosylation requires exposure of the protein to the compound trifluoromethanesulfonic acid, or an equivalent compound. This treatment results in the cleavage of most or all sugars except the linking sugar (N-acetylglucosamine or N-acetylgalactosamine), while leaving the polypeptide intact. Chemical deglycosylation is described by Hakimuddin et al., 1987, *Arch. Biochem. Biophys.* 259:52 and by Edge et al., 1981, *Anal. Biochem.* 118: 131. Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., 1987, *Meth. Enzymol.* 138:350. Glycosylation at potential glycosylation sites may be prevented by the use of the compound tunicamycin as described by Duskin et al., 1982, *J. Biol. Chem.* 257:3105. Tunicamycin blocks the formation of protein-N-glycoside linkages.

Hence, aspects include glycosylation variants of the antigen binding proteins wherein the number and/or type of glycosylation site(s) has been altered compared to the amino acid sequences of the parent polypeptide. In certain embodiments, antigen binding protein variants comprise a greater or a lesser number of N-linked glycosylation sites than the parent polypeptide. Substitutions that eliminate or alter this sequence will prevent addition of an N-linked carbohydrate chain present in the parent polypeptide. For example, the glycosylation can be reduced by the deletion of an Asn or by substituting the Asn with a different amino acid. Antibodies typically have a N-linked glycosylation site in the Fc region.

Labels and Effector Groups

Antigen binding proteins may comprise one or more labels. The term "label" or "labeling group" refers to any detectable label. In general, labels fall into a variety of classes, depending on the assay in which they are to be detected: a) isotopic labels, which may be radioactive or heavy isotopes; b) magnetic labels (e.g., magnetic particles); c) redox active moieties; d) optical dyes; enzymatic groups (e.g. horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase); e) biotinylated groups; and f) predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags, etc.). In some embodiments, the labeling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art. Examples of suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labeling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labeling proteins are known in the art and may be used as is seen fit.

The term "effector group" means any group coupled to an antigen binding protein that acts as a cytotoxic agent. Examples for suitable effector groups are radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I). Other suitable groups include toxins, therapeutic groups, or chemotherapeutic groups. Examples of suitable groups include calicheamicin, auristatins, geldanamycin and maytansine. In some embodiments, the effector group is

coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance.

Polynucleotides Encoding IL-23 Antigen Binding Proteins

Polynucleotides that encode the antigen binding proteins described herein, or portions thereof, are also provided, including polynucleotides encoding one or both chains of an antibody, or a fragment, derivative, mutein, or variant thereof, polynucleotides encoding heavy chain variable regions or only CDRs, polynucleotides sufficient for use as hybridization probes, PCR primers or sequencing primers for identifying, analyzing, mutating or amplifying a polynucleotide encoding a polypeptide, anti-sense nucleic acids for inhibiting expression of a polynucleotide, and complementary sequences of the foregoing. The polynucleotides can be any length. They can be, for example, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 75, 85, 95, 100, 125, 150, 175, 200, 250, 300, 350, 400, 450, 500, 750, 1,000, 1,500, 3,000, 5,000 or more nucleic acids in length, including all values in between, and/or can comprise one or more additional sequences, for example, regulatory sequences, and/or be part of a larger polynucleotide, for example, a vector. The polynucleotides can be single-stranded or double-stranded and can comprise RNA and/or DNA nucleic acids and artificial variants thereof (e.g., peptide nucleic acids).

Polynucleotides encoding certain antigen binding proteins, or portions thereof (e.g., full length antibody, heavy or light chain, variable domain, or a CDRH1, CDRH2, CDRH3, CDRL1, CDRL2, or CDRL3) may be isolated from B-cells of mice that have been immunized with IL-23 or an immunogenic fragment thereof. The polynucleotide may be isolated by conventional procedures such as polymerase chain reaction (PCR). Phage display is another example of a known technique whereby derivatives of antibodies and other antigen binding proteins may be prepared. In one approach, polypeptides that are components of an antigen binding protein of interest are expressed in any suitable recombinant expression system, and the expressed polypeptides are allowed to assemble to form antigen binding protein molecules. Phage display is also used to derive antigen binding proteins having different properties (i.e., varying affinities for the antigen to which they bind) via chain shuffling, see Marks et al., 1992, *BioTechnology* 10:779.

Due to the degeneracy of the genetic code, each of the polypeptide sequences depicted herein are also encoded by a large number of other polynucleotide sequences besides those provided. For example, heavy chain variable domains provided herein in may be encoded by polynucleotide sequences SEQ ID NOs: 32, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, or 59. Light chain variable domains may be encoded by polynucleotide sequences SEQ ID NOs:2, 5, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, or 28. One of ordinary skill in the art will appreciate that the present application thus provides adequate written description and enablement for each degenerate nucleotide sequence encoding each antigen binding protein.

An aspect further provides polynucleotides that hybridize to other polynucleotide molecules under particular hybridization conditions. Methods for hybridizing nucleic acids, basic parameters affecting the choice of hybridization conditions and guidance for devising suitable conditions are well-known in the art. See, e.g., Sambrook, Fritsch, and Maniatis (2001, Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. and Current Protocols in Molecular Biology, 1995, Ausubel et al., eds., John Wiley & Sons, Inc. As defined herein, a moderately stringent hybridization condition uses a prewashing solution containing 5× sodium chloride/sodium citrate (SSC), 0.5% SDS, 1.0 mM EDTA (pH 8.0), hybridization buffer of about 50% formamide, 6×SSC, and a hybridization temperature of 55° C. (or other similar hybridization solutions, such as one containing about 50% formamide, with a hybridization temperature of 42° C.), and washing conditions of 60° C., in 0.5×SSC, 0.1% SDS. A stringent hybridization condition hybridizes in 6×SSC at 45° C., followed by one or more washes in 0.1×SSC, 0.2% SDS at 68° C. Furthermore, one of skill in the art can manipulate the hybridization and/or washing conditions to increase or decrease the stringency of hybridization such that polynucleotides comprising nucleic acid sequences that are at least 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92, 93%, 94%, 95%, 96%, 97%, 98% or 99% identical to each other, including all values in between, typically remain hybridized to each other.

Changes can be introduced by mutation into a polynucleotide, thereby leading to changes in the amino acid sequence of a polypeptide (e.g., an antigen binding protein or antigen binding protein derivative) that it encodes. Mutations can be introduced using any technique known in the art, such as site-directed mutagenesis and random mutagenesis. Mutant polypeptides can be expressed and selected for a desired property. Mutations can be introduced into a polynucleotide without significantly altering the biological activity of a polypeptide that it encodes. For example, substitutions at non-essential amino acid residues. Alternatively, one or more mutations can be introduced into a polynucleotide that selectively change the biological activity of a polypeptide that it encodes. For example, the mutation can quantitatively or qualitatively change the biological activity, such as increasing, reducing or eliminating the activity and changing the antigen specificity of an antigen binding protein.

Another aspect provides polynucleotides that are suitable for use as primers or hybridization probes for the detection of nucleic acid sequences. A polynucleotide can comprise only a portion of a nucleic acid sequence encoding a full-length polypeptide, for example, a fragment that can be used as a probe or primer or a fragment encoding an active portion (e.g., an IL-23 binding portion) of a polypeptide. Probes based on the sequence of a nucleic acid can be used to detect the nucleic acid or similar nucleic acids, for example, transcripts encoding a polypeptide. The probe can comprise a label group, e.g., a radioisotope, a fluorescent compound, an enzyme, or an enzyme co-factor. Such probes can be used to identify a cell that expresses the polypeptide.

Methods of Expressing Antigen Binding Proteins

The antigen binding proteins provided herein may be prepared by any of a number of conventional techniques. For example, IL-23 antigen binding proteins may be produced by recombinant expression systems, using any technique known in the art. See, e.g., Monoclonal Antibodies, Hybridomas: A New Dimension in Biological Analyses, Kennet et al. (eds.) Plenum Press, New York (1980); and Antibodies: A Laboratory Manual, Harlow and Lane (eds.), Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1988).

Expression systems and constructs in the form of plasmids, expression vectors, transcription or expression cassettes that comprise at least one polynucleotide as described above are also provided herein, as well host cells comprising such expression systems or constructs. As used herein, "vector" means any molecule or entity (e.g., nucleic acid, plasmid, bacteriophage or virus) suitable for use to transfer protein coding information into a host cell. Examples of vectors include, but are not limited to, plasmids, viral vectors, non-episomal mammalian vectors and expression vectors, for example, recombinant expression vectors. Expression vectors, such as recombinant expression vectors, are useful for

transformation of a host cell and contain nucleic acid sequences that direct and/or control (in conjunction with the host cell) expression of one or more heterologous coding regions operatively linked thereto. An expression construct may include, but is not limited to, sequences that affect or control transcription, translation, and, if introns are present, affect RNA splicing of a coding region operably linked thereto. "Operably linked" means that the components to which the term is applied are in a relationship that allows them to carry out their inherent functions. For example, a control sequence, e.g., a promoter, in a vector that is "operably linked" to a protein coding sequence are arranged such that normal activity of the control sequence leads to transcription of the protein coding sequence resulting in recombinant expression of the encoded protein.

Another aspect provides host cells into which an expression vector, such as a recombinant expression vector, has been introduced. A host cell can be any prokaryotic cell (for example, *E. coli*) or eukaryotic cell (for example, yeast, insect, or mammalian cells (e.g., CHO cells)). Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene that encodes a selectable marker (e.g., for resistance to antibiotics) is generally introduced into the host cells along with the gene of interest. Preferred selectable markers include those which confer resistance to drugs, such as G418, hygromycin and methotrexate. Cells stably transfected with the introduced polynucleotide can be identified by drug selection (e.g., cells that have incorporated the selectable marker gene will survive, while the other cells die), among other methods.

Antigen binding proteins can be expressed in hybridoma cell lines (e.g., in particular antibodies may be expressed in hybridomas) or in cell lines other than hybridomas. Expression constructs encoding the antigen binding proteins can be used to transform a mammalian, insect or microbial host cell. Transformation can be performed using any known method for introducing polynucleotides into a host cell, including, for example packaging the polynucleotide in a virus or bacteriophage and transducing a host cell with the construct by transfection procedures known in the art, as exemplified by U.S. Pat. Nos. 4,399,216; 4,912,040; 4,740,461; 4,959,455. The optimal transformation procedure used will depend upon which type of host cell is being transformed. Methods for introduction of heterologous polynucleotides into mammalian cells are well known in the art and include, but are not limited to, dextran-mediated transfection, calcium phosphate precipitation, polybrene mediated transfection, protoplast fusion, electroporation, encapsulation of the polynucleotide(s) in liposomes, mixing nucleic acid with positively-charged lipids, and direct microinjection of the DNA into nuclei.

Recombinant expression constructs typically comprise a polynucleotide encoding a polypeptide. The polypeptide may comprise one or more of the following: one or more CDRs such as provided herein; a light chain variable region; a heavy chain variable region; a light chain constant region; a heavy chain constant region (e.g., C_H1, C_H2 and/or C_H3); and/or another scaffold portion of an IL-23 antigen binding protein. These nucleic acid sequences are inserted into an appropriate expression vector using standard ligation techniques. In one embodiment, the heavy or light chain constant region is appended to the C-terminus of a heavy or light chain variable region provided herein and is ligated into an expression vector. The vector is typically selected to be functional in the particular host cell employed (i.e., the vector is compatible with the host cell machinery, permitting amplification and/or expression of the gene can occur). In some embodiments, vectors are used that employ protein-fragment complementation assays using protein reporters, such as dihydrofolate reductase (see, for example, U.S. Pat. No. 6,270,964). Suitable expression vectors can be purchased, for example, from Invitrogen Life Technologies (Carlsbad, Calif.) or BD Biosciences (San Jose, Calif.). Other useful vectors for cloning and expressing the antibodies and fragments include those described in Bianchi and McGrew, 2003, *Biotech. Biotechnol. Bioeng.* 84:439-44. Additional suitable expression vectors are discussed, for example, in *Methods Enzymol., vol.* 185 (D. V. Goeddel, ed.), 1990, New York: Academic Press.

Typically, expression vectors used in any of the host cells will contain sequences for plasmid maintenance and for cloning and expression of exogenous nucleotide sequences. Such sequences, collectively referred to as "flanking sequences" in certain embodiments will typically include one or more of the following nucleotide sequences: a promoter, one or more enhancer sequences, an origin of replication, a transcriptional termination sequence, a complete intron sequence containing a donor and acceptor splice site, a sequence encoding a leader sequence for polypeptide secretion, a ribosome binding site, a polyadenylation sequence, a polylinker region for inserting the polynucleotide encoding the polypeptide to be expressed, and a selectable marker element. The expression vectors that are provided may be constructed from a starting vector such as a commercially available vector. Such vectors may or may not contain all of the desired flanking sequences. Where one or more of the flanking sequences described herein are not already present in the vector, they may be individually obtained and ligated into the vector. Methods used for obtaining each of the flanking sequences are well known to one skilled in the art.

Optionally, the vector may contain a "tag"-encoding sequence, i.e., an oligonucleotide molecule located at the 5' or 3' end of the IL-23 antigen binding protein coding sequence; the oligonucleotide sequence encodes polyHis (such as hexa-His), or another "tag" such as FLAG®, HA (hemaglutinin influenza virus), or myc, for which commercially available antibodies exist. This tag is typically fused to the polypeptide upon expression of the polypeptide, and can serve as a means for affinity purification or detection of the IL-23 antigen binding protein from the host cell. Affinity purification can be accomplished, for example, by column chromatography using antibodies against the tag as an affinity matrix. Optionally, the tag can subsequently be removed from the purified IL-23 antigen binding protein by various means such as using certain peptidases for cleavage.

Flanking sequences may be homologous (i.e., from the same species and/or strain as the host cell), heterologous (i.e., from a species other than the host cell species or strain), hybrid (i.e., a combination of flanking sequences from more than one source), synthetic or native. As such, the source of a flanking sequence may be any prokaryotic or eukaryotic organism, any vertebrate or invertebrate organism, or any plant, provided that the flanking sequence is functional in, and can be activated by, the host cell machinery.

Flanking sequences useful in the vectors may be obtained by any of several methods well known in the art. Typically, flanking sequences useful herein will have been previously identified by mapping and/or by restriction endonuclease digestion and can thus be isolated from the proper tissue source using the appropriate restriction endonucleases. In

some cases, the full nucleotide sequence of a flanking sequence may be known. Here, the flanking sequence may be synthesized using the methods described herein for nucleic acid synthesis or cloning.

Whether all or only a portion of the flanking sequence is known, it may be obtained using polymerase chain reaction (PCR) and/or by screening a genomic library with a suitable probe such as an oligonucleotide and/or flanking sequence fragment from the same or another species. Where the flanking sequence is not known, a fragment of DNA containing a flanking sequence may be isolated from a larger piece of DNA that may contain, for example, a coding sequence or even another gene or genes. Isolation may be accomplished by restriction endonuclease digestion to produce the proper DNA fragment followed by isolation using agarose gel purification, Qiagen® column chromatography (Qiagen, Chatsworth, Calif.), or other methods known to the skilled artisan. The selection of suitable enzymes to accomplish this purpose will be readily apparent to one of ordinary skill in the art.

An origin of replication is typically a part of those prokaryotic expression vectors purchased commercially, and the origin aids in the amplification of the vector in a host cell. If the vector of choice does not contain an origin of replication site, one may be chemically synthesized based on a known sequence, and ligated into the vector. For example, the origin of replication from the plasmid pBR322 (New England Biolabs, Beverly, Mass.) is suitable for most gram-negative bacteria, and various viral origins (e.g., SV40, polyoma, adenovirus, vesicular stomatitus virus (VSV), or papillomaviruses such as HPV or BPV) are useful for cloning vectors in mammalian cells. Generally, the origin of replication component is not needed for mammalian expression vectors (for example, the SV40 origin is often used only because it also contains the virus early promoter).

A transcription termination sequence is typically located 3' to the end of a polypeptide coding region and serves to terminate transcription. Usually, a transcription termination sequence in prokaryotic cells is a G-C rich fragment followed by a poly-T sequence. While the sequence is easily cloned from a library or even purchased commercially as part of a vector, it can also be readily synthesized using methods for nucleic acid synthesis such as those described herein.

A selectable marker gene encodes a protein necessary for the survival and growth of a host cell grown in a selective culture medium. Typical selection marker genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, tetracycline, or kanamycin for prokaryotic host cells; (b) complement auxotrophic deficiencies of the cell; or (c) supply critical nutrients not available from complex or defined media. Specific selectable markers are the kanamycin resistance gene, the ampicillin resistance gene, and the tetracycline resistance gene. Advantageously, a neomycin resistance gene may also be used for selection in both prokaryotic and eukaryotic host cells.

Other selectable genes may be used to amplify the gene that will be expressed. Amplification is the process wherein genes that are required for production of a protein critical for growth or cell survival are reiterated in tandem within the chromosomes of successive generations of recombinant cells. Examples of suitable selectable markers for mammalian cells include dihydrofolate reductase (DHFR) and promoterless thymidine kinase genes. Mammalian cell transformants are placed under selection pressure wherein only the transformants are uniquely adapted to survive by virtue of the selectable gene present in the vector. Selection pressure is imposed by culturing the transformed cells under conditions in which the concentration of selection agent in the medium is successively increased, thereby leading to the amplification of both the selectable gene and the DNA that encodes another gene, such as an antigen binding protein that binds to IL-23. As a result, increased quantities of a polypeptide such as an antigen binding protein are synthesized from the amplified DNA.

A ribosome-binding site is usually necessary for translation initiation of mRNA and is characterized by a Shine-Dalgarno sequence (prokaryotes) or a Kozak sequence (eukaryotes). The element is typically located 3' to the promoter and 5' to the coding sequence of the polypeptide to be expressed.

In some cases, such as where glycosylation is desired in a eukaryotic host cell expression system, one may manipulate the various pre- or pro-sequences to improve glycosylation or yield. For example, one may alter the peptidase cleavage site of a particular signal peptide, or add prosequences, which also may affect glycosylation. The final protein product may have, in the −1 position (relative to the first amino acid of the mature protein), one or more additional amino acids incident to expression, which may not have been totally removed. For example, the final protein product may have one or two amino acid residues found in the peptidase cleavage site, attached to the amino-terminus. Alternatively, use of some enzyme cleavage sites may result in a slightly truncated form of the desired polypeptide, if the enzyme cuts at such area within the mature polypeptide.

Expression and cloning will typically contain a promoter that is recognized by the host organism and operably linked to the molecule encoding an IL-23 antigen binding protein. Promoters are untranscribed sequences located upstream (i.e., 5') to the start codon of a structural gene (generally within about 100 to 1000 bp) that control transcription of the structural gene. Promoters are conventionally grouped into one of two classes: inducible promoters and constitutive promoters. Inducible promoters initiate increased levels of transcription from DNA under their control in response to some change in culture conditions, such as the presence or absence of a nutrient or a change in temperature. Constitutive promoters, on the other hand, uniformly transcribe a gene to which they are operably linked, that is, with little or no control over gene expression. A large number of promoters, recognized by a variety of potential host cells, are well known. A suitable promoter is operably linked to the DNA encoding a heavy chain variable region or a light chain variable region of an IL-23 antigen binding protein by removing the promoter from the source DNA by restriction enzyme digestion and inserting the desired promoter sequence into the vector.

Suitable promoters for use with yeast hosts are also well known in the art. Yeast enhancers are advantageously used with yeast promoters. Suitable promoters for use with mammalian host cells are well known and include, but are not limited to, those obtained from the genomes of viruses such as polyoma virus, fowlpox virus, adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, retroviruses, hepatitis-B virus, and Simian Virus 40 (SV40). Other suitable mammalian promoters include heterologous mammalian promoters, for example, heat-shock promoters and the actin promoter.

Additional promoters which may be of interest include, but are not limited to: SV40 early promoter (Benoist and Chambon, 1981, *Nature* 290:304-310); CMV promoter (Thornsen et al., 1984, *Proc. Natl. Acad. U.S.A.* 81:659-663); the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797); herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. U.S.A.* 78:1444-1445); promoter and regulatory sequences from the metallothionine gene (Prinster et al.,

1982, *Nature* 296:39-42); and prokaryotic promoters such as the beta-lactamase promoter (Villa-Kamaroff et al., 1978, *Proc. Natl. Acad. Sci. U.S.A.* 75:3727-3731); or the tac promoter (DeBoer et al., 1983, *Proc. Natl. Acad. Sci. U.S.A.* 80:21-25). Also of interest are the following animal transcriptional control regions, which exhibit tissue specificity and have been utilized in transgenic animals: the elastase I gene control region that is active in pancreatic acinar cells (Swift et al., 1984, *Cell* 38:639-646; Ornitz et al., 1986, *Cold Spring Harbor Symp. Quant. Biol.* 50:399-409; MacDonald, 1987, *Hepatology* 7:425-515); the insulin gene control region that is active in pancreatic beta cells (Hanahan, 1985, *Nature* 315: 115-122); the immunoglobulin gene control region that is active in lymphoid cells (Grosschedl et al., 1984, *Cell* 38:647-658; Adames et al., 1985, *Nature* 318:533-538; Alexander et al., 1987, *Mol. Cell. Biol.* 7:1436-1444); the mouse mammary tumor virus control region that is active in testicular, breast, lymphoid and mast cells (Leder et al., 1986, *Cell* 45:485-495); the albumin gene control region that is active in liver (Pinkert et al., 1987, *Genes and Devel.* 1:268-276); the alpha-feto-protein gene control region that is active in liver (Krumlauf et al., 1985, *Mol. Cell. Biol.* 5:1639-1648; Hammer et al., 1987, *Science* 253:53-58); the alpha 1-antitrypsin gene control region that is active in liver (Kelsey et al., 1987, *Genes and Devel.* 1:161-171); the beta-globin gene control region that is active in myeloid cells (Mogram et al., 1985, *Nature* 315:338-340; Kollias et al., 1986, *Cell* 46:89-94); the myelin basic protein gene control region that is active in oligodendrocyte cells in the brain (Readhead et al., 1987, *Cell* 48:703-712); the myosin light chain-2 gene control region that is active in skeletal muscle (Sani, 1985, *Nature* 314:283-286); and the gonadotropic releasing hormone gene control region that is active in the hypothalamus (Mason et al., 1986, *Science* 234:1372-1378).

An enhancer sequence may be inserted into the vector to increase transcription by higher eukaryotes. Enhancers are cis-acting elements of DNA, usually about 10-300 bp in length, that act on the promoter to increase transcription. Enhancers are relatively orientation and position independent, having been found at positions both 5' and 3' to the transcription unit. Several enhancer sequences available from mammalian genes are known (e.g., globin, elastase, albumin, alpha-feto-protein and insulin). Typically, however, an enhancer from a virus is used. The SV40 enhancer, the cytomegalovirus early promoter enhancer, the polyoma enhancer, and adenovirus enhancers known in the art are exemplary enhancing elements for the activation of eukaryotic promoters. While an enhancer may be positioned in the vector either 5' or 3' to a coding sequence, it is typically located at a site 5' from the promoter. A sequence encoding an appropriate native or heterologous signal sequence (leader sequence or signal peptide) can be incorporated into an expression vector, to promote extracellular secretion of the antibody. The choice of signal peptide or leader depends on the type of host cells in which the antibody is to be produced, and a heterologous signal sequence can replace the native signal sequence. Examples of signal peptides that are functional in mammalian host cells include the following: the signal sequence for interleukin-7 described in U.S. Pat. No. 4,965,195; the signal sequence for interleukin-2 receptor described in Cosman et al., 1984, *Nature* 312:768; the interleukin-4 receptor signal peptide described in EP Patent No. 0367 566; the type I interleukin-1 receptor signal peptide described in U.S. Pat. No. 4,968,607; the type II interleukin-1 receptor signal peptide described in EP Patent No. 0 460 846.

After the vector has been constructed, the completed vector may be inserted into a suitable host cell for amplification and/or polypeptide expression. The transformation of an expression vector for an antigen binding protein into a selected host cell may be accomplished by well known methods including transfection, infection, calcium phosphate co-precipitation, electroporation, microinjection, lipofection, DEAE-dextran mediated transfection, or other known techniques. The method selected will in part be a function of the type of host cell to be used. These methods and other suitable methods are well known to the skilled artisan, and are set forth, for example, in Sambrook et al., Molecular Cloning: A Laboratory Manual, 3rd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (2001).

A host cell, when cultured under appropriate conditions, synthesizes protein that can be subsequently collected from the culture medium (if the host cell secretes it into the medium) or directly from the host cell producing it (if it is not secreted). The selection of an appropriate host cell will depend upon various factors, such as desired expression levels, polypeptide modifications that are desirable or necessary for activity (such as glycosylation or phosphorylation) and ease of folding into a biologically active molecule.

Mammalian cell lines available as hosts for expression are well known in the art and include, but are not limited to, immortalized cell lines available from the American Type Culture Collection (ATCC), including but not limited to Chinese hamster ovary (CHO) cells, HeLa cells, baby hamster kidney (BHK) cells, monkey kidney cells (COS), human hepatocellular carcinoma cells (e.g., Hep G2), and a number of other cell lines. In certain embodiments, cell lines may be selected through determining which cell lines have high expression levels and constitutively produce antigen binding proteins with IL-23 binding properties. In another embodiment, a cell line from the B cell lineage that does not make its own antibody but has a capacity to make and secrete a heterologous antibody can be also selected.

Use of Human IL-23 Antigen Binding Proteins for Diagnostic and Therapeutic Purposes

Antigen binding proteins are useful for detecting IL-23 in biological samples and identification of cells or tissues that produce IL-23. Antigen binding proteins that specifically bind to IL-23 may be used in diagnosis and/or treatment of diseases related to IL-23 in a patient in need thereof. For one, the IL-23 antigen binding proteins can be used in diagnostic assays, e.g., binding assays to detect and/or quantify IL-23 expressed in blood, serum, cells or tissue. In addition, IL-23 antigen binding proteins can be used to reduce, inhibit, interfere with or modulate one or more biological activities of IL-23 in a cell or tissue. Thus antigen binding proteins that bind to IL-23 may have therapeutic use in ameliorating diseases related to IL-23.

Indications

The present invention also relates to the use of IL-23 antigen binding proteins for use in the prevention or therapeutic treatment of medical disorders, such as those disclosed herein. The IL-23 antigen binding proteins are useful to treat a variety of conditions in which IL-23 is associated with or plays a role in contributing to the underlying disease or disorder or otherwise contributes to a negative symptom.

Conditions effectively treated by IL-23 antigen binding proteins play a role in the inflammatory response. Such inflammatory disorders include periodontal disease; lung disorders such as asthma; skin disorders such as psoriasis, atopic dermatitis, contact dermatitis; rheumatic disorders such as rheumatoid arthritis, progressive systemic sclerosis (scleroderma); systemic lupus erythematosus; spondyloarthritis including ankylosing spondylitis, psoriatic arthritis, enteropathic arthritis and reactive arthritis. Also contemplated is

uveitis including Vogt-Koyanagi-Harada disease, idiopathic anterior and posterior uveitis, and uveitis associated with spondyloarthritis. Use of IL-23 antigen binding proteins is also contemplated for the treatment of autoimmune disorders including multiple sclerosis; autoimmune myocarditis; type 1 diabetes and autoimmune thyroiditis.

Degenerative conditions of the gastrointestinal system are treatable or preventable with IL-23 antigen binding proteins. Such gastrointestinal disorders including inflammatory bowel disease: Crohn's disease, ulcerative colitis and Celiac disease.

Also included are use of IL-23 antigen binding proteins in treatments for graft-versus-host disease, and complications such as graft rejection, resulting from solid organ transplantation, such as heart, liver, skin, kidney, lung or other transplants, including bone marrow transplants.

Also provided herein are methods for using IL-23 antigen binding proteins to treat various oncologic disorders including various forms of cancer including colon, stomach, prostate, renal cell, cervical and ovarian cancers, and lung cancer (SCLC and NSCLC). Also included are solid tumors, including sarcoma, osteosarcoma, and carcinoma, such as adenocarcinoma and squamous cell carcinoma, esophogeal cancer, gastric cancer, gall bladder carcinoma, leukemia, including acute myelogenous leukemia, chronic myelogenous leukemia, myeloid leukemia, chronic or acute lymphoblastic leukemia and hairy cell leukemia, and multiple myeloma.

Diagnostic Methods

The antigen binding proteins of the described can be used for diagnostic purposes to detect, diagnose, or monitor diseases and/or conditions associated with IL-23. Examples of methods useful in the detection of the presence of IL-23 include immunoassays, such as the enzyme linked immunosorbent assay (ELISA) and the radioimmunoassay (RIA).

For diagnostic applications, the antigen binding protein typically will be labeled with a detectable labeling group. Suitable labeling groups include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ^{3}H, ^{14}C, ^{15}N, ^{35}S, ^{90}Y, ^{99}Tc, ^{111}In, ^{125}I, ^{131}I), fluorescent groups (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic groups (e.g., horseradish peroxidase, β-galactosidase, luciferase, alkaline phosphatase), chemiluminescent groups, biotinyl groups, or predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, the labelling group is coupled to the antigen binding protein via spacer arms of various lengths to reduce potential steric hindrance. Various methods for labelling proteins are known in the art and may be used.

Other diagnostic methods are provided for identifying a cell or cells that express IL-23. In a specific embodiment, the antigen binding protein is labeled with a labeling group and the binding of the labeled antigen binding protein to IL-23 is detected. In a further specific embodiment, the binding of the antigen binding protein to IL-23 is detected in vivo. In a further specific embodiment, the IL-23 antigen binding protein is isolated and measured using techniques known in the art. See, for example, Harlow and Lane, 1988, *Antibodies: A Laboratory Manual*, New York: Cold Spring Harbor (ed. 1991 and periodic supplements); John E. Coligan, ed., 1993, *Current Protocols In Immunology* New York: John Wiley & Sons.

Other methods provide for detecting the presence of a test molecule that competes for binding to IL-23 with the antigen binding proteins provided. An example of one such assay would involve detecting the amount of free antigen binding protein in a solution containing an amount of IL-23 in the presence or absence of the test molecule. An increase in the amount of free antigen binding protein (i.e., the antigen binding protein not bound to IL-23) would indicate that the test molecule is capable of competing for IL-23 binding with the antigen binding protein. In one embodiment, the antigen binding protein is labeled with a labeling group. Alternatively, the test molecule is labeled and the amount of free test molecule is monitored in the presence and absence of an antigen binding protein.

Methods of Treatment: Pharmaceutical Formulations, Routes of Administration

Pharmaceutical compositions that comprise a therapeutically effective amount of one or a plurality of the antigen binding proteins and a pharmaceutically acceptable excipient, diluent, carrier, solubilizer, emulsifier, preservative, and/or adjuvant are provided. In addition, methods of treating a patient by administering such pharmaceutical composition are included. The term "patient" includes human patients. The terms "treat" and "treatment" encompass alleviation or prevention of at least one symptom or other aspect of a disorder, or reduction of disease severity, and the like. The term "therapeutically effective amount" or "effective amount" refers to the amount of an IL-23 antigen binding protein determined to produce any therapeutic response in a mammal. Such therapeutically effective amounts are readily ascertained by one of ordinary skill in the art.

An antigen binding protein need not affect a complete cure, or eradicate every symptom or manifestation of a disease, to constitute a viable therapeutic agent. As is recognized in the pertinent field, drugs employed as therapeutic agents may reduce the severity of a given disease state, but need not abolish every manifestation of the disease to be regarded as useful therapeutic agents. Similarly, a prophylactically administered treatment need not be completely effective in preventing the onset of a condition in order to constitute a viable prophylactic agent. Simply reducing the impact of a disease (for example, by reducing the number or severity of its symptoms, or by increasing the effectiveness of another treatment, or by producing another beneficial effect), or reducing the likelihood that the disease will occur or worsen in a subject, is sufficient. Certain methods provided herein comprise administering to a patient an IL-23 antagonist (such as the antigen binding proteins disclosed herein) in an amount and for a time sufficient to induce a sustained improvement over baseline of an indicator that reflects the severity of the particular disorder.

As is understood in the pertinent field, pharmaceutical compositions comprising the molecules of the invention are administered to a patient in a manner appropriate to the indication. Pharmaceutical compositions may be administered by any suitable technique, including but not limited to, parenterally, topically, or by inhalation. If injected, the pharmaceutical composition can be administered, for example, via intraarticular, intravenous, intramuscular, intralesional, intraperitoneal or subcutaneous routes, by bolus injection, or continuous infusion. Localized administration, e.g. at a site of disease or injury is contemplated, as are transdermal delivery and sustained release from implants. Delivery by inhalation includes, for example, nasal or oral inhalation, use of a nebulizer, inhalation of the antagonist in aerosol form, and the like. Other alternatives include eyedrops; oral preparations including pills, syrups, lozenges or chewing gum; and topical preparations such as lotions, gels, sprays, and ointments.

Use of antigen binding proteins in ex vivo procedures also is contemplated. For example, a patient's blood or other bodily fluid may be contacted with an antigen binding protein

that binds IL-23 ex vivo. The antigen binding protein may be bound to a suitable insoluble matrix or solid support material.

Advantageously, antigen binding proteins are administered in the form of a composition comprising one or more additional components such as a physiologically acceptable carrier, excipient or diluent. Optionally, the composition additionally comprises one or more physiologically active agents for combination therapy. A pharmaceutical composition may comprise an IL-23 antigen binding protein together with one or more substances selected from the group consisting of a buffer, an antioxidant such as ascorbic acid, a low molecular weight polypeptide (such as those having fewer than 10 amino acids), a protein, an amino acid, a carbohydrate such as glucose, sucrose or dextrins, a chelating agent such as EDTA, glutathione, a stabilizer, and an excipient. Neutral buffered saline or saline mixed with conspecific serum albumin are examples of appropriate diluents. In accordance with appropriate industry standards, preservatives such as benzyl alcohol may also be added. The composition may be formulated as a lyophilizate using appropriate excipient solutions (e.g., sucrose) as diluents. Suitable components are nontoxic to recipients at the dosages and concentrations employed. Further examples of components that may be employed in pharmaceutical formulations are presented in any Remington's Pharmaceutical Sciences including the 21st Ed. (2005), Mack Publishing Company, Easton, Pa.

Kits for use by medical practitioners include an IL-23 antigen binding protein and a label or other instructions for use in treating any of the conditions discussed herein. In one embodiment, the kit includes a sterile preparation of one or more IL-23 binding antigen binding proteins, which may be in the form of a composition as disclosed above, and may be in one or more vials.

Dosages and the frequency of administration may vary according to such factors as the route of administration, the particular antigen binding proteins employed, the nature and severity of the disease to be treated, whether the condition is acute or chronic, and the size and general condition of the subject. Appropriate dosages can be determined by procedures known in the pertinent art, e.g. in clinical trials that may involve dose escalation studies.

A typical dosage may range from about 0.1 μg/kg to up to about 30 mg/kg or more, depending on the factors mentioned above. In specific embodiments, the dosage may range from 0.1 μg/kg up to about 30 mg/kg, optionally from 1 μg/kg up to about 30 mg/kg, optionally from 10 μg/kg up to about 10 mg/kg, optionally from about 0.1 mg/kg to 5 mg/kg, or optionally from about 0.3 mg/kg to 3 mg/kg.

Dosing frequency will depend upon the pharmacokinetic parameters of the particular human IL-23 antigen binding protein in the formulation used. Typically, a clinician administers the composition until a dosage is reached that achieves the desired effect. The composition may therefore be administered as a single dose, or as two or more doses (which may or may not contain the same amount of the desired molecule) over time, or as a continuous infusion via an implantation device or catheter. Appropriate dosages may be ascertained through use of appropriate dose-response data. An IL-23 antigen binding protein of the invention may be administered, for example, once or more than once, e.g., at regular intervals over a period of time. In particular embodiments, an IL-23 antigen binding protein is administered over a period of at least a month or more, e.g., for one, two, or three months or even indefinitely. For treating chronic conditions, long-term treatment is generally most effective. However, for treating acute conditions, administration for shorter periods, e.g. from one to six weeks, may be sufficient. In general, the antigen binding protein is administered until the patient manifests a medically relevant degree of improvement over baseline for the chosen indicator or indicators.

It is contemplated that an IL-23 antigen binding protein be administered to the patient in an amount and for a time sufficient to induce an improvement, preferably a sustained improvement, in at least one indicator that reflects the severity of the disorder that is being treated. Various indicators that reflect the extent of the patient's illness, disease or condition may be assessed for determining whether the amount and time of the treatment is sufficient. Such indicators include, for example, clinically recognized indicators of disease severity, symptoms, or manifestations of the disorder in question. In one embodiment, an improvement is considered to be sustained if the subject exhibits the improvement on at least two occasions separated by two to four weeks. The degree of improvement generally is determined by a physician, who may make this determination based on signs, symptoms, biopsies, or other test results, and who may also employ questionaires that are administered to the subject, such as quality-of-life questionaires developed for a given disease.

Particular embodiments of methods and compositions of the invention involve the use of an IL-23 antigen binding protein and one or more additional IL-23 antagonists, for example, two or more antigen binding proteins of the invention, or an antigen binding protein of the invention and one or more other IL-23 antagonists. Also provided are IL-23 antigen binding proteins administered alone or in combination with other agents useful for treating the condition with which the patient is afflicted. Examples of such agents include both proteinaceous and non-proteinaceous drugs. Such agents include therapeutic moieties having anti-inflammatory properties (for example, non-steroidal anti-inflammatory agents, steroids, immunomodulators and/or other cytokine inhibitors such as those that antagonize, for example, IFN-γ, GM-CSF, IL-6, IL-8, IL-17, IL-22 and TNFs), or of an IL-23 antigen binding protein and one or more other treatments (e.g., surgery, ultrasound, or treatment effective to reduce inflammation). When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized or known in the pertinent art. Useful agents that may be combined with IL-23 antigen binding proteins include those used to treat, for example, Crohn's disease or ulcerative colitis, such as aminosalicylate (for example, mesalamine), corticosteroids (including predisone), antibiotics such as metronidazole or ciprofloxacin (or other antibiotics useful for treating, for example, patients afflicted with fistulas), and immunosuppressives such as azathioprine, 6-mercaptopurine, methotrexate, tacrolimus and cyclosporine. Such agent(s) may be administered orally or by another route, for example via suppository or enema. Agents which may be combined with IL-23 binding proteins in treatment of psoriasis include corticosteroids, calcipotriene and other vitamin D derivatives, acetretin and other retinoic acid derivatives, methotrexate, tacrolimus, and cyclosporine used topically or systemically. Such agents can be administered simultaneously, consecutively, alternately, or according to any other regimen that allows the total course of therapy to be effective.

In addition to human patients, IL-23 antigen binding proteins are useful in the treatment of non-human animals, such as domestic pets (dogs, cats, birds, primates, etc.), domestic farm animals (horses cattle, sheep, pigs, birds, etc). In such instances, an appropriate dose may be determined according to the animal's body weight. For example, a dose of 0.2-1 mg/kg may be used. Alternatively, the dose is determined according to the animal's surface area, an exemplary dose ranging from 0.1-20 mg/m2, or more preferably, from 5-12

mg/m2. For small animals, such as dogs or cats, a suitable dose is 0.4 mg/kg. IL-23 antigen binding protein (preferably constructed from genes derived from the recipient species) is administered by injection or other suitable route one or more times per week until the animal's condition is improved, or it may be administered indefinitely.

The following examples, including the experiments conducted and the results achieved, are provided for illustrative purposes only and are not to be construed as limiting the scope of the appended claims.

EXAMPLES

Example 1

Generation of Human IL-23 Antibodies

XenoMouse™ technology (Amgen, Thousand Oaks, Calif.) was used to develop human monoclonal antibodies that recognize and inhibit native human IL-23 activity while sparing human IL-12. The antibodies also recognize and inhibit recombinant cynomologous IL-23 but do not recognize murine or rat IL-23.

Antibodies were selected for recognition and complete inhibition of native human IL-23 obtained from human monocyte-derived dendritic cells (MoDCs), using the STAT-luciferase reporter assay described below. Human monocytes were isolated from peripheral blood mononuclear cells from healthy donors using negative selection (Monocyte Isolation Kit II, Miltenyi Biotec, Auburn, Calif.). MoDCs were generated by culturing monocytes with human GM-CSF (50 ng/ml) and human IL-4 (100 ng/ml) for 7 days in RPMI 1640 with 10% fetal bovine serum complete medium. MoDCs were then washed twice with PBS followed by stimulation with human CD40L (1 μg/ml) for an additional 48 hours. CD40L-stimulated MoDC supernatant contains IL-23, IL-12 and IL-12/23p40. ELISAs are used to determine the amount of IL-12p70 (R&D System, Minneapolis, Minn.), IL-23 (eBiosciences, San Diego, Calif.) and IL-12/23p40 (R&D Systems). The STAT-luciferase assay responds to IL-23 and not to IL-12 or to free IL-12/23p40, therefore the assay could be used with crude supernatants to assess IL-23 activity. For use in the NK cell assay, described below, the native human IL-23 crude supernatant was purified using an IL-23 affinity column followed by size exclusion chromatography. Concentration was determined using an IL-23 specific ELISA (eBiosciences).

The purified antibody supernatants were also tested against recombinant human (rhu) IL-23 and recombinant cynomolgous (cyno) IL-23 in the STAT-luciferase assay. Of the antibodies tested that completely inhibited recombinant human IL-23, only half of those antibodies recognized and completely inhibited native human IL-23. Recognition and complete inhibition of recombinant human IL-23 was not predictive of, nor correlated to, recognition and complete inhibition of native human IL-23. As shown in FIGS. **1**A and **1**B, of the antibody supernatants that completely inhibited recombinant human IL-23, only half of those antibodies completely inhibited native human IL-23. Those antibodies that recognized and completely inhibited native human IL-23 were selected for further characterization.

Example 2

Functional Assays

a) STAT-Luciferase Assay

It is known that IL-23 binds its heterodimeric receptor and signals through JAK2 and Tyk2 to activate STAT 1, 3, 4 and 5. In this assay, cells transfected with a STAT/luciferase reporter gene are used to assess the ability of the IL-23 antibodies to inhibit IL-23-induced bioactivity.

Chinese hamster ovary cells expressing human IL-23 receptor are transiently transfected with STAT-luciferase reporter overnight. IL-23 antibodies are serially diluted (12 points of 1:4 serial dilutions starting at 37.5 μg/ml) into 96 well plates. Native human IL-23 (preparation method is described in Example 1) is added to each well at a concentration of 2 ng/ml and incubated at room temperature for 15-20 minutes. The transiently transfected cells are added (8×10^3 cells) to a final volume of 100 μl/well and incubated for 5 hours at 37° C., 10% CO_2. Following incubation, cells are lysed using 100 μL/well Glo Lysis buffer (1×) (Promega, Madison, Wis.) at room temperature for 5 minutes. Fifty microliters of cell lysate is added to a 96 well plate along with 50 μL Bright-Glo luciferase substrate (Promega) and read on a luminometer.

Statistical analysis can be performed using GraphPad PRISM software (GraphPad Software, La Jolla, Calif.). Results can be expressed as the mean±standard deviation (SD).

As seen in TABLE 5, all IL-23 antibodies potently and completely inhibited native human IL-23-induced STAT/luciferase reporter in a dose dependent manner. The antibodies also potently and completely inhibited recombinant human (rhu) IL-23 and recombinant cyno (cyno) IL-23. The antibodies all had IC_{50} values in the picomolar range.

TABLE 5

Table of mean IC_{50} (pM) values for IL-23 antibodies in the STAT-luciferase assay.

	Native huIL-23		rhuIL-23		Cyno IL-23	
antibody	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats
A	114 +/− 70	3	190 +/− 99	3	379 +/− 213	3
B	45 +/− 5	4	100 +/− 59	4	130 +/− 60	3
C	107 +/− 31	3	211 +/− 93	3	376 +/− 89	3
D	65 +/− 5	3	107 +/− 30	3	184 +/− 77	3
E	140 +/− 52	3	142 +/− 52	3	188 +/− 59	3
F	86 +/− 47	4	187 +/− 116	4	366 +/− 219	4
G	156 +/− 74	5	296 +/− 133	5	421 +/− 174	5
H	192 +/− 35	4	253 +/− 184	4	1024 +/− 533	4
I	208 +/− 33	3	338 +/− 140	3	650 +/− 42	3
J	83 +/− 54	2	26 +/− 6	2	56 +/− 2	2
K	71 +/− 38	3	43 +/− 20	3	61 +/− 10	3
L	113 +/− 80	3	23 +/− 7	3	47 +/− 1	3
M	34 +/− 11	2	40 +/− 8	2	56 +/− 6	2
N	361 +/− 164	3	145	1	238	1

b) NK Cell Assay

It is known that IL-23 acts on natural killer cells to induce expression of pro-inflammatory cytokines, such as interferon γ (IFNγ). In this assay, human primary natural killer (NK) cells are used to assess the ability of the IL-23 antibodies to inhibit IL-23-induced IFNγ activity in cells expressing the native receptor for human IL-23.

NK cells are isolated from multiple human donors via negative selection (NK Cell Isolation Kit, Miltenyi Biotec, Auburn, Calif.). Purified NK cells (1×10^6 cells/ml) are added

to 6 well plates in RPMI 1640 plus 10% fetal bovine serum complete medium supplemented with recombinant human IL-2 (10 ng/ml, R&D Systems, Minneapolis, Minn.), to a final volume of 10 ml/well. Cells are cultured for 7 days at 37° C., 5% CO_2. The IL-2-activated NK cells are then stimulated with rhuIL-23 or cyno IL-23 (10 ng/ml) and recombinant human IL-18 (20 ng/ml, R&D Systems, Minneapolis, Minn.) in the presence of serial dilutions (11 points of 1:3 serial dilutions starting at 3 μg/ml) of IL-23 antibodies for 24 hours. IFNγ levels are measured in the supernatant by IFNγ ELISA (R&D Systems, Minneapolis, Minn.) according to manufacturer's instructions.

Statistical analysis can be performed using GraphPad PRISM software. Results can be expressed as the mean±standard deviation (SD).

As seen in TABLE 6, all antibodies potently inhibited rhuIL-23 and cyno IL-23-induced IFNγ expression in NK cells in a dose dependent manner. The antibodies all had IC_{50} values in the picomolar range. The assay was performed on a subset of antibodies using native human IL-23 (30 μg/ml, preparation method is described in Example 1) and rhuIL-18 (40 ng/ml, R&D Systems) and yielded the results shown in TABLE 6. Consistent with the selection for IL-23 specific antibodies, these anti-IL-23 antibodies had no effect on IL-12 stimulated IFNγ production in NK cells using the assay described above, whereas an IL-12p35 specific neutralizing antibody, mAb219 (R&D Systems, Minneapolis, Minn.) potently inhibited recombinant human IL-12.

TABLE 6

Table of mean IC_{50} (pM) values for IL-23 antibodies in the NK cell assay.

	Native huIL-23		rhuIL-23		Cyno IL-23	
antibody	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats
A			42 +/− 12	2	31 +/− 21	2
B	85 +/− 30	2	48 +/− 30	3	19 +/− 8	2
C			32 +/− 19	4	29 +/− 16	2
D			37 +/− 21	2	29 +/− 19	2
E	158 +/− 50	2	57 +/− 14	3	21 +/− 3	2
F			25 +/− 15	2	21 +/− 17	2
G	152 +/− 72	2	45 +/− 30	3	23 +/− 8	2
H			29 +/− 28	2	33 +/− 17	2
I			69	1	52	1
J			4 +/− 3	2	5 +/− 3	2
K			7 +/− 2	2	8 +/− 6	2
L			3 +/− 1	2	4 +/− 1	2
M			8	1	12	1

c) Human Whole Blood Assay

Human whole blood is collected from multiple healthy donors using Refludan® (Bayer Pittsburgh, Pa.) as an anticoagulant. The final concentration of Refludan® in whole blood is 10 μg/ml. A stimulation mixture of rhuIL-23 or cyno IL-23 (final concentration 1 ng/ml)+rhuIL-18 (final concentration 20 ng/ml)+rhuIL-2 (final concentration 5 ng/ml) in RPMI 1640+10% FBS, is added to a 96 well plate, final volume 20 μl/well. Serially diluted IL-23 antibodies (11 points of 1:3 serial dilutions starting from 3 μg/ml) are added at 20 μl/well and incubated with the stimulation mixture for 30 minutes at room temperature. Whole blood is then added (120 μl/well) and the final volume adjusted to 200 μl/well with RPMI 1640+10% FBS. The final concentration of whole blood is 60%. The plates are incubated for 24 hours at 37° C., 5% CO_2. Cell free supernatants are harvested and IFNγ levels are measured from the supernatants by IFNγ ELISA (R&D Systems) according to manufacturer's instructions.

Statistical analysis can be performed using GraphPad PRISM software. Results can be expressed as the mean±standard deviation (SD).

As seen in TABLE 7, all antibodies potently inhibited rhuIL-23-induced and cyno-IL-23-induced IFNγ expression in whole blood cells in a dose dependent manner. The antibodies all had IC_{50} values in the picomolar range.

TABLE 7

Table of mean IC_{50} (pM) values for IL-23 antibodies in the IFNγ human whole blood assay

	rhuIL-23		Cyno IL-23	
antibody	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats
B	117 +/− 94	7	161 +/− 95	6
E	29 +/− 8	3	54 +/− 33	3
G	53 +/− 13	3	93 +/− 44	3
F	66 +/− 13	3	166 +/− 189	3
D	88 +/− 6	3	110 +/− 14	3
C	97 +/− 31	3	186 +/− 194	3

d) IL-22 Assay

It is known that IL-23 is a potent inducer of proinflammatory cytokines. IL-23 acts on activated and memory T cells and promotes the survival and expansion of Th17 cells which produce proinflammatory cytokines including IL-22. In this assay, human whole blood is used to assess the ability of the IL-23 antibodies to inhibit IL-23-induced IL-22 production.

A whole blood assay is conducted in the same manner as described above with the modification of using rhuIL-23 or cynoIL-23 at 1 ng/ml and rhuIL-18 at 10 ng/ml to induce IL-22 production. IL-22 concentration is determined by IL-22 ELISA (R&D Systems, Minneapolis, Minn.).

As seen in TABLE 8, the antibodies potently inhibited rhuIL-23-induced and cyno IL-23-induced IL-22 production in whole blood cells in a dose dependent manner. The antibodies all had IC_{50} values in the picomolar range.

TABLE 8

Table of mean IC_{50} (pM) values for IL-23 antibodies in the IL-22 human whole blood assay

	rhuIL-23		Cyno IL-23	
antibody	IC_{50} +/− SD	Repeats	IC_{50} +/− SD	Repeats
B	117 +/− 68	4	113 +/− 65	3
E	87 +/− 109	3	56 +/− 60	3
G	83 +/− 59	3	66 +/− 45	3

Example 3

Determining the Equilibrium Dissociation Constant (K_D) for Anti-IL-23 Antibodies Using KinExA Technology

Binding affinity of rhuIL-23 to IL-23 antibodies is evaluated using a kinetic exclusion assay (KinExA assay, Sapidyne Instruments, Inc., Boise, Id.). Normal human serum (NHS)-activated Sepharose 4 fast flow beads (Amersham Biosciences, part of GE Healthcare, Uppsala, Sweden), are precoated with rhuIL-23 and blocked with 1 m Tris buffer with 10 mg/mL BSA. 50 pM of IL-23 antibody is incubated with rhuIL-23 (12 points of 1:2 dilutions starting from 800 pM) at room temperature for 72 hours before it is run through the rhuIL-23-coated Sepharose beads. The amount of the bead-bound antibody was quantified by fluorescent (Cy5) labeled goat anti-human-Fc antibody (Jackson Immuno Research,

West Grove, Pa.). The binding signal is proportional to the amount of free antibody at equilibrium.

The dissociation equilibrium constant (K_D) and the association rate (K_{on}) are obtained from curve fitting using KinExA Pro software. The dissociation rate (K_{off}) is derived from: $K_D=K_{off}/K_{on}$

As seen in TABLE 9, the antibodies have high affinity for binding to human IL-23. All had K_D values in the low to sub pM range.

TABLE 9

Table of K_D (pM), K_{on} (1/MS) and K_{off} (1/s) rates

Antibody	KD (pM)	Kon (1/MS)	Koff (1/s)
E	0.131	9.12E+05	1.4E−07
D	0.126	1.72E+06	2.2E−07
B	3.99	1.17E+06	4.7E−06
C	2.56	1.36E+06	4.1E−06
F	2.62	5.69E+05	1.5E−06
L	1.08	3.34E+06	3.7E−06
G	2.00	4.00E+05	8.1E−07

Example 4

Structure Determination Using X-Ray Crystallography

One way to determine the structure of an antibody-antigen complex is by using X-ray crystallography, see for example, Harlow and Lane Antibodies: A Laboratory Manual Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1990), p. 23. The crystal structure of IL-23 has been determined, (see Lupardus and Garcia, J Mol Biol, 2008, 382: 931-941) and the crystal structure of an IL-23/Fab complex has been disclosed, (see Beyer et al. J Mol Biol, 2008. 382(4): 942-55). Structural determination of IL-23 with Fab fragments of antibodies claimed herein was obtained using X-ray crystallography.

Protein for Crystallization

A recombinantly derived human IL-23 heterodimer was used for the crystallization studies (see Beyer et al., supra). The sequence of the human p19 subunit comprised of residues 20-189 of SEQ ID NO: 145, the signal sequence of SEQ ID NO:154 and a C-terminal 6-His tag SEQ ID NO:155. The sequence of the human p40 subunit was mutated from asparagine to glutamine at position 222 of SEQ ID NO:147 in order to prevent glycosylation at this site (Beyer, et al., supra).

Fabs derived from Antibody B and Antibody E were expressed on an IgG1 scaffold that incorporated a caspase cleavage site. The Fabs were processed by means of protease cleavage.

Complex Formation and Crystallization

The IL-23-Antibody B Fab complex was made by mixing a 2× molar excess of the Antibody B Fab with the human heterodimeric IL-23 described above. The complex was purified by size exclusion chromatography to remove excess Antibody B Fab and concentrated to ~12 mg/ml for crystallization. The IL-23-Antibody B Fab complex crystallized in 0.1 M Hepes pH 7, 8% PEG 8000.

The IL-23-Antibody E Fab complex was made by mixing a 2× molar excess of the Antibody E Fab with the human heterodimeric IL-23 described above. The complex was methylated using a JBS Methylation Kit according to manufacturer's instructions (Jena Bioscience, Jena, Germany). The complex was then treated with PNGase to deglycosylate the protein. Following these treatments, the complex was purified by size exclusion chromatography to remove excess Antibody E Fab and concentrated to 13.5 mg/ml for crystallization. The IL-23-Antibody E Fab complex crystallized in 0.1 M Tris pH 8.5, 0.2 M magnesium chloride, 15% PEG 4000.

Data Collection and Structure Determination

IL-23-Antibody B Fab crystals grew in the $P2_1$ space group with unit cell dimensions a=70.93, b=71.27, c=107.37 Å, β=104.98° and diffract to 2.0 Å resolution. The IL-23-Antibody B Fab structure was solved by molecular replacement with the program MOLREP (CCP4, *The CCP*4 *suite: programs for protein crystallography*. Acta Crystallogr D Biol Crystallogr, 1994. 50(Pt 5): p. 760-3) using the IL-23 structure (Beyer et al. supra) as the starting search model. Keeping the IL-23 solution fixed, an antibody variable domain was used as a search model. Keeping the IL-23-antibody variable domain solution fixed, an antibody constant domain was used as a search model. The complete structure was improved with multiple rounds of model building with Quanta and refinement with cnx (Brunger, et al., Acta Crystallogr D Biol Crystallogr, 1998, 54(Pt 5): p. 905-21).

Distances between protein atoms were calculated using the program PyMOL (DeLano, W. L. The PyMOL Graphics System. Palo Alto, 2002) (Schrodinger, LLC; New York, N.Y.)). Amino acids were chosen if at least one atom was located within the required distance threshold to the partner protein.

Boundaries of the A, B, C and D helices of the p19 subunit of IL-23 when bound to the Antibody B Fab include A helix residues 28-47, B helix residues 86-105, C helix residues 119-134 and D helix residues 154-187 of SEQ ID NO:145.

The regions of interaction on the IL-23p19 subunit when bound to the Antibody B Fab include residues within Ser46-Glu58, Glu112-Glu123 and Pro155-Phe163 of SEQ ID NO:145.

IL-23p19 subunit amino acid residues with atoms 4 Å or less from the Antibody B Fab include Ser46, Ala47, His48, Pro49, Leu50, His53, Met54, Asp55, Glu58, Pro113, Ser114, Leu115, Leu116, Pro120, Val121, Trp156, Leu159, Leu160, Arg162 and Phe163 of SEQ ID NO:145. IL-23p19 amino acid residues with atoms between 4 Å and 5 Å from the Antibody B Fab include Val51, Arg57, Glu112, Asp118, Ser119, Gln123, Pro155 of SEQ ID NO:145.

IL-23p40 subunit amino acid residues with atoms 4 Å or less from the Antibody B Fab include Glu 122 and Lys 124 of SEQ ID NO:147.

The Antibody B Fab heavy chain amino acid residues with atoms 4 Å or less from the IL-23 heterodimer include Gly32, Gly33, Tyr34, Tyr35, His54, Asn58, Thr59, Tyr60, Lys66, Arg101, Gly102, Phe103, Tyr104 and Tyr105 of SEQ ID NO:46. The Antibody B Fab heavy chain amino acid residues with atoms≤5 Å from the IL-23 heterodimer include Ser31, Gly32, Gly33, Tyr34, Tyr35, His54, Ser56, Asn58, Thr59, Tyr60, Lys66, Arg101, Gly102, Phe103, Tyr104 and Tyr105 of SEQ ID NO:46.

The Antibody B Fab light chain amino acid residues with atoms 4 Å or less from the IL-23 heterodimer include Ser30, Ser31, Trp32, Tyr49, Ser52, Ser53, Ala91, Asn92, Ser93, Phe94, and Phe96 of SEQ ID NO:15. The Antibody B Fab light chain amino acid residues with atoms≤5 Å from the IL-23 heterodimer include Ser30, Ser31, Trp32, Tyr49, Ala50, Ser52, Ser53, Ser56, Ala91, Asn92, Ser93, Phe94, and Phe96 of SEQ ID NO:15

The IL-23-Antibody E Fab complex crystals grew in the $P222_1$ space group with unit cell dimensions a=61.60, b=97.59, c=223.95 Å and diffract to 3.5 Å resolution. The IL-23-Antibody E Fab complex structure was solved by molecular replacement with the program Phaser (CCP4, supra) using the IL-23 structure, an antibody variable domain,

and an antibody constant domain as the three starting search models, as described above. The complete structure was improved with multiple rounds of model building with Quanta and refinement with cnx (Brunger, et al., supra). The Antibody E Fab constant domain was left out of the final refined structure due to very poor electron density for that portion of the protein.

The regions of interaction on the IL-23p19 subunit identified when bound to the Antibody E Fab include residues within Ser46-His53, Glu112-Val120 and Trp156-Phe163 of SEQ ID NO:145.

IL-23p19 amino acid residues with atoms 4 Å or less from the Antibody E Fab include Ser46, Ala47, His48, Pro49, Leu50, Glu112, Pro113, Ser114, Leu115, Leu116, Pro117, Asp118, Ser119, Pro120, Trp156, Leu159, Leu160 and Phe163 of SEQ ID NO: 145. IL-23p19 amino acid residues with atoms between 4 Å and 5 Å from the Antibody E Fab include His53 of SEQ ID NO:145.

IL-23p40 amino acid residues with atoms 4 Å or less from the Antibody E Fab include Lys121, Glu 122, Pro123 and Asn 125 of SEQ ID NO:147.

The Antibody E Fab heavy chain amino acid residues with atoms 4 Å or less from the IL-23 heterodimer include Gly26, Phe27, Thr28, Ser31, Tyr53, Tyr59, Tyr102, Ser104, Ser105, Trp106, Tyr107, and Pro108 of SEQ ID NO:31. The Antibody E Fab heavy chain amino acid residues with atoms≤5 Å from the IL-23 heterodimer include Gln1, Gly26, Phe27, Thr28, Ser30, Ser31, Tyr32, Trp52, Tyr53, Tyr59, Arg100, Tyr102, Thr103, Ser104, Ser105, Trp106, Tyr107, and Pro108 of SEQ ID NO:31.

The Antibody E Fab light chain amino acid residues with atoms 4 Å or less from the IL-23 heterodimer include Ala31, Gly32, Tyr33, Asp34, Tyr51, Gly52, Asn55, Lys68, and Tyr93 of SEQ ID NO:1. The Antibody B Fab light chain amino acid residues with atoms≤5 Å from the IL-23 heterodimer include Thr29, Ala31, Gly32, Tyr33, Asp34, Tyr51, Gly52, Asn55, Lys68, Tyr93, and Trp100 of SEQ ID NO:1.

Example 5

Determination of IL-23-Antibody Complex Contact Residues Through Solvent Accessible Surface Area Differences

The residue contacts in the paratope (the portion of the antibody that recognizes the antigen) and the portion of the antigen that it binds bound by the paratope in a human IL-23-Antibody B Fab complex and in a human IL-23-Antibody E Fab complex were determined using solvent accessible surface area differences. The solvent accessible surface area calculations were performed using Molecular Operating Environment (Chemical Computing Group, Montreal, Quebec).

The solvent accessible surface area differences of the paratope residues in the IL-23-Antibody B Fab complex were calculated by setting the Antibody B Fab residues as the desired set. The structural information obtained in Example 4 for the IL-23-Antibody B Fab complex was used and the residue solvent accessible surface area of the amino acid residues of the Antibody B Fab in the presence of the IL-23 heterodimer were calculated and represent the "bound areas" for the set.

The residue solvent accessible surface area of each of the Antibody B Fab residues in the absence of the IL-23 antigen were calculated and represent the "free areas" of the set.

The "bound areas" were then subtracted from the "free areas" resulting in the "solvent exposed surface area difference" for each residue in the set. The Antibody B Fab residues that had no change in surface area, or a zero difference, had no contact with the residues of the IL-23 antigen when complexed. The Antibody B Fab residues that had a difference value≥10 Å^2 were considered to be in significant contact with residues in the IL-23 antigen such that these Antibody B Fab residues were at least partially to completely occluded when the Antibody B Fab was bound to human IL-23. This set of Antibody B Fab residues make up the "covered patch", the residues involved in the structure of the interface when Antibody B Fab is bound to human IL-23, see Tables 10 and 11. The Antibody B Fab residues in this covered patch may not be involved in binding interactions with residues of the IL-23 antigen, but mutation of any single residue within the covered patch could introduce energetic differences that would impact the binding of Antibody B Fab to human IL-23. With the exception of Tyr49, all of the residues are located in the CDR regions of the Antibody B Fab light and heavy chains. These residues were also within 5 Å or less of the 11-23 antigen when bound to the Antibody B Fab, as described in Example 4.

TABLE 10

Solvent Accessibility Surface Area Differences for Antibody B Fab Light Chain

Residue AHO Number	Residue Position SEQ ID NO: 15	Solvent exposed surface area difference (Å^2)
Ser32	Ser30	44.9
Ser33	Ser31	41.1
Trp40	Trp32	79.0
Tyr57	Tyr49	40.7
Ala58	Ala50	20.3
Ser68	Ser52	43.6
Ser69	Ser53	38.9
Ser72	Ser56	19.1
Asn110	Asn92	34.0
Phe135	Phe94	51.4

TABLE 11

Solvent Accessibility Surface Area Differences for Antibody B Fab Heavy Chain

Residue AHO Number	Residue Positioin SEQ ID NO: 46	Solvent exposed surface area difference (Å^2)
Ser33	Ser31	18.2
Gly34	Gly32	49.5
Gly38	Gly33	33.8
Tyr39	Tyr34	51.4
Tyr40	Tyr35	30.7
His59	His54	29.5
Asn67	Asn58	66.7
Thr68	Thr59	26.0
Tyr69	Tyr60	59.4
Lys75	Lys66	32.6
Arg110	Arg101	47.2
Gly111	Gly102	21.7
Phe112	Phe103	35.5
Tyr133	Tyr104	83.0
Tyr134	Tyr105	91.7

The solvent accessible surface area differences of the residues in the IL-23-Antibody E Fab complex were calculated as described above. The Antibody E Fab residues that had a difference value≥10 Å^2 were considered to be in significant contact with residues in the IL-23 antigen and these Antibody E Fab residues were at least partially to completely occluded when the Antibody E Fab was bound to human IL-23. This set of Antibody E Fab residues make up the covered patch, the

residues involved in the structure of the interface when the Antibody E Fab is bound to human IL-23, see Tables 12 and 13. The Antibody E Fab residues in this covered patch may not be involved in binding interactions with residues of the IL-23 antigen, but mutation of any single residue within the covered patch could introduce energetic differences that would impact the binding of Antibody E Fab to human IL-23. For the most part, these covered patch residues were located within the CDR regions of the Antibody E Fab heavy and light chains. These residues were also within 5 Å or less of the IL-23 antigen when bound to the Antibody E Fab, as described in Example 4.

TABLE 12

Solvent Accessibility Surface Area Differences for Antibody E Fab Light Chain

Residue AHO Number	Residue Position SEQ ID NO: 1	Solvent exposed surface area difference (Å^2)
Ala33	Ala31	11.6
Gly34	Gly32	51.2
Tyr39	Tyr33	47.2
Asp40	Asp34	36.8
Tyr57	Tyr51	16.1
Gly58	Gly52	11.1
Asn69	Asn55	29.4
Lys82	Lys68	20.1
Tyr109	Tyr93	27.3
Ser135	Ser98	11.3

TABLE 13

Solvent Accessibility Surface Area Differences for Antibody E Fab Heavy Chain

Residue AHO Number	Residue Position SEQ ID NO: 31	Solvent exposed surface area difference (Å^2)
Gln1	Gln1	41.1
Gly27	Gly26	24.6
Thr30	Thr28	82.2
Ser33	Ser31	40.7
Tyr39	Tyr32	30.7
Trp59	Trp52	11.3
Tyr60	Tyr53	44.7
Tyr69	Tyr59	42.4
Lys86	Lys76	17.4
Gly111	Gly101	12.8
Tyr112	Tyr102	103.1
Ser114	Ser104	21.0
Ser115	Ser105	91.4
Trp131	Trp106	145.0
Tyr132	Tyr107	71.6
Pro133	Pro108	20.4

The solvent accessible surface area differences of the portion of the IL-23 heterodimer bound by the paratope of the Antibody B Fab were calculated by setting the IL-23 heterodimer residues as the desired set. The structural information obtained in Example 4 for the Antibody B Fab-IL-23 complex was used and the residue solvent accessible surface area of the amino acid residues of the IL-23 heterodimer in the presence of the Antibody B Fab were calculated and represent the bound areas for the set.

The residue solvent accessible surface area of each of the IL-23 heterodimer residues in the absence of the Antibody B Fab were calculated and represent the free areas of the set.

As described above, the bound areas were subtracted from the free areas resulting in the solvent exposed surface area difference for each IL-23 residue. The IL-23 heterodimer residues that had no change in surface area, or a zero difference, had no contact with the residues of the Antibody B Fab when complexed. The IL-23 heterodimer residues that had a difference value≥10 Å^2 were considered to be in significant contact with residues of the Antibody B Fab and these 11-23 heterodimer residues were at least partially to completely occluded when the human IL-23 heterodimer was bound to the Antibody B Fab. This set of IL-23 heterodimer residues make up the covered patch, the residues involved in the structure of the interface when the human IL-23 heterodimer is bound to the Antibody E Fab, see Table 14. The 11-23 heterodimer residues in this covered patch may not all be involved in binding interactions with residues on the Antibody B Fab, but mutation of any single residue within the covered patch could introduce energetic differences that would impact the binding of Antibody B Fab to human IL-23. These residues are also within 4 Å or less from the Antibody B Fab, as described Example 4.

TABLE 14

Solvent Accessibility Surface Area Differences for IL-23 heterodimer residues

	Solvent exposed surface area difference (Å^2)
p19 residues (SEQ ID NO: 145)	
Ser46	26.5
Ala47	12.7
Pro49	59.6
Leu50	122.2
His53	47.8
Met54	13.9
Asp55	20.5
Arg57	14.6
Glu58	96.5
Glu112	29.7
Pro113	64.8
Ser114	30.0
Leu115	31.4
Leu116	60.0
Asp118	14.4
Ser119	19.7
Pro120	64.7
Pro155	19.4
Typ156	61.9
Leu159	72.8
Leu160	27.0
Arg162	14.4
Phe163	67.5
p40 residues (SEQ ID NO: 147)	
Glu122	29.1
Lys124	60.9

The solvent accessible surface area differences of the portion of the IL-23 heterodimer bound by the paratope of the Antibody E Fab were calculated as described above. The IL-23 heterodimer residues that had a difference value≥10 Å^2 were considered to be in significant contact with residues of the Antibody E Fab and these 11-23 heterodimer residues were at least partially to completely occluded when the human IL-23 heterodimer was bound to the Antibody E Fab. This set of IL-23 heterodimer residues make up the covered patch, the residues involved in the structure of the interface when the human IL-23 heterodimer is bound to the Antibody E Fab, see Table 15. The 11-23 heterodimer residues in this covered patch may not all be involved in binding interactions with residues on the Antibody E Fab, but mutation of any single residue within the covered patch could introduce energetic differences that would impact the binding of Antibody E Fab to human IL-23. These residues are also within 5 Å or less from the Antibody E Fab, as described in Example 4.

TABLE 15

Solvent Accessibility Surface Area Differences for IL-23 heterodimer residues

	Solvent exposed surface area difference (Å^2)
p19 residues (SEQ ID NO: 145)	
Ser46	18.7
Ala47	14.9
Pro49	79.8
Leu50	99.5
His53	61.2
Glu112	62.8
Pro113	45.7
Ser114	69.5
Leu115	50.3
Leu116	127.2
Pro117	54.1
Asp118	37.0

TABLE 15-continued

Solvent Accessibility Surface Area Differences for IL-23 heterodimer residues

	Solvent exposed surface area difference (Å^2)
Pro120	18.8
Pro155	16.9
Trp156	140.7
Leu159	21.8
Leu160	17.0
Phe163	56.6
p40 residues (SEQ ID NO: 147)	
Lys121	86.2
Glu122	21.8
Pro123	22.1
Asn125	26.7
Arg283	22.6

SEQUENCE LISTING

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Tyr Asp Val His Trp Tyr Gln Gln Val Pro Gly Thr Ala Pro Lys Leu
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Leu Ile Tyr Gly Ser Gly Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
    50                  55                  60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65                  70                  75                  80

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Leu Ile Tyr Gly Ser Asn Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
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Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
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35 40 45

Leu Leu Arg Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser Gly Val
50 55 60

Pro Ser Arg Phe Ser Gly Ser Lys Asp Ala Ser Ala Asn Ala Gly Ile
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Leu Leu Ile Ser Gly Leu Gln Ser Glu Asp Glu Ala Asp Tyr Tyr Cys
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20 25 30

Val Asp Trp Tyr Gln Gln Arg Pro Gly Lys Gly Pro Arg Phe Val Met
35 40 45

Arg Val Gly Thr Gly Gly Ile Val Gly Ser Lys Gly Asp Gly Ile Pro
50 55 60

Asp Arg Phe Ser Val Leu Gly Ser Gly Leu Asn Arg Tyr Leu Thr Ile
65 70 75 80

Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys Gly Ala Asp
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100 105 110

Val Thr Val Leu
115

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Asp Arg Phe Ser Val Leu Gly Ser Gly Leu Asn Arg Tyr Leu Thr Ile
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Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys Gly Ala Asp
                85                  90                  95

His Gly Ser Gly Asn Asn Phe Val Tyr Val Phe Gly Thr Gly Thr Lys
            100                 105                 110

Val Thr Val Leu
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Val Asp Trp Tyr Gln Leu Arg Pro Gly Lys Gly Pro Arg Phe Val Met
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Arg Val Gly Thr Gly Gly Thr Val Gly Ser Lys Gly Glu Gly Ile Pro
    50                  55                  60

Asp Arg Phe Ser Val Leu Gly Ser Gly Leu Asn Arg Ser Leu Thr Ile
65                  70                  75                  80

Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys Gly Ala Asp
                85                  90                  95

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Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asp Ser Phe Pro Pro
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Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
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Ser Val Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 18
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 18

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggaagtagc agctggtttg cctggtatca gcagaaacca 120

gggaaagccc caaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagac ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 19
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 19

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```
Asp Ser Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30

Phe Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Asn Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 20
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 20

gacagccaga tgacccagtc tccatcttcc gtgtctgcct ctgtaggaga cagagtcacc     60

atcacttgtc gggcgagtca gggtattagc agctggtttg cctggtatca gcagaaacca    120

gggcaagccc ctaacctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagaa ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccattcac tttcggccct    300

gggaccaaag tggatatcaa a                                              321


<210> SEQ ID NO 21
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 21

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Gly Gln Val Ile Ser Ser Trp
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Asp Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Thr Ser Phe Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
            100                 105


<210> SEQ ID NO 22
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 22

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60
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atcacttgtc gggcgggtca ggttattagc agctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatcg 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gacgattttg caacttacta ttgtcaacag gctaccagtt ttcccctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 23
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 23

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Phe Ser Gly Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
85 90 95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 24
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 24

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggttttagc ggttggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ctgtcaacag gctaacagtt tcccattcac tttcggccct 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 25
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 25

Asp Ile Gln Leu Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Val Ile Ser Ser Trp
20 25 30

Phe Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

-continued

```
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Ala Asp Phe Ala Thr Tyr Phe Cys Gln Gln Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Val Lys
            100                 105


<210> SEQ ID NO 26
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 26

gacatccagt tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcacttgtc gggcgagtca ggttattagc agctggtttg cctggtatca gcagaaacca    120

gggaaagccc ctaacctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gcagattttg caacttactt ttgtcaacag gctaacagtt tcccattcac tttcggccct    300

gggaccaaag tggatgtcaa a                                              321


<210> SEQ ID NO 27
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 27

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ser Ser Ser Trp
            20                  25                  30

Phe Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Phe
                85                  90                  95

Thr Phe Gly Pro Gly Thr Lys Val Asp Ile Lys
            100                 105


<210> SEQ ID NO 28
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 28

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc     60

atcacttgtc gggcgagtca gggtagtagc agctggtttg cctggtatca acagaaacca    120

gggaaagccc caaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca    180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct    240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccattcac tttcggccct    300

gggaccaaag tggatatcaa a                                              321


<210> SEQ ID NO 29
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-continued

<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 29

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Asn Ser Tyr Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Glu
100 105

<210> SEQ ID NO 30
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus Sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa can be Ile or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be Met or Leu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Xaa can be Gly or Val
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Xaa can be Ser, Phe or Ile
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (32)..(32)
<223> OTHER INFORMATION: Xaa can be Ser or Gly
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (34)..(34)
<223> OTHER INFORMATION: Xaa can be Phe or Leu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (43)..(43)
<223> OTHER INFORMATION: Xaa can be Lys or Gln
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (46)..(46)
<223> OTHER INFORMATION: Xaa can be Lys, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (67)..(67)
<223> OTHER INFORMATION: Xaa can be Gly or Val
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: Xaa can be Asp or Glu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (82)..(82)
<223> OTHER INFORMATION: Xaa can be Glu or Ala
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (88)..(88)
<223> OTHER INFORMATION: Xaa can be Tyr or Phe
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: Xaa can be Ile, Val or Phe

<400> SEQUENCE: 30

Asp Xaa Gln Xaa Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Xaa Xaa Ser Xaa
20 25 30

Trp Xaa Ala Trp Tyr Gln Gln Lys Pro Gly Xaa Ala Pro Xaa Leu Leu
35 40 45

Ile Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser
50 55 60

Gly Ser Xaa Ser Gly Thr Xaa Phe Thr Leu Thr Ile Ser Ser Leu Gln
65 70 75 80

Pro Xaa Asp Phe Ala Thr Tyr Xaa Cys Gln Gln Ala Asn Ser Phe Pro
85 90 95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Xaa Lys
100 105

<210> SEQ ID NO 31
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 31

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Thr Ser Ser Trp Tyr Pro Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 32
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 32

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatggtatg atggaagtaa tgaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagagatcgg 300

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gggtatacca gtagctggta ccctgatgct tttgatatct ggggccaagg gacaatggtc 360

accgtctctt ca 372

<210> SEQ ID NO 33
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 33

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Ser Ser Ser Trp Tyr Pro Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 34
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 34

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Ser Phe Asp Gly Ser Leu Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Arg Thr Thr Leu Ser Gly Ser Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 35
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 35

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

-continued

ccaggcaagg ggctggagtg ggtggcagtt atatcatttg atggaagtct taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa caccctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagaacgg 300

actactttaa gtgggagcta ctttgactac tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 36
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 36

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Leu
35 40 45

Ser Val Ile Ser His Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Arg Thr Thr Leu Ser Gly Ser Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 37
<211> LENGTH: 363
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 37

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatgcca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg gttgtcagtt atatcacatg atggaagtat taaatactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacgctgtat 240

ctgcaaatga acagcctgag agctgaggac acggctgtgt attactgtgc gagagaacgg 300

actactctaa gtgggagcta ctttgactac tggggccagg gaaccctggt caccgtctcc 360

tca 363

<210> SEQ ID NO 38
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 38

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

-continued

Ser Tyr Ile Ser Ser Arg Ser Ser Thr Ile Tyr Ile Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ile Ala Ala Ala Gly Gly Phe His Tyr Tyr Tyr Ala Leu
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 39
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 39

gaggtgcagc tggtggagtc tgggggaggc ctggtacagc ctgggggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt agctatagta tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcgtac attagtagta ggagtagtac catatacatc 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agacgaagac acggctgtgt attactgtgc gagacggata 300

gcagcagctg gtgggttcca ctactactac gctttggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 40
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 40

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Ser Ser Ser Thr Arg Tyr His Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ile Ala Ala Ala Gly Pro Trp Gly Tyr Tyr Tyr Ala Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 41
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 41

gaggtgcagc tggtggagtc tgggggaggc ttggtacaac ctgggggtc cctgagactc 60

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tcctgtgcag cctctggatt caccttcagt acctatagca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtagca gtagtagtac cagataccac 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agacgaggac acggctgtgt attactgtgc gagacgtata 300

gcagcagctg gtccgtgggg ctactactac gctatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 42
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 42

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Val Ser Gly Phe Thr Phe Ser Ser Phe
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Arg Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ile Ala Ala Ala Gly Pro Trp Gly Tyr Tyr Tyr Ala Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 43
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 43

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtgtag tctctggatt caccttcagt agttttagca tgaactgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtagtc gtagtagtac catatactac 180

gcagactctg tgaagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaaatga acagcctgag agacgaggac acggctgtgt attattgtgc gagacgtata 300

gcagcagctg gtccgtgggg ctactactac gctatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

<210> SEQ ID NO 44
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 44

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Thr Tyr
20 25 30

-continued

```
Tyr Trp Ser Trp Ile Arg Gln Pro Ala Gly Lys Gly Leu Glu Trp Ile
        35                  40                  45

Gly Leu Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Met Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Arg Leu Thr Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
                85                  90                  95

Arg Asp Arg Gly Tyr Tyr Tyr Gly Val Asp Val Trp Gly Gln Gly Thr
            100                 105                 110

Thr Val Thr Val Ser Ser
        115


<210> SEQ ID NO 45
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 45

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc     60

acctgcactg tctctggtgg ctccatcagt acttactact ggagctggat ccggcagccc    120

gccgggaagg gactggagtg gattgggctt atctatacca gtgggagcac caactacaac    180

ccctccctca agagtcgagt caccatgtca ttagacacgt ccaagaacca gttctccctg    240

aggctgacct ctgtgaccgc cgcggacacg gccgtttatt actgtgcgag agatcgtggg    300

tactactacg gtgtggacgt ctggggccag gggaccacgg tcaccgtctc ctca          354


<210> SEQ ID NO 46
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 46

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly His Ile His Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Lys Asn Arg Gly Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 47
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 47

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc     60
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acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggcacatcc attacagtgg gaacacctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaatcagttc 240

tccctgaaac tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgaaaaat 300

cgcgggttct actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> SEQ ID NO 48
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 48

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Ser Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Gln Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Arg Gly His Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 49
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 49

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcaac agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagctcctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctca gaaccagttc 240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300

cgggggcact actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> SEQ ID NO 50
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 50

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser

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    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Asp Arg Gly His Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 51
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 51

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc     60

acctgcactg tctctggtgg ctccatcagt agtggtggtt actactggag ctggatccgc    120

cagcacccag ggaagggcct ggagtggatt gggtacattt attacagtgg gagcacctac    180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaaccagttc    240

tccctgaagc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagagat    300

cggggccact actatggaat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca    360


<210> SEQ ID NO 52
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 52

Gln Val Gln Leu Gln Glu Ser Gly Pro Arg Leu Val Lys Pro Ser Glu
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Asp Ser Ile Ser Ser Tyr
            20                  25                  30

Phe Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Leu
        35                  40                  45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys
    50                  55                  60

Ser Arg Val Thr Ile Ser Ile Asp Thr Ser Lys Asn Gln Phe Ser Leu
65                  70                  75                  80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Thr
                85                  90                  95

Arg Asp Arg Gly Ser Tyr Tyr Gly Ser Asp Tyr Trp Gly Gln Gly Thr
            100                 105                 110

Leu Val Thr Val Ser Ser
        115


<210> SEQ ID NO 53
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 53

caggtgcagc tgcaggagtc gggcccaaga ctggtgaagc cttcggagac cctgtccctc     60

acctgcactg tctctggtga ctccatcagt agttacttct ggagctggat ccggcagccc    120

ccagggaagg gactggagtg gcttgggtat atctattaca gtgggagcac caactacaac    180
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ccctccctca agagtcgagt caccatatca atagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgaccgc tgcggacacg gccgtgtatt actgtacgag agatcggggg 300

agctactacg gatctgacta ctggggccag ggaaccctgg tcaccgtctc ctca 354

<210> SEQ ID NO 54
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 54

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Thr Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Ile Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Ser Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asn Arg Gly Tyr Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 55
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 55

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggac ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gaacacctac 180

tacaacccgt ccctcaagag tcgaattacc atatcagtgg acacgtctaa gaaccagttc 240

tccctgagcc tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgagaaat 300

cgcgggtact actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> SEQ ID NO 56
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 56

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Met Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

-continued

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Lys Asn Arg Gly Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 57
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 57

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcacctac 180

tacaacccgt ccctcaagag tcgagttacc atgtcagtag acacgtctaa gaaccagttc 240

tccctgaaac tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgaaaaat 300

cgcgggttct actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> SEQ ID NO 58
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 58

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Asn Ser Gly
20 25 30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Tyr Ile Tyr Tyr Ser Gly Ser Ser Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65 70 75 80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Arg Asp Arg Gly His Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 59
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 59

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcaat agtggtggtt actactggag ctggatccgc 120

cagcacccag ggaagggcct ggagtggatt gggtacatct attacagtgg gagcagctac 180

tacaacccgt ccctcaagag tcgagttacc atatcagttg acacgtctaa gaaccagttc 240

tccctgaagc tgagttctgt gactgccgcg gacacggccg tgtattactg tgcgagagat 300

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cgggggcact actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360

<210> SEQ ID NO 60
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 60

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Leu Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Asn Thr Val Thr Ile Tyr Tyr Asn Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 61
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus Sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be Val or Glu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (25)..(25)
<223> OTHER INFORMATION: Xaa can be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (38)..(38)
<223> OTHER INFORMATION: Xaa can be Gln or Leu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (55)..(55)
<223> OTHER INFORMATION: Xaa can be Ile or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (61)..(61)
<223> OTHER INFORMATION: Xaa can be Asp or Glu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: Xaa can be Tyr or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (101)..(101)
<223> OTHER INFORMATION: Xaa can be Ser or Asn

<400> SEQUENCE: 61

Gln Pro Xaa Leu Thr Gln Pro Pro Ser Ala Ser Ala Ser Leu Gly Ala
1 5 10 15

Ser Val Thr Leu Thr Cys Thr Leu Xaa Ser Gly Tyr Ser Asp Tyr Lys
20 25 30

Val Asp Trp Tyr Gln Xaa Arg Pro Gly Lys Gly Pro Arg Phe Val Met
35 40 45

-continued

Arg Val Gly Thr Gly Gly Xaa Val Gly Ser Lys Gly Xaa Gly Ile Pro
50 55 60

Asp Arg Phe Ser Val Leu Gly Ser Gly Leu Asn Arg Xaa Leu Thr Ile
65 70 75 80

Lys Asn Ile Gln Glu Glu Asp Glu Ser Asp Tyr His Cys Gly Ala Asp
85 90 95

His Gly Ser Gly Xaa Asn Phe Val Tyr Val Phe Gly Thr Gly Thr Lys
100 105 110

Val Thr Val Leu
115

<210> SEQ ID NO 62
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 62

Thr Gly Ser Ser Ser Asn Thr Gly Ala Gly Tyr Asp Val His
1 5 10

<210> SEQ ID NO 63
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 63

Gly Ser Gly Asn Arg Pro Ser
1 5

<210> SEQ ID NO 64
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 64

Gln Ser Tyr Asp Ser Ser Leu Ser Gly Trp Val
1 5 10

<210> SEQ ID NO 65
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 65

Thr Gly Ser Ser Ser Asn Ile Gly Ala Gly Tyr Asp Val His
1 5 10

<210> SEQ ID NO 66
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 66

Gly Ser Asn Asn Arg Pro Ser
1 5

<210> SEQ ID NO 67
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 67

Met Ile Trp His Ser Ser Ala Ser Val

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1 5

<210> SEQ ID NO 68
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 68

Thr Leu Arg Ser Gly Ile Asn Val Gly Thr Tyr Arg Ile Tyr
1 5 10

<210> SEQ ID NO 69
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 69

Tyr Lys Ser Asp Ser Asp Lys Gln Gln Gly Ser
1 5 10

<210> SEQ ID NO 70
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 70

Gly Ala Asp His Gly Ser Gly Ser Asn Phe Val Tyr Val
1 5 10

<210> SEQ ID NO 71
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 71

Thr Leu Asn Ser Gly Tyr Ser Asp Tyr Lys Val
1 5 10

<210> SEQ ID NO 72
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 72

Val Gly Thr Gly Gly Ile Val Gly Ser Lys Gly Asp
1 5 10

<210> SEQ ID NO 73
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 73

Gly Ala Asp His Gly Ser Gly Asn Asn Phe Val Tyr Val
1 5 10

<210> SEQ ID NO 74
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 74

Thr Leu Ser Ser Gly Tyr Ser Asp Tyr Lys Val
1 5 10

-continued

<210> SEQ ID NO 75
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 75

Val Gly Thr Gly Gly Ile Val Gly Ser Lys Gly Glu
1 5 10

<210> SEQ ID NO 76
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 76

Gln Gln Ala Asn Ser Phe Pro Phe Thr
1 5

<210> SEQ ID NO 77
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 77

Arg Ala Ser Gln Gly Phe Ser Gly Trp Leu Ala
1 5 10

<210> SEQ ID NO 78
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 78

Val Gly Thr Gly Gly Thr Val Gly Ser Lys Gly Glu
1 5 10

<210> SEQ ID NO 79
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 79

Gln Gln Ala Thr Ser Phe Pro Leu Thr
1 5

<210> SEQ ID NO 80
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 80

Arg Ala Ser Gln Val Ile Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 81
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 81

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 82
<211> LENGTH: 9
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 82

Gln Gln Ala Asp Ser Phe Pro Pro Thr
1 5

<210> SEQ ID NO 83
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 83

Arg Ala Ser Gln Val Ile Ser Ser Trp Phe Ala
1 5 10

<210> SEQ ID NO 84
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 84

Leu Gln His Asn Ser Tyr Pro Pro Thr
1 5

<210> SEQ ID NO 85
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 85

Arg Ala Ser Gln Gly Ser Ser Ser Trp Phe Ala
1 5 10

<210> SEQ ID NO 86
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 86

Arg Ala Ser Gln Gly Ile Ser Ser Trp Phe Ala
1 5 10

<210> SEQ ID NO 87
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 87

Arg Ala Gly Gln Val Ile Ser Ser Trp Leu Ala
1 5 10

<210> SEQ ID NO 88
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 88

Arg Ala Ser Gln Gly Ile Ala Gly Trp Leu Ala
1 5 10

<210> SEQ ID NO 89
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 89

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Arg Ala Ser Gln Gly Ile Arg Asn Asp Leu Gly
1 5 10

<210> SEQ ID NO 90
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 90

Leu Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 91
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 91

Ser Tyr Gly Met His
1 5

<210> SEQ ID NO 92
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 92

Val Ile Trp Tyr Asp Gly Ser Asn Glu Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 93
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 93

Asp Arg Gly Tyr Thr Ser Ser Trp Tyr Pro Asp Ala Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 94
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 94

Ser Tyr Ala Met His
1 5

<210> SEQ ID NO 95
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 95

Val Ile Trp Tyr Asp Gly Ser Asn Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 96
<211> LENGTH: 15
<212> TYPE: PRT

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<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 96

Asp Arg Gly Tyr Ser Ser Ser Trp Tyr Pro Asp Ala Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 97
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 97

Thr Tyr Ser Met Asn
1 5

<210> SEQ ID NO 98
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 98

Val Ile Ser Phe Asp Gly Ser Leu Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 99
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 99

Glu Arg Thr Thr Leu Ser Gly Ser Tyr Phe Asp Tyr
1 5 10

<210> SEQ ID NO 100
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 100

Ser Tyr Ser Met Asn
1 5

<210> SEQ ID NO 101
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 101

Val Ile Ser His Asp Gly Ser Ile Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 102
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 102

Arg Ile Ala Ala Ala Gly Gly Phe His Tyr Tyr Tyr Ala Leu Asp Val
1 5 10 15

<210> SEQ ID NO 103
<211> LENGTH: 5

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 103

Ser Phe Ser Met Asn
1 5

<210> SEQ ID NO 104
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 104

Tyr Ile Ser Ser Arg Ser Ser Thr Ile Tyr Ile Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 105
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 105

Arg Ile Ala Ala Ala Gly Pro Trp Gly Tyr Tyr Tyr Ala Met Asp Val
1 5 10 15

<210> SEQ ID NO 106
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 106

Ser Gly Gly Tyr Tyr Trp Thr
1 5

<210> SEQ ID NO 107
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 107

Tyr Ile Ser Ser Ser Ser Ser Thr Arg Tyr His Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 108
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 108

Asn Arg Gly Tyr Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 109
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 109

Ser Gly Gly Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 110

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<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 110

Tyr Ile Ser Ser Arg Ser Ser Thr Ile Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 111
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 111

Asn Arg Gly Phe Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 112
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 112

Ser Tyr Phe Trp Ser
1 5

<210> SEQ ID NO 113
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 113

Tyr Ile Tyr Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 114
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 114

Asp Arg Gly His Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 115
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 115

Thr Tyr Tyr Trp Ser
1 5

<210> SEQ ID NO 116
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 116

His Ile His Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 117
<211> LENGTH: 10

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<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 117

Asp Arg Gly Ser Tyr Tyr Gly Ser Asp Tyr
1 5 10

<210> SEQ ID NO 118
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 118

Tyr Ile Tyr Tyr Ser Gly Ser Thr Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 119
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 119

Asp Arg Gly Tyr Tyr Tyr Gly Val Asp Val
1 5 10

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 120

Tyr Ile Tyr Tyr Ser Gly Ser Ser Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 121

Tyr Ile Tyr Tyr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 122
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 122

Leu Ile Tyr Thr Ser Gly Ser Thr Asn Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 123
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
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<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be Gly or Val
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be Ile, Phe or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE

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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be Ser or Gly
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (10)..(10)
<223> OTHER INFORMATION: Xaa can be Phe or Leu.

<400> SEQUENCE: 123

Arg Ala Ser Gln Xaa Xaa Ser Xaa Trp Xaa Ala
1 5 10

<210> SEQ ID NO 124
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be Asn or Ser

<400> SEQUENCE: 124

Thr Leu Xaa Ser Gly Tyr Ser Asp Tyr Lys Val Asp
1 5 10

<210> SEQ ID NO 125
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be Ile or Thr

<400> SEQUENCE: 125

Thr Gly Ser Ser Ser Asn Xaa Gly Ala Gly Tyr Asp Val His
1 5 10

<210> SEQ ID NO 126
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa can be Ile or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (12)..(12)
<223> OTHER INFORMATION: Xaa can be Asp or Glu

<400> SEQUENCE: 126

Val Gly Thr Gly Gly Xaa Val Gly Ser Lys Gly Xaa
1 5 10

<210> SEQ ID NO 127
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be Asn or Gly

<400> SEQUENCE: 127

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Gly Ser Xaa Asn Arg Pro Ser
1 5

<210> SEQ ID NO 128
<211> LENGTH: 13
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be Ser or Asn

<400> SEQUENCE: 128

Gly Ala Asp His Gly Ser Gly Xaa Asn Phe Val Tyr Val
1 5 10

<210> SEQ ID NO 129
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be Ser or Thr

<400> SEQUENCE: 129

Ser Gly Gly Tyr Tyr Trp Xaa
1 5

<210> SEQ ID NO 130
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be Gly or Ala

<400> SEQUENCE: 130

Ser Tyr Xaa Met His
1 5

<210> SEQ ID NO 131
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa can be Tyr or Phe

<400> SEQUENCE: 131

Xaa Xaa Ser Met Asn
1 5

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<210> SEQ ID NO 132
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be Tyr or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa can be Thr or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be Ser or Asn
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be Thr or Ser

<400> SEQUENCE: 132

Xaa Ile Xaa Tyr Ser Gly Xaa Xaa Tyr Tyr Asn Pro Ser Leu Lys Ser
1 5 10 15

<210> SEQ ID NO 133
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be Phe or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be Leu or Thr

<400> SEQUENCE: 133

Val Ile Ser Xaa Asp Gly Ser Xaa Lys Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 134
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa can be Arg or Ser
<220> FEATURE:
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (11)..(11)
<223> OTHER INFORMATION: Xaa can be Ile, His or Try

<400> SEQUENCE: 134

Tyr Ile Ser Ser Xaa Ser Ser Thr Xaa Tyr Xaa Ala Asp Ser Val Lys
1 5 10 15

Gly

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<210> SEQ ID NO 135
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be Lys or Glu

<400> SEQUENCE: 135

Val Ile Trp Tyr Asp Gly Ser Asn Xaa Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

Gly

<210> SEQ ID NO 136
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa can be Asn or Asp
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa can be His, Tyr or Phe

<400> SEQUENCE: 136

Xaa Arg Gly Xaa Tyr Tyr Gly Met Asp Val
1 5 10

<210> SEQ ID NO 137
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa can be Gly or Phe
<220> FEATURE:
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<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa can be Phe or Trp
<220> FEATURE:
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<222> LOCATION: (9)..(9)
<223> OTHER INFORMATION: Xaa can be His or Gly
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (14)..(14)
<223> OTHER INFORMATION: Xaa can be Leu and Met

<400> SEQUENCE: 137

Arg Ile Ala Ala Ala Gly Xaa Xaa Xaa Tyr Tyr Tyr Ala Xaa Asp Val
1 5 10 15

<210> SEQ ID NO 138
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus sequence
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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa can be Ser or Thr

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<400> SEQUENCE: 138

Asp Arg Gly Tyr Xaa Ser Ser Trp Tyr Pro Asp Ala Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 139
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (29)..(29)
<223> OTHER INFORMATION: Xaa can be Ile or Thr
<220> FEATURE:
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<222> LOCATION: (41)..(41)
<223> OTHER INFORMATION: Xaa can be Val or Leu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: Xaa can be Gly or Asn
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: Xaa can be Arg or Lys

<400> SEQUENCE: 139

Gln Ser Val Leu Thr Gln Pro Pro Ser Val Ser Gly Ala Pro Gly Gln
1 5 10 15

Arg Val Thr Ile Ser Cys Thr Gly Ser Ser Ser Asn Xaa Gly Ala Gly
20 25 30

Tyr Asp Val His Trp Tyr Gln Gln Xaa Pro Gly Thr Ala Pro Lys Leu
35 40 45

Leu Ile Tyr Gly Ser Xaa Asn Arg Pro Ser Gly Val Pro Asp Arg Phe
50 55 60

Ser Gly Ser Lys Ser Gly Thr Ser Ala Ser Leu Ala Ile Thr Gly Leu
65 70 75 80

Gln Ala Glu Asp Glu Ala Asp Tyr Tyr Cys Gln Ser Tyr Asp Ser Ser
85 90 95

Leu Ser Gly Trp Val Phe Gly Gly Gly Thr Xaa Arg Leu Thr Val Leu
100 105 110

<210> SEQ ID NO 140
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
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<222> LOCATION: (30)..(30)
<223> OTHER INFORMATION: Xaa can be And or Ser
<220> FEATURE:
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<222> LOCATION: (37)..(37)
<223> OTHER INFORMATION: Xaa can be Ser or Thr
<220> FEATURE:
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<222> LOCATION: (52)..(52)
<223> OTHER INFORMATION: Xaa can be Tyr or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: Xaa can be Tyr or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (58)..(58)
<223> OTHER INFORMATION: Xaa can be Ser or Asn
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (59)..(59)
<223> OTHER INFORMATION: Xaa can be Ser or Asn
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (69)..(69)
<223> OTHER INFORMATION: Xaa can be Ser or Thr
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (71)..(71)
<223> OTHER INFORMATION: Xaa can be Val or Ile
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (77)..(77)
<223> OTHER INFORMATION: Xaa can be Ile or Met
<220> FEATURE:
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<222> LOCATION: (83)..(83)
<223> OTHER INFORMATION: Xaa can be Lys or Gln
<220> FEATURE:
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<222> LOCATION: (99)..(99)
<223> OTHER INFORMATION: Xaa can be Arg or Lys
<220> FEATURE:
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<222> LOCATION: (100)..(100)
<223> OTHER INFORMATION: Xaa can be Asp or Asn
<220> FEATURE:
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<222> LOCATION: (103)..(103)
<223> OTHER INFORMATION: Xaa can be His, Phe or Try

<400> SEQUENCE: 140

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Xaa Ser Gly
20 25 30

Gly Tyr Tyr Trp Xaa Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
35 40 45

Trp Ile Gly Xaa Ile Xaa Tyr Ser Gly Xaa Xaa Tyr Tyr Asn Pro Ser
50 55 60

Leu Lys Ser Arg Xaa Thr Xaa Ser Val Asp Thr Ser Xaa Asn Gln Phe
65 70 75 80

Ser Leu Xaa Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
85 90 95

Cys Ala Xaa Xaa Arg Gly Xaa Tyr Tyr Gly Met Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 141
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial
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<223> OTHER INFORMATION: Xaa can be Ala or Val
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<223> OTHER INFORMATION: Xaa can be Ala or Val
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<222> LOCATION: (31)..(31)
<223> OTHER INFORMATION: Xaa can be Thr or Ser
<220> FEATURE:
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<222> LOCATION: (32)..(32)

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<223> OTHER INFORMATION: Xaa can be Tyr or Phe
<220> FEATURE:
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<222> LOCATION: (54)..(54)
<223> OTHER INFORMATION: Xaa can be Ser or Arg
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<223> OTHER INFORMATION: Xaa can be Arg or Ile
<220> FEATURE:
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<222> LOCATION: (60)..(60)
<223> OTHER INFORMATION: Xaa can be His, Try or Ile
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa can be Pro or Gly
<220> FEATURE:
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<222> LOCATION: (106)..(106)
<223> OTHER INFORMATION: Xaa can be Trp or Phe
<220> FEATURE:
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<222> LOCATION: (107)..(107)
<223> OTHER INFORMATION: Xaa can be Gly or His
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (112)..(112)
<223> OTHER INFORMATION: Xaa can be Met or Leu

<400> SEQUENCE: 141

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Xaa Xaa Ser Gly Phe Thr Phe Ser Xaa Xaa
20 25 30

Ser Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Xaa Ser Ser Thr Xaa Tyr Xaa Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Asp Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Ile Ala Ala Ala Gly Xaa Xaa Xaa Tyr Tyr Tyr Ala Xaa
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 142
<211> LENGTH: 121
<212> TYPE: PRT
<213> ORGANISM: Artificial
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<222> LOCATION: (33)..(33)
<223> OTHER INFORMATION: Xaa can be Gly or Ala
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (48)..(48)
<223> OTHER INFORMATION: Xaa can be Val or Leu
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (49)..(49)
<223> OTHER INFORMATION: Xaa can be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (53)..(53)
<223> OTHER INFORMATION: Xaa can be Phe or His
<220> FEATURE:

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<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (57)..(57)
<223> OTHER INFORMATION: Xaa can be Leu or Ile

<400> SEQUENCE: 142

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Xaa Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Xaa
35 40 45

Xaa Val Ile Ser Xaa Asp Gly Ser Xaa Lys Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Arg Thr Thr Leu Ser Gly Ser Tyr Phe Asp Tyr Trp Gly
100 105 110

Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 143
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial
<220> FEATURE:
<223> OTHER INFORMATION: Consensus Sequence
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (58)..(58)
<223> OTHER INFORMATION: Xaa can be Glu or Lys
<220> FEATURE:
<221> NAME/KEY: MISC_FEATURE
<222> LOCATION: (103)..(103)
<223> OTHER INFORMATION: Xaa can be Thr or Ser

<400> SEQUENCE: 143

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Trp Tyr Asp Gly Ser Asn Xaa Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Arg Gly Tyr Xaa Ser Ser Trp Tyr Pro Asp Ala Phe Asp
100 105 110

Ile Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 144
<211> LENGTH: 1026
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 144

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agatttgaga agaaggcaaa aagatgctgg ggagcagagc tgtaatgctg ctgttgctgc    180

tgccctggac agctcagggc agagctgtgc ctgggggcag cagccctgcc tggactcagt    240

gccagcagct ttcacagaag ctctgcacac tggcctggag tgcacatcca ctagtgggac    300

acatggatct aagagaagag ggagatgaag agactacaaa tgatgttccc catatccagt    360

gtggagatgg ctgtgacccc caaggactca gggacaacag tcagttctgc ttgcaaagga    420

tccaccaggg tctgattttt tatgagaagc tgctaggatc ggatattttc acaggggagc    480

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aactcctgca gcctgagggt caccactggg agactcagca gattccaagc ctcagtccca    600

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aaaaaa                                                              1026


<210> SEQ ID NO 145
<211> LENGTH: 189
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 145

Met Leu Gly Ser Arg Ala Val Met Leu Leu Leu Leu Leu Pro Trp Thr
1               5                   10                  15

Ala Gln Gly Arg Ala Val Pro Gly Gly Ser Ser Pro Ala Trp Thr Gln
            20                  25                  30

Cys Gln Gln Leu Ser Gln Lys Leu Cys Thr Leu Ala Trp Ser Ala His
        35                  40                  45

Pro Leu Val Gly His Met Asp Leu Arg Glu Glu Gly Asp Glu Glu Thr
    50                  55                  60

Thr Asn Asp Val Pro His Ile Gln Cys Gly Asp Gly Cys Asp Pro Gln
65                  70                  75                  80

Gly Leu Arg Asp Asn Ser Gln Phe Cys Leu Gln Arg Ile His Gln Gly
                85                  90                  95

Leu Ile Phe Tyr Glu Lys Leu Leu Gly Ser Asp Ile Phe Thr Gly Glu
            100                 105                 110

Pro Ser Leu Leu Pro Asp Ser Pro Val Gly Gln Leu His Ala Ser Leu
        115                 120                 125

Leu Gly Leu Ser Gln Leu Leu Gln Pro Glu Gly His His Trp Glu Thr
    130                 135                 140

Gln Gln Ile Pro Ser Leu Ser Pro Ser Gln Pro Trp Gln Arg Leu Leu
145                 150                 155                 160

Leu Arg Phe Lys Ile Leu Arg Ser Leu Gln Ala Phe Val Ala Val Ala
                165                 170                 175

Ala Arg Val Phe Ala His Gly Ala Ala Thr Leu Ser Pro
            180                 185
```

<210> SEQ ID NO 146
<211> LENGTH: 1399
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 146

ctgtttcagg gccattggac tctccgtcct gcccagagca agatgtgtca ccagcagttg 60

gtcatctctt ggttttccct ggtttttctg gcatctcccc tcgtggccat atgggaactg 120

aagaaagatg tttatgtcgt agaattggat tggtatccgg atgcccctgg agaaatggtg 180

gtcctcacct gtgacacccc tgaagaagat ggtatcacct ggaccttgga ccagagcagt 240

gaggtcttag gctctggcaa aaccctgacc atccaagtca aagagtttgg agatgctggc 300

cagtacacct gtcacaaagg aggcgaggtt ctaagccatt cgctcctgct gcttcacaaa 360

aaggaagatg gaatttggtc cactgatatt ttaaaggacc agaaagaacc caaaaataag 420

acctttctaa gatgcgaggc caagaattat tctggacgtt tcacctgctg gtggctgacg 480

acaatcagta ctgatttgac attcagtgtc aaaagcagca gaggctcttc tgacccccaa 540

ggggtgacgt gcggagctgc tacactctct gcagagagag tcagagggga caacaaggag 600

tatgagtact cagtggagtg ccaggaggac agtgcctgcc cagctgctga ggagagtctg 660

cccattgagg tcatggtgga tgccgttcac aagctcaagt atgaaaacta caccagcagc 720

ttcttcatca gggacatcat caaacctgac ccacccaaga acttgcagct gaagccatta 780

aagaattctc ggcaggtgga ggtcagctgg gagtaccctg acacctggag tactccacat 840

tcctacttct ccctgacatt ctgcgttcag gtccagggca agagcaagag agaaaagaaa 900

gatagagtct tcacggacaa gacctcagcc acggtcatct gccgcaaaaa tgccagcatt 960

agcgtgcggg cccaggaccg ctactatagc tcatcttgga gcgaatgggc atctgtgccc 1020

tgcagttagg ttctgatcca ggatgaaaat ttggaggaaa agtggaagat attaagcaaa 1080

atgtttaaag acacaacgga atagacccaa aaagataatt tctatctgat ttgctttaaa 1140

acgtttttt aggatcacaa tgatatcttt gctgtatttg tatagttaga tgctaaatgc 1200

tcattgaaac aatcagctaa tttatgtata gattttccag ctctcaagtt gccatgggcc 1260

ttcatgctat ttaaatattt aagtaattta tgtatttatt agtatattac tgttatttaa 1320

cgtttgtctg ccaggatgta tggaatgttt catactctta tgacctgatc catcaggatc 1380

agtccctatt atgcaaaat 1399

<210> SEQ ID NO 147
<211> LENGTH: 328
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 147

Met Cys His Gln Gln Leu Val Ile Ser Trp Phe Ser Leu Val Phe Leu
1 5 10 15

Ala Ser Pro Leu Val Ala Ile Trp Glu Leu Lys Lys Asp Val Tyr Val
20 25 30

Val Glu Leu Asp Trp Tyr Pro Asp Ala Pro Gly Glu Met Val Val Leu
35 40 45

Thr Cys Asp Thr Pro Glu Glu Asp Gly Ile Thr Trp Thr Leu Asp Gln
50 55 60

Ser Ser Glu Val Leu Gly Ser Gly Lys Thr Leu Thr Ile Gln Val Lys
65 70 75 80

Glu Phe Gly Asp Ala Gly Gln Tyr Thr Cys His Lys Gly Gly Glu Val

-continued

```
               85                  90                  95

Leu Ser His Ser Leu Leu Leu Leu His Lys Lys Glu Asp Gly Ile Trp
            100                 105                 110

Ser Thr Asp Ile Leu Lys Asp Gln Lys Glu Pro Lys Asn Lys Thr Phe
        115                 120                 125

Leu Arg Cys Glu Ala Lys Asn Tyr Ser Gly Arg Phe Thr Cys Trp Trp
    130                 135                 140

Leu Thr Thr Ile Ser Thr Asp Leu Thr Phe Ser Val Lys Ser Ser Arg
145                 150                 155                 160

Gly Ser Ser Asp Pro Gln Gly Val Thr Cys Gly Ala Ala Thr Leu Ser
                165                 170                 175

Ala Glu Arg Val Arg Gly Asp Asn Lys Glu Tyr Glu Tyr Ser Val Glu
            180                 185                 190

Cys Gln Glu Asp Ser Ala Cys Pro Ala Ala Glu Glu Ser Leu Pro Ile
       195                 200                 205

Glu Val Met Val Asp Ala Val His Lys Leu Lys Tyr Glu Asn Tyr Thr
    210                 215                 220

Ser Ser Phe Phe Ile Arg Asp Ile Ile Lys Pro Asp Pro Pro Lys Asn
225                 230                 235                 240

Leu Gln Leu Lys Pro Leu Lys Asn Ser Arg Gln Val Glu Val Ser Trp
                245                 250                 255

Glu Tyr Pro Asp Thr Trp Ser Thr Pro His Ser Tyr Phe Ser Leu Thr
            260                 265                 270

Phe Cys Val Gln Val Gln Gly Lys Ser Lys Arg Glu Lys Lys Asp Arg
        275                 280                 285

Val Phe Thr Asp Lys Thr Ser Ala Thr Val Ile Cys Arg Lys Asn Ala
    290                 295                 300

Ser Ile Ser Val Arg Ala Gln Asp Arg Tyr Tyr Ser Ser Ser Trp Ser
305                 310                 315                 320

Glu Trp Ala Ser Val Pro Cys Ser
                325
```

<210> SEQ ID NO 148
<211> LENGTH: 2826
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 148

```
acaagggtgg cagcctggct ctgaagtgga attatgtgct tcaaacaggt tgaaagaggg     60

aaacagtctt ttcctgcttc cagacatgaa tcaggtcact attcaatggg atgcagtaat    120

agccctttac atactcttca gctggtgtca tggaggaatt acaaatataa actgctctgg    180

ccacatctgg gtagaaccag ccacaatttt taagatgggt atgaatatct ctatatattg    240

ccaagcagca attaagaact gccaaccaag gaaacttcat ttttataaaa atggcatcaa    300

agaaagattt caaatcacaa ggattaataa aacaacagct cggctttggt ataaaaactt    360

tctggaacca catgcttcta tgtactgcac tgctgaatgt cccaaacatt ttcaagagac    420

actgatatgt ggaaaagaca tttcttctgg atatccgcca gatattcctg atgaagtaac    480

ctgtgtcatt tatgaatatt caggcaacat gacttgcacc tggaatgctg ggaagctcac    540

ctacatagac acaaaatacg tggtacatgt gaagagttta gagacagaag aagagcaaca    600

gtatctcacc tcaagctata ttaacatctc cactgattca ttacaaggtg gcaagaagta    660

cttggtttgg gtccaagcag caaacgcact aggcatggaa gagtcaaaac aactgcaaat    720

tcacctggat gatatagtga taccttctgc agccgtcatt tccagggctg agactataaa    780
```

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tgctacagtg cccaagacca taatttattg ggatagtcaa acaacaattg aaaaggtttc 840

ctgtgaaatg agatacaagg ctacaacaaa ccaaacttgg aatgttaaag aatttgacac 900

caattttaca tatgtgcaac agtcagaatt ctacttggag ccaaacatta agtacgtatt 960

tcaagtgaga tgtcaagaaa caggcaaaag gtactggcag ccttggagtt cactgttttt 1020

tcataaaaca cctgaaacag ttccccaggt cacatcaaaa gcattccaac atgacacatg 1080

gaattctggg ctaacagttg cttccatctc tacagggcac cttacttctg acaacagagg 1140

agacattgga cttttattgg gaatgatcgt ctttgctgtt atgttgtcaa ttctttcttt 1200

gattgggata tttaacagat cattccgaac tgggattaaa agaaggatct tattgttaat 1260

accaaagtgg ctttatgaag atattcctaa tatgaaaaac agcaatgttg tgaaaatgct 1320

acaggaaaat agtgaactta tgaataataa ttccagtgag caggtcctat atgttgatcc 1380

catgattaca gagataaaag aaatcttcat cccagaacac aagcctacag actacaagaa 1440

ggagaataca ggacccctgg agacaagaga ctacccgcaa aactcgctat tcgacaatac 1500

tacagttgta tatattcctg atctcaacac tggatataaa ccccaaattt caaattttct 1560

gcctgaggga agccatctca gcaataataa tgaaattact tccttaacac ttaaaccacc 1620

agttgattcc ttagactcag gaaataatcc caggttacaa aagcatccta attttgcttt 1680

ttctgtttca agtgtgaatt cactaagcaa cacaatattt cttggagaat taagcctcat 1740

attaaatcaa ggagaatgca gttctcctga catacaaaac tcagtagagg aggaaaccac 1800

catgcttttg gaaaatgatt cacccagtga aactattcca gaacagaccc tgcttcctga 1860

tgaatttgtc tcctgtttgg ggatcgtgaa tgaggagttg ccatctatta atacttattt 1920

tccacaaaat attttggaaa gccacttcaa taggatttca ctcttggaaa agtagagctg 1980

tgtggtcaaa atcaatatga gaaagctgcc ttgcaatctg aacttgggtt ttccctgcaa 2040

tagaaattga attctgcctc tttttgaaaa aaatgtattc acatacaaat cttcacatgg 2100

acacatgttt tcatttccct tggataaata cctaggtagg ggattgctgg gccatatgat 2160

aagcatatgt ttcagttcta ccaatcttgt ttccagagta gtgacatttc tgtgctccta 2220

ccatcaccat gtaagaattc ccgggagctc catgcctttt taattttagc cattcttctg 2280

cctcatttct taaaattaga gaattaaggt cccgaaggtg gaacatgctt catggtcaca 2340

catacaggca caaaaacagc attatgtgga cgcctcatgt atttttttata gagtcaacta 2400

tttcctcttt attttccctc attgaaagat gcaaaacagc tctctattgt gtacagaaag 2460

ggtaaataat gcaaaatacc tggtagtaaa ataaatgctg aaaattttcc tttaaaatag 2520

aatcattagg ccaggcgtgg tggctcatgc ttgtaatccc agcactttgg taggctgagg 2580

taggtggatc acctgaggtc aggagttcga gtccagcctg gccaatatgc tgaaaccctg 2640

tctctactaa aattacaaaa attagccggc catggtggca ggtgcttgta atcccagcta 2700

cttgggaggc tgaggcagga gaatcacttg aaccaggaag gcagaggttg cactgagctg 2760

agattgtgcc actgcactcc agcctgggca acaagagcaa aactctgtct ggaaaaaaaa 2820

aaaaaa 2826

<210> SEQ ID NO 149
<211> LENGTH: 629
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 149

Met Asn Gln Val Thr Ile Gln Trp Asp Ala Val Ile Ala Leu Tyr Ile

-continued

```
1               5                  10                  15

Leu Phe Ser Trp Cys His Gly Gly Ile Thr Asn Ile Asn Cys Ser Gly
            20                  25                  30

His Ile Trp Val Glu Pro Ala Thr Ile Phe Lys Met Gly Met Asn Ile
        35                  40                  45

Ser Ile Tyr Cys Gln Ala Ala Ile Lys Asn Cys Gln Pro Arg Lys Leu
    50                  55                  60

His Phe Tyr Lys Asn Gly Ile Lys Glu Arg Phe Gln Ile Thr Arg Ile
65                  70                  75                  80

Asn Lys Thr Thr Ala Arg Leu Trp Tyr Lys Asn Phe Leu Glu Pro His
                85                  90                  95

Ala Ser Met Tyr Cys Thr Ala Glu Cys Pro Lys His Phe Gln Glu Thr
            100                 105                 110

Leu Ile Cys Gly Lys Asp Ile Ser Ser Gly Tyr Pro Pro Asp Ile Pro
        115                 120                 125

Asp Glu Val Thr Cys Val Ile Tyr Glu Tyr Ser Gly Asn Met Thr Cys
    130                 135                 140

Thr Trp Asn Ala Gly Lys Leu Thr Tyr Ile Asp Thr Lys Tyr Val Val
145                 150                 155                 160

His Val Lys Ser Leu Glu Thr Glu Glu Glu Gln Gln Tyr Leu Thr Ser
                165                 170                 175

Ser Tyr Ile Asn Ile Ser Thr Asp Ser Leu Gln Gly Gly Lys Lys Tyr
            180                 185                 190

Leu Val Trp Val Gln Ala Ala Asn Ala Leu Gly Met Glu Glu Ser Lys
        195                 200                 205

Gln Leu Gln Ile His Leu Asp Asp Ile Val Ile Pro Ser Ala Ala Val
    210                 215                 220

Ile Ser Arg Ala Glu Thr Ile Asn Ala Thr Val Pro Lys Thr Ile Ile
225                 230                 235                 240

Tyr Trp Asp Ser Gln Thr Thr Ile Glu Lys Val Ser Cys Glu Met Arg
                245                 250                 255

Tyr Lys Ala Thr Thr Asn Gln Thr Trp Asn Val Lys Glu Phe Asp Thr
            260                 265                 270

Asn Phe Thr Tyr Val Gln Gln Ser Glu Phe Tyr Leu Glu Pro Asn Ile
        275                 280                 285

Lys Tyr Val Phe Gln Val Arg Cys Gln Glu Thr Gly Lys Arg Tyr Trp
    290                 295                 300

Gln Pro Trp Ser Ser Leu Phe Phe His Lys Thr Pro Glu Thr Val Pro
305                 310                 315                 320

Gln Val Thr Ser Lys Ala Phe Gln His Asp Thr Trp Asn Ser Gly Leu
                325                 330                 335

Thr Val Ala Ser Ile Ser Thr Gly His Leu Thr Ser Asp Asn Arg Gly
            340                 345                 350

Asp Ile Gly Leu Leu Leu Gly Met Ile Val Phe Ala Val Met Leu Ser
        355                 360                 365

Ile Leu Ser Leu Ile Gly Ile Phe Asn Arg Ser Phe Arg Thr Gly Ile
    370                 375                 380

Lys Arg Arg Ile Leu Leu Leu Ile Pro Lys Trp Leu Tyr Glu Asp Ile
385                 390                 395                 400

Pro Asn Met Lys Asn Ser Asn Val Val Lys Met Leu Gln Glu Asn Ser
                405                 410                 415

Glu Leu Met Asn Asn Asn Ser Ser Glu Gln Val Leu Tyr Val Asp Pro
            420                 425                 430
```

-continued

```
Met Ile Thr Glu Ile Lys Glu Ile Phe Ile Pro Glu His Lys Pro Thr
        435                 440                 445

Asp Tyr Lys Lys Glu Asn Thr Gly Pro Leu Glu Thr Arg Asp Tyr Pro
    450                 455                 460

Gln Asn Ser Leu Phe Asp Asn Thr Thr Val Val Tyr Ile Pro Asp Leu
465                 470                 475                 480

Asn Thr Gly Tyr Lys Pro Gln Ile Ser Asn Phe Leu Pro Glu Gly Ser
                485                 490                 495

His Leu Ser Asn Asn Asn Glu Ile Thr Ser Leu Thr Leu Lys Pro Pro
            500                 505                 510

Val Asp Ser Leu Asp Ser Gly Asn Asn Pro Arg Leu Gln Lys His Pro
        515                 520                 525

Asn Phe Ala Phe Ser Val Ser Ser Val Asn Ser Leu Ser Asn Thr Ile
    530                 535                 540

Phe Leu Gly Glu Leu Ser Leu Ile Leu Asn Gln Gly Glu Cys Ser Ser
545                 550                 555                 560

Pro Asp Ile Gln Asn Ser Val Glu Glu Glu Thr Thr Met Leu Leu Glu
                565                 570                 575

Asn Asp Ser Pro Ser Glu Thr Ile Pro Glu Gln Thr Leu Leu Pro Asp
            580                 585                 590

Glu Phe Val Ser Cys Leu Gly Ile Val Asn Glu Glu Leu Pro Ser Ile
        595                 600                 605

Asn Thr Tyr Phe Pro Gln Asn Ile Leu Glu Ser His Phe Asn Arg Ile
    610                 615                 620

Ser Leu Leu Glu Lys
625
```

<210> SEQ ID NO 150
<211> LENGTH: 2100
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 150

```
ggtggctgaa cctcgcaggt ggcagagagg ctcccctggg gctgtggggc tctacgtgga     60

tccgatggag ccgctggtga cctgggtggt ccccctcctc ttcctcttcc tgctgtccag    120

gcagggcgct gcctgcagaa ccagtgagtg ctgttttcag gacccgccat atccggatgc    180

agactcaggc tcggcctcgg gccctaggga cctgagatgc tatcggatat ccagtgatcg    240

ttacgagtgc tcctggcagt atgagggtcc cacagctggg gtcagccact tcctgcggtg    300

ttgccttagc tccgggcgct gctgctactt cgccgccggc tcagccacca ggctgcagtt    360

ctccgaccag gctggggtgt ctgtgctgta cactgtcaca ctctgggtgg aatcctgggc    420

caggaaccag acagagaagt ctcctgaggt gaccctgcag ctctacaact cagttaaata    480

tgagcctcct ctgggagaca tcaaggtgtc caagttggcc gggcagctgc gtatggagtg    540

ggagaccccg gataaccagg ttggtgctga ggtgcagttc cggcaccgga cacccagcag    600

cccatggaag ttgggcgact gcggacctca ggatgatgat actgagtcct gcctctgccc    660

cctggagatg aatgtggccc aggaattcca gctccgacga cggcagctgg ggagccaagg    720

aagttcctgg agcaagtgga gcagccccgt gtgcgttccc cctgaaaacc ccccacagcc    780

tcaggtgaga ttctcggtgg agcagctggg ccaggatggg aggaggcggc tgaccctgaa    840

agagcagcca acccagctgg agcttccaga aggctgtcaa gggctggcgc ctggcacgga    900

ggtcacttac cgactacagc tccacatgct gtcctgcccg tgtaaggcca aggccaccag    960

gaccctgcac ctggggaaga tgccctatct ctcgggtgct gcctacaacg tggctgtcat   1020
```

-continued

ctcctcgaac caatttggtc ctggcctgaa ccagacgtgg cacattcctg ccgacaccca 1080

cacagaacca gtggctctga atatcagcgt cggaaccaac gggaccacca tgtattggcc 1140

agcccgggct cagagcatga cgtattgcat tgaatggcag cctgtgggcc aggacggggg 1200

ccttgccacc tgcagcctga ctgcgccgca agacccggat ccggctggaa tggcaaccta 1260

cagctggagt cgagagtctg gggcaatggg gcaggaaaag tgttactaca ttaccatctt 1320

tgcctctgcg caccccgaga agctcacctt gtggtctacg gtcctgtcca cctaccactt 1380

tgggggcaat gcctcagcag ctgggacacc gcaccacgtc tcggtgaaga atcatagctt 1440

ggactctgtg tctgtggact gggcaccatc cctgctgagc acctgtcccg gcgtcctaaa 1500

ggagtatgtt gtccgctgcc gagatgaaga cagcaaacag gtgtcagagc atcccgtgca 1560

gcccacagag acccaagtta ccctcagtgg cctgcgggct ggtgtagcct acacggtgca 1620

ggtgcgagca gacacagcgt ggctgagggg tgtctggagc cagccccagc gcttcagcat 1680

cgaagtgcag gtttctgatt ggctcatctt cttcgcctcc ctggggagct tcctgagcat 1740

ccttctcgtg ggcgtccttg gctaccttgg cctgaacagg gccgcacggc acctgtgccc 1800

gccgctgccc acaccctgtg ccagctccgc cattgagttc cctggaggga aggagacttg 1860

gcagtggatc aacccagtgg acttccagga agaggcatcc ctgcaggagg ccctggtggt 1920

agagatgtcc tgggacaaag gcgagaggac tgagcctctc gagaagacag agctacctga 1980

gggtgcccct gagctggccc tggatacaga gttgtccttg gaggatggag acaggtgcaa 2040

ggccaagatg tgatcgttga ggctcagaga gggtgagtga ctcgcccgag gctacgtagc 2100

<210> SEQ ID NO 151
<211> LENGTH: 662
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 151

Met Glu Pro Leu Val Thr Trp Val Val Pro Leu Leu Phe Leu Phe Leu
1 5 10 15

Leu Ser Arg Gln Gly Ala Ala Cys Arg Thr Ser Glu Cys Cys Phe Gln
20 25 30

Asp Pro Pro Tyr Pro Asp Ala Asp Ser Gly Ser Ala Ser Gly Pro Arg
35 40 45

Asp Leu Arg Cys Tyr Arg Ile Ser Ser Asp Arg Tyr Glu Cys Ser Trp
50 55 60

Gln Tyr Glu Gly Pro Thr Ala Gly Val Ser His Phe Leu Arg Cys Cys
65 70 75 80

Leu Ser Ser Gly Arg Cys Cys Tyr Phe Ala Ala Gly Ser Ala Thr Arg
85 90 95

Leu Gln Phe Ser Asp Gln Ala Gly Val Ser Val Leu Tyr Thr Val Thr
100 105 110

Leu Trp Val Glu Ser Trp Ala Arg Asn Gln Thr Glu Lys Ser Pro Glu
115 120 125

Val Thr Leu Gln Leu Tyr Asn Ser Val Lys Tyr Glu Pro Pro Leu Gly
130 135 140

Asp Ile Lys Val Ser Lys Leu Ala Gly Gln Leu Arg Met Glu Trp Glu
145 150 155 160

Thr Pro Asp Asn Gln Val Gly Ala Glu Val Gln Phe Arg His Arg Thr
165 170 175

Pro Ser Ser Pro Trp Lys Leu Gly Asp Cys Gly Pro Gln Asp Asp Asp
180 185 190

-continued

```
Thr Glu Ser Cys Leu Cys Pro Leu Glu Met Asn Val Ala Gln Glu Phe
        195                 200                 205

Gln Leu Arg Arg Arg Gln Leu Gly Ser Gln Gly Ser Ser Trp Ser Lys
    210                 215                 220

Trp Ser Ser Pro Val Cys Val Pro Pro Glu Asn Pro Pro Gln Pro Gln
225                 230                 235                 240

Val Arg Phe Ser Val Glu Gln Leu Gly Gln Asp Gly Arg Arg Arg Leu
                245                 250                 255

Thr Leu Lys Glu Gln Pro Thr Gln Leu Glu Leu Pro Glu Gly Cys Gln
            260                 265                 270

Gly Leu Ala Pro Gly Thr Glu Val Thr Tyr Arg Leu Gln Leu His Met
        275                 280                 285

Leu Ser Cys Pro Cys Lys Ala Lys Ala Thr Arg Thr Leu His Leu Gly
    290                 295                 300

Lys Met Pro Tyr Leu Ser Gly Ala Ala Tyr Asn Val Ala Val Ile Ser
305                 310                 315                 320

Ser Asn Gln Phe Gly Pro Gly Leu Asn Gln Thr Trp His Ile Pro Ala
                325                 330                 335

Asp Thr His Thr Glu Pro Val Ala Leu Asn Ile Ser Val Gly Thr Asn
            340                 345                 350

Gly Thr Thr Met Tyr Trp Pro Ala Arg Ala Gln Ser Met Thr Tyr Cys
        355                 360                 365

Ile Glu Trp Gln Pro Val Gly Gln Asp Gly Gly Leu Ala Thr Cys Ser
    370                 375                 380

Leu Thr Ala Pro Gln Asp Pro Asp Pro Ala Gly Met Ala Thr Tyr Ser
385                 390                 395                 400

Trp Ser Arg Glu Ser Gly Ala Met Gly Gln Glu Lys Cys Tyr Tyr Ile
                405                 410                 415

Thr Ile Phe Ala Ser Ala His Pro Glu Lys Leu Thr Leu Trp Ser Thr
            420                 425                 430

Val Leu Ser Thr Tyr His Phe Gly Gly Asn Ala Ser Ala Ala Gly Thr
        435                 440                 445

Pro His His Val Ser Val Lys Asn His Ser Leu Asp Ser Val Ser Val
    450                 455                 460

Asp Trp Ala Pro Ser Leu Leu Ser Thr Cys Pro Gly Val Leu Lys Glu
465                 470                 475                 480

Tyr Val Val Arg Cys Arg Asp Glu Asp Ser Lys Gln Val Ser Glu His
                485                 490                 495

Pro Val Gln Pro Thr Glu Thr Gln Val Thr Leu Ser Gly Leu Arg Ala
            500                 505                 510

Gly Val Ala Tyr Thr Val Gln Val Arg Ala Asp Thr Ala Trp Leu Arg
        515                 520                 525

Gly Val Trp Ser Gln Pro Gln Arg Phe Ser Ile Glu Val Gln Val Ser
    530                 535                 540

Asp Trp Leu Ile Phe Phe Ala Ser Leu Gly Ser Phe Leu Ser Ile Leu
545                 550                 555                 560

Leu Val Gly Val Leu Gly Tyr Leu Gly Leu Asn Arg Ala Ala Arg His
                565                 570                 575

Leu Cys Pro Pro Leu Pro Thr Pro Cys Ala Ser Ser Ala Ile Glu Phe
            580                 585                 590

Pro Gly Gly Lys Glu Thr Trp Gln Trp Ile Asn Pro Val Asp Phe Gln
        595                 600                 605

Glu Glu Ala Ser Leu Gln Glu Ala Leu Val Val Glu Met Ser Trp Asp
```

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```
    610                 615                 620

Lys Gly Glu Arg Thr Glu Pro Leu Glu Lys Thr Glu Leu Pro Glu Gly
625                 630                 635                 640

Ala Pro Glu Leu Ala Leu Asp Thr Glu Leu Ser Leu Glu Asp Gly Asp
                645                 650                 655

Arg Cys Lys Ala Lys Met
            660
```

<210> SEQ ID NO 152
<211> LENGTH: 360
<212> TYPE: DNA
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 152

```
caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcacagac cctgtccctc     60

acctgcactg tctctggtgg ctccatcagc agtggtggtt actactggag ctggatccgc    120

cagcacccag ggaagggcct ggagtggatt gggcacatcc attacagtgg gaacacctac    180

tacaacccgt ccctcaagag tcgagttacc atatcagtag acacgtctaa gaatcagttc    240

tccctgaaac tgagctctgt gactgccgcg gacacggccg tgtattactg tgcgcgaaat    300

cgcgggttct actacggtat ggacgtctgg ggccaaggga ccacggtcac cgtctcctca    360
```

<210> SEQ ID NO 153
<211> LENGTH: 120
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

<400> SEQUENCE: 153

```
Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Gln
1               5                   10                  15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Ser Gly
            20                  25                  30

Gly Tyr Tyr Trp Ser Trp Ile Arg Gln His Pro Gly Lys Gly Leu Glu
        35                  40                  45

Trp Ile Gly His Ile His Tyr Ser Gly Asn Thr Tyr Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe
65                  70                  75                  80

Ser Leu Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr
                85                  90                  95

Cys Ala Arg Asn Arg Gly Phe Tyr Tyr Gly Met Asp Val Trp Gly Gln
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser
        115                 120
```

<210> SEQ ID NO 154
<211> LENGTH: 23
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Honeybee melittin signal

<400> SEQUENCE: 154

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Met Lys Phe Leu Val Asn Val Ala Leu Val Phe Met Val Val Tyr Ile
1               5                   10                  15

Ser Tyr Ile Tyr Ala Ala Ala
            20
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-continued

<210> SEQ ID NO 155
<211> LENGTH: 6
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<213> ORGANISM: Artificial Sequence
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<223> OTHER INFORMATION: His Tag

<400> SEQUENCE: 155

His His His His His His
1 5

What is claimed is:

1. An isolated antigen binding protein that binds IL-23, comprising at least one heavy chain variable region comprising:

a CDRH1 of SEQ ID NO: 91;

a CDRH2 of SEQ ID NO:92; and

a CDRH3 of SEQ ID NO: 93; and

at least one light chain variable region comprising:

a CDRL1 of SEQ ID NO: 62;

a CDRL2 of SEQ ID NO:63; and

a CDRL3 of SEQ ID NO:64.

2. An isolated antigen binding protein that binds IL-23 comprising a heavy chain variable region comprising amino acid residues 31-35, 50-65 and 99-113 of SEQ ID NO:31; and a light chain variable region comprising amino acid residues 23-36, 52-58 and 91-101 of SEQ ID NO:1.

3. An isolated antigen binding protein that binds IL-23 comprising

a heavy chain variable region of SEQ ID NO: 31 and

a light chain variable region of SEQ ID NO: 1.

4. An isolated antigen binding protein of claim **1**, **2** or **3** wherein said antigen binding protein has at least one property selected from the group consisting of:

a) reducing human IL-23 activity;

b) reducing production of a proinflammatory cytokine;

c) binding to human IL-23 with a K_D of less than or equal to 5×10^{-8} M;

d) having a K_{off} rate of less than or equal to 5×10^{-6} l/s; and

e) having an IC_{50} of less than or equal to 400 pM.

5. A pharmaceutical composition comprising at least one antigen binding protein of claim **1**, **2**, or **3** and a pharmaceutically acceptable excipient.

6. A pharmaceutical composition comprising at least one antigen binding protein of claim **4** and a pharmaceutically acceptable excipient.

* * * * *

US006258562B1

(12) **United States Patent**
Salfeld et al.

(10) **Patent No.: US 6,258,562 B1**
(45) **Date of Patent: Jul. 10, 2001**

(54) **HUMAN ANTIBODIES THAT BIND HUMAN TNFα**

(75) Inventors: **Jochen G. Salfeld**, North Grafton, MA (US); **Deborah J. Allen**, Cambridge (GB); **Hendricus R. J. M. Hoogenboom**, Hertogsingel, MA (US); **Zehra Kaymakcalan**, Westboro, MA (US); **Boris Labkovsky**, Framingham, MA (US); **John A. Mankovich**, Andover, MA (US); **Brian T. McGuinness**, Comberton; **Andrew J. Roberts**, Cambridge, both of (GB); **Paul Sakorafas**, Newton, MA (US); **David Schoenhaut**, Garfield, NJ (US); **Tristan J. Vaughan**, Impington (GB); **Michael White**, Framingham, MA (US); **Alison J. Wilton**, Cambridge (GB)

(73) Assignee: **BASF Aktiengesellschaft**, Rheiland-Pfalz (DE)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/125,098**

(22) PCT Filed: **Feb. 10, 1997**

(86) PCT No.: **PCT/US97/02219**

§ 371 Date: **Mar. 16, 1999**

§ 102(e) Date: **Mar. 16, 1999**

(87) PCT Pub. No.: **WO97/29131**

PCT Pub. Date: **Aug. 14, 1997**

Related U.S. Application Data

(63) Continuation-in-part of application No. 08/599,226, filed on Feb. 9, 1996, now Pat. No. 6,090,382.
(60) Provisional application No. 60/031,476, filed on Nov. 25, 1996.

(51) **Int. Cl.**[7] **C07M 21/00**; C12P 21/08
(52) **U.S. Cl.** **435/69.6**; 435/335; 435/320.1; 536/23.53
(58) **Field of Search** 435/69.6, 320.1, 435/335; 536/23.53

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WO 92/16553	10/1992	(WO) .
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Primary Examiner—David Saunders
(74) *Attorney, Agent, or Firm*—Lahive & Cockfield, LLP; Giulio A. DeConti, Jr.; Elizabeth A. Hanley

(57) **ABSTRACT**

Human antibodies, preferably recombinant human antibodies, that specifically bind to human tumor necrosis factor α(hTNFα) are disclosed. These antibodies have high affinity for hTNFα (e.g., K_d=10^{-8} M or less), a slow off rate for hTNFα dissociation (e.g., K_{off}=$10^{-3}$$sec^{-1}$ or less) and neutralize hTNFα activity in vitro and in vivo. An antibody of the invention can be a full-length antibody or an antigen-binding portion thereof. The antibodies, or antibody portions, of the invention are useful for detecting hTNFα and for inhibiting hTNFα activity, e.g., in a human subject suffering from a disorder in which hTNFα activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human antibodies of the invention, and methods of synthesizing the recombinant human antibodies, are also encompassed by the invention.

20 Claims, 11 Drawing Sheets

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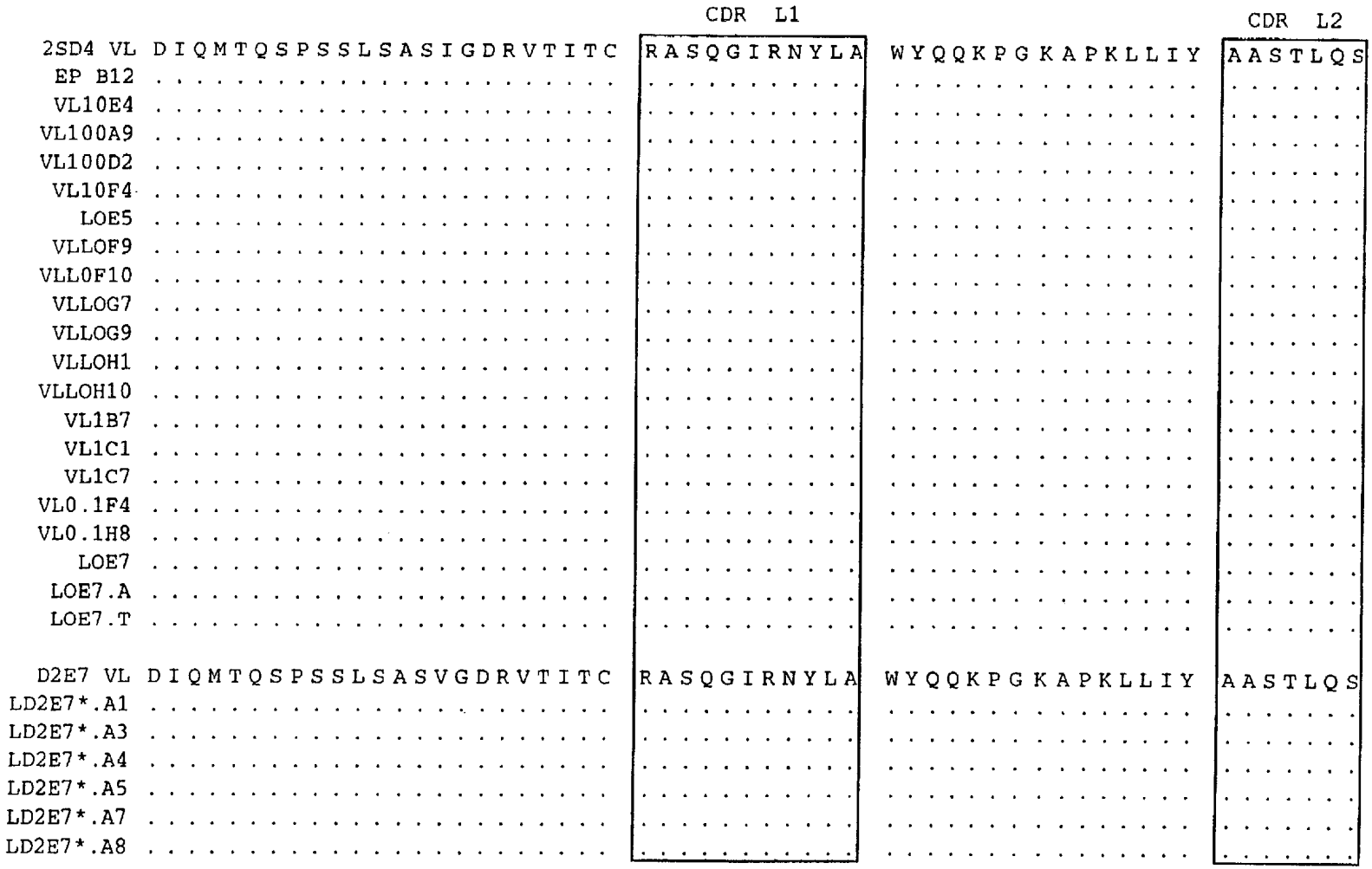

CDR L1
CDR L2
2SD4 VL DIQMTQSPSSLSASIGDRVTITC RASQGIRNYLA WYQQKPGKAPKLLIY AASTLQS
EP B12
VL10E4
VL100A9
VL100D2
VL10F4
LOE5
VLLOF9
VLL0F10
VLLOG7
VLLOG9
VLLOH1
VLLOH10
VL1B7
VL1C1
VL1C7
VL0.1F4
VL0.1H8
LOE7
LOE7.A
LOE7.T
D2E7 VL DIQMTQSPSSLSASVGDRVTITC RASQGIRNYLA WYQQKPGKAPKLLIY AASTLQS
LD2E7*.A1
LD2E7*.A3
LD2E7*.A4
LD2E7*.A5
LD2E7*.A7
LD2E7*.A8

Figure 1A

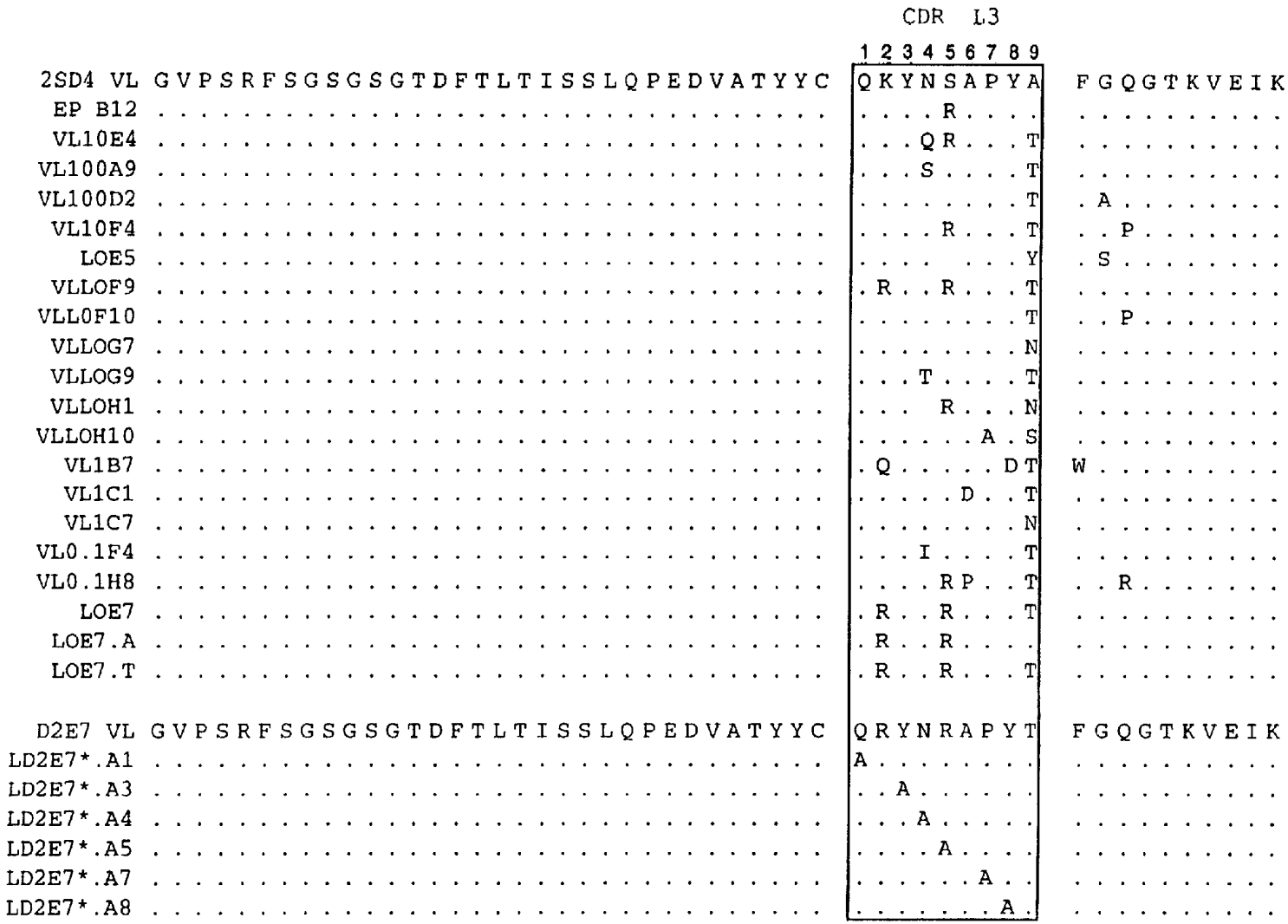

CDR L3
1 2 3 4 5 6 7 8 9
2SD4 VL GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC QKYNSAPYA FGQGTKVEIK
EP B12 R T
VL10E4 QR T
VL100A9 S T
VL100D2 T A
VL10F4 R T P
LOE5 Y S
VLLOF9 R R T
VLL0F10 T P
VLLOG7 N
VLLOG9 T T
VLLOH1 R N
VLLOH10 A S
VL1B7 Q D T W
VL1C1 D T
VL1C7 N
VL0.1F4 I T
VL0.1H8 RP T R
LOE7 R R T
LOE7.A R R
LOE7.T R R T
D2E7 VL GVPSRFSGSGSGTDFTLTISSLQPEDVATYYC QRYNRAPYT FGQGTKVEIK
LD2E7*.A1 A
LD2E7*.A3 A
LD2E7*.A4 A
LD2E7*.A5 A
LD2E7*.A7 A
LD2E7*.A8 A

Figure 1B

		CDR H1		CDR H2
2SD4 VH	QVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLDWVS	AITWNSGHIDYADSVEG
VH1B11	....	.....	....	....
VH1D8	....	.....	....	....
VH1A11	....	.....	....	....
VH1B12	....	.....	....	....
VH1-D2	....	.....	....	....
VH1E4	....	.....	....	....
VH1F6	....	.....	....	....
VH1G1	....	.....	....	....
3C-H2	....	.....	....	....
VH1-D2.N	....	.....	....	....
VH1-D2.Y	....	.....	....	....
D2E7 VH	EVQLVESGGGLVQPGRSLRLSCAASGFTFD	DYAMH	WVRQAPGKGLEWVS	AITWNSGHIDYADSVEG
HD2E7*.A1	....	.....	....	....
HD2E7*.A2	....	.....	....	....
HD2E7*.A3	....	.....	....	....
HD2E7*.A4	....	.....	....	....
HD2E7*.A5	....	.....	....	....
HD2E7*.A6	....	.....	....	....
HD2E7*.A7	....	.....	....	....
HD2E7*.A8	....	.....	....	....
HD2E7*.A9	....	.....	....	....

Figure 2A

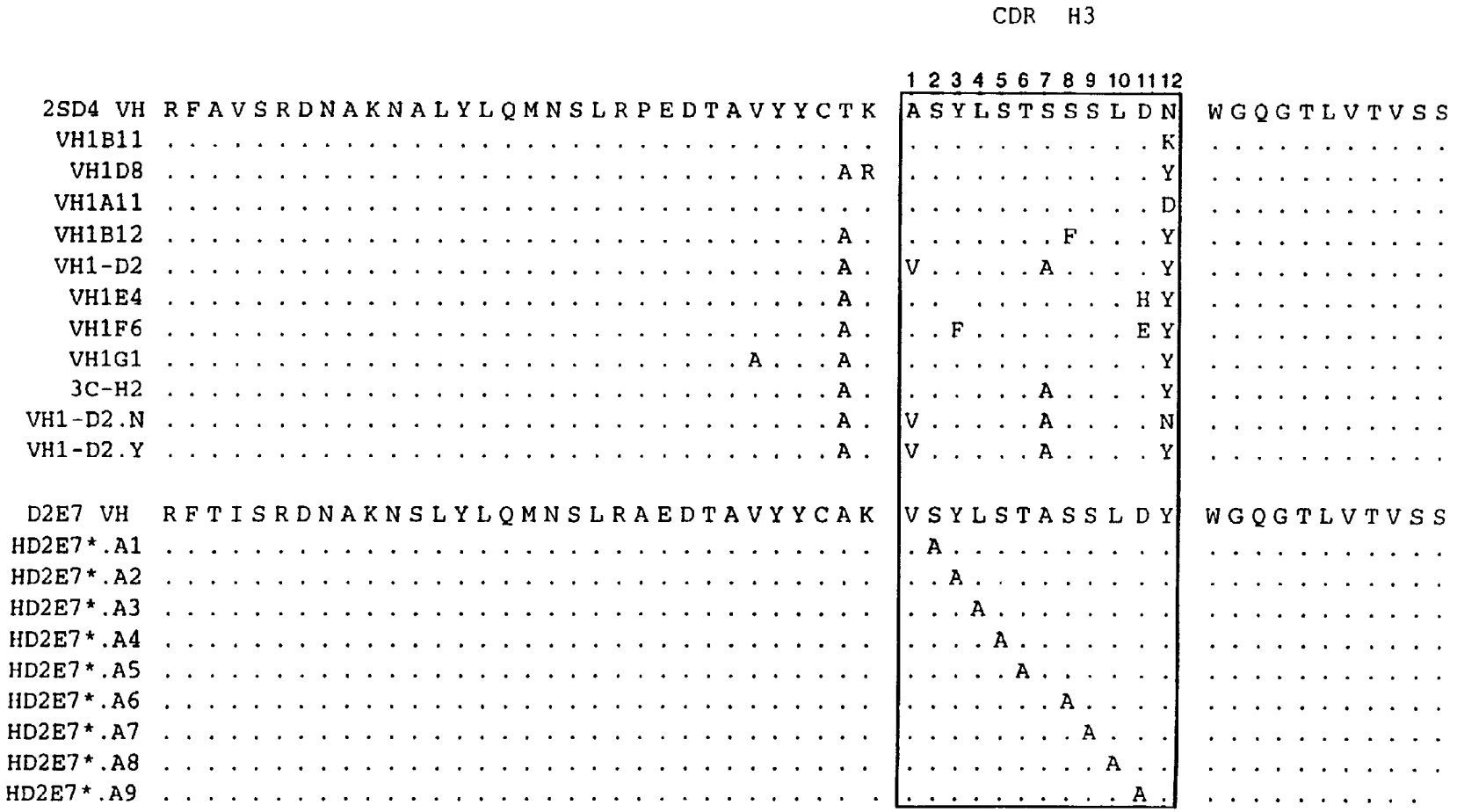

CDR H3
1 2 3 4 5 6 7 8 9 10 11 12
2SD4 VH R F A V S R D N A K N A L Y L Q M N S L R P E D T A V Y Y C T K A S Y L S T S S S L D N W G Q G T L V T V S S
VH1B11 K
VH1D8 A R Y
VH1A11 D
VH1B12 A F Y
VH1-D2 A V A Y
VH1E4 A H Y
VH1F6 A F E Y
VH1G1 A A Y
3C-H2 A A Y
VH1-D2.N A V A N
VH1-D2.Y A V A Y
D2E7 VH R F T I S R D N A K N S L Y L Q M N S L R A E D T A V Y Y C A K V S Y L S T A S S L D Y W G Q G T L V T V S S
HD2E7*.A1 A
HD2E7*.A2 A
HD2E7*.A3 A
HD2E7*.A4 A
HD2E7*.A5 A
HD2E7*.A6 A
HD2E7*.A7 A
HD2E7*.A8 A
HD2E7*.A9 A

Figure 2B

FIG. 3

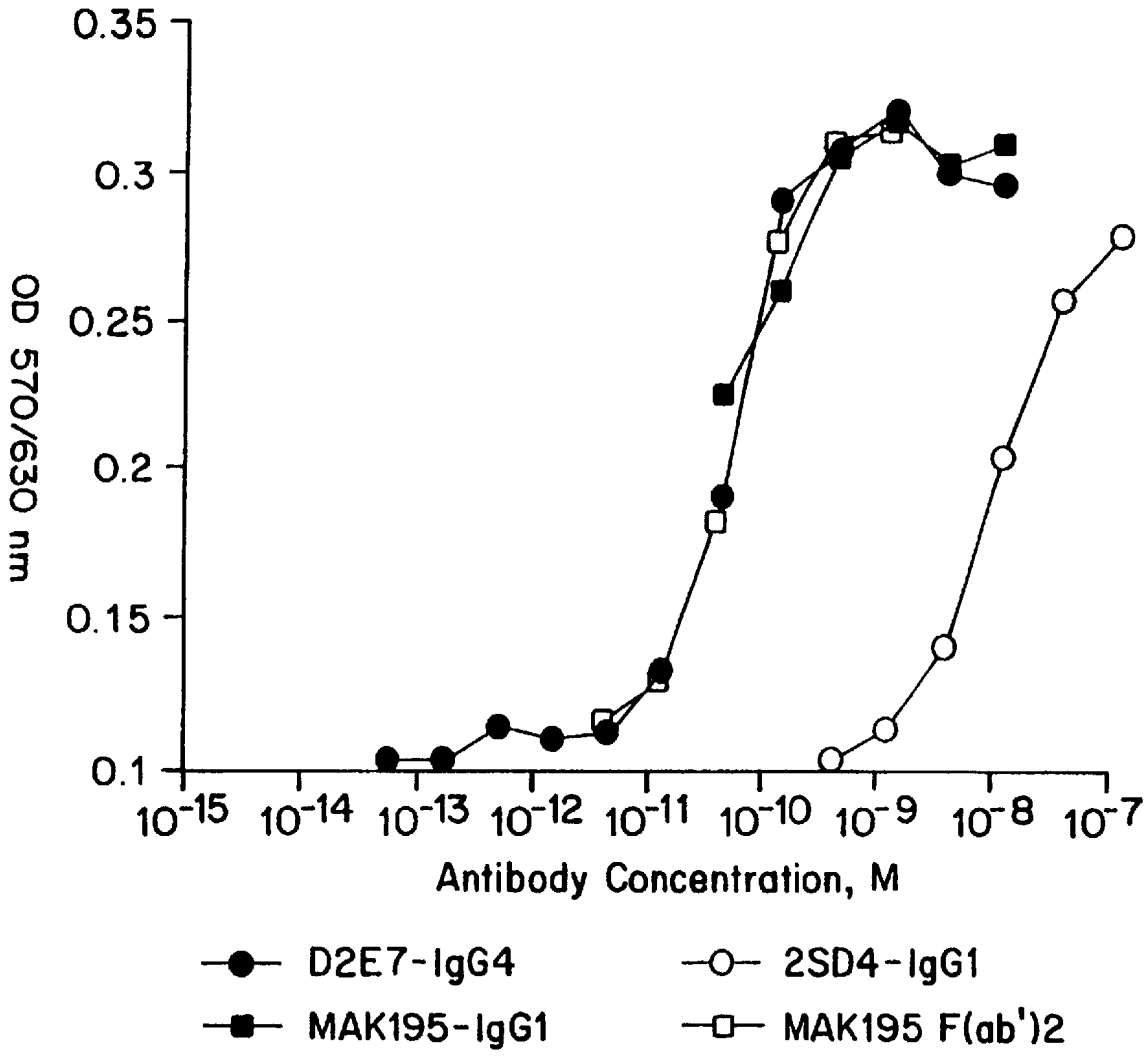

0.35
0.3
0.25
0.2
0.15
0.1
OD 570/630 nm
10^{-15} 10^{-14} 10^{-13} 10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7}
Antibody Concentration, M
D2E7-IgG4
2SD4-IgG1
MAK195-IgG1
MAK195 F(ab')2

FIG. 4

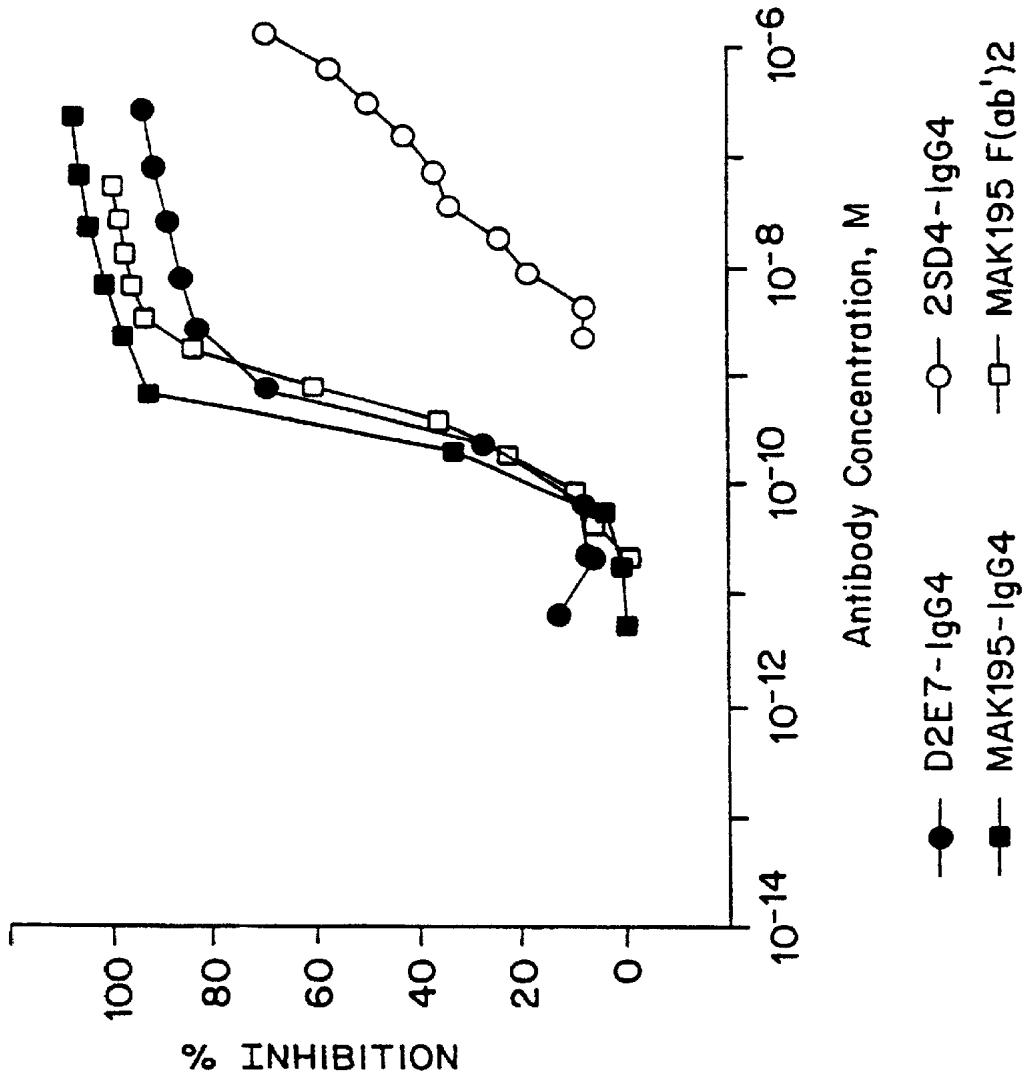

% INHIBITION
100
80
60
40
20
0
10^{-14}
10^{-12}
10^{-10}
10^{-8}
10^{-6}
Antibody Concentration, M
D2E7-IgG4
2SD4-IgG4
MAK195-IgG4
MAK195 F(ab')2

FIG. 5

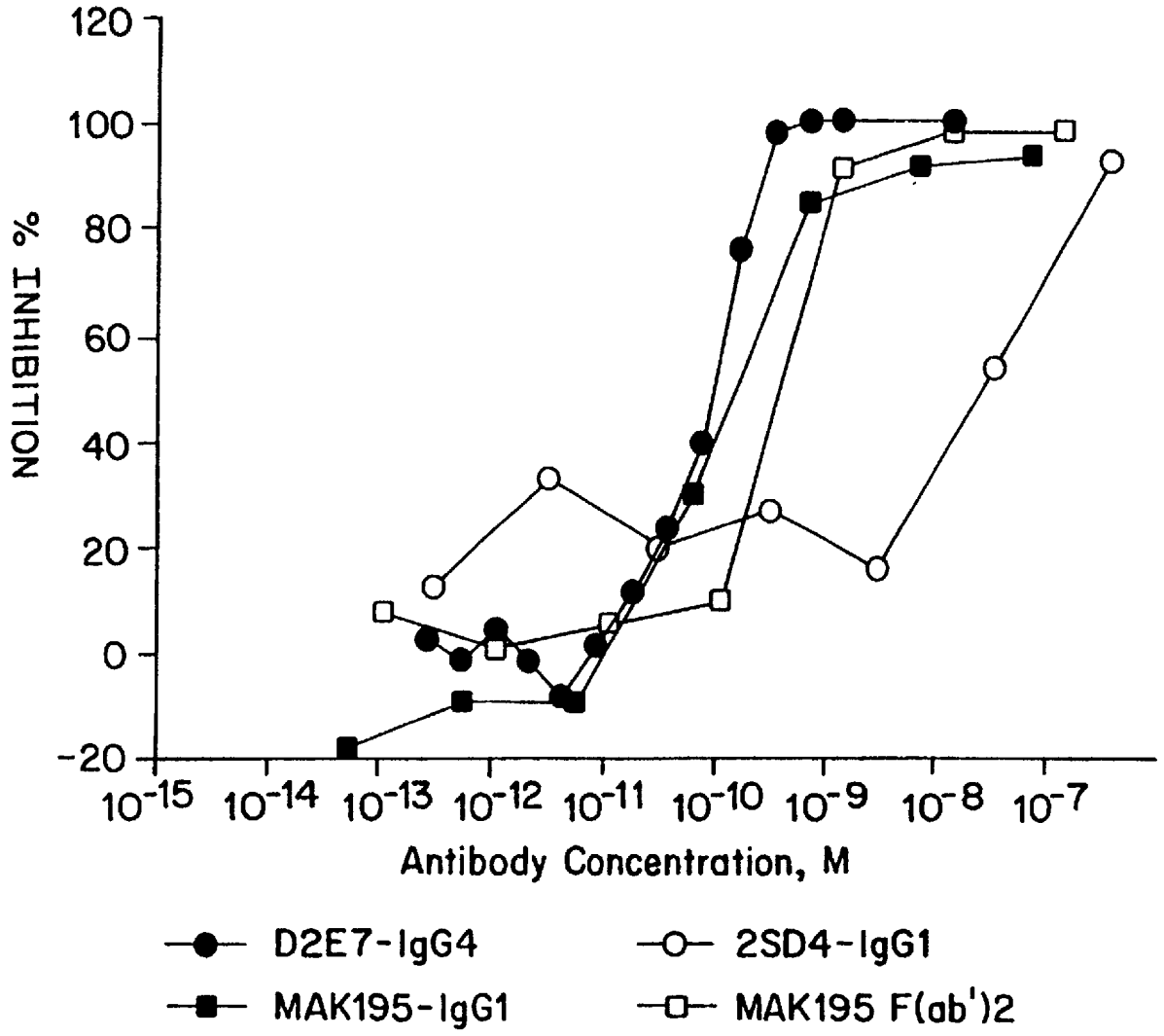
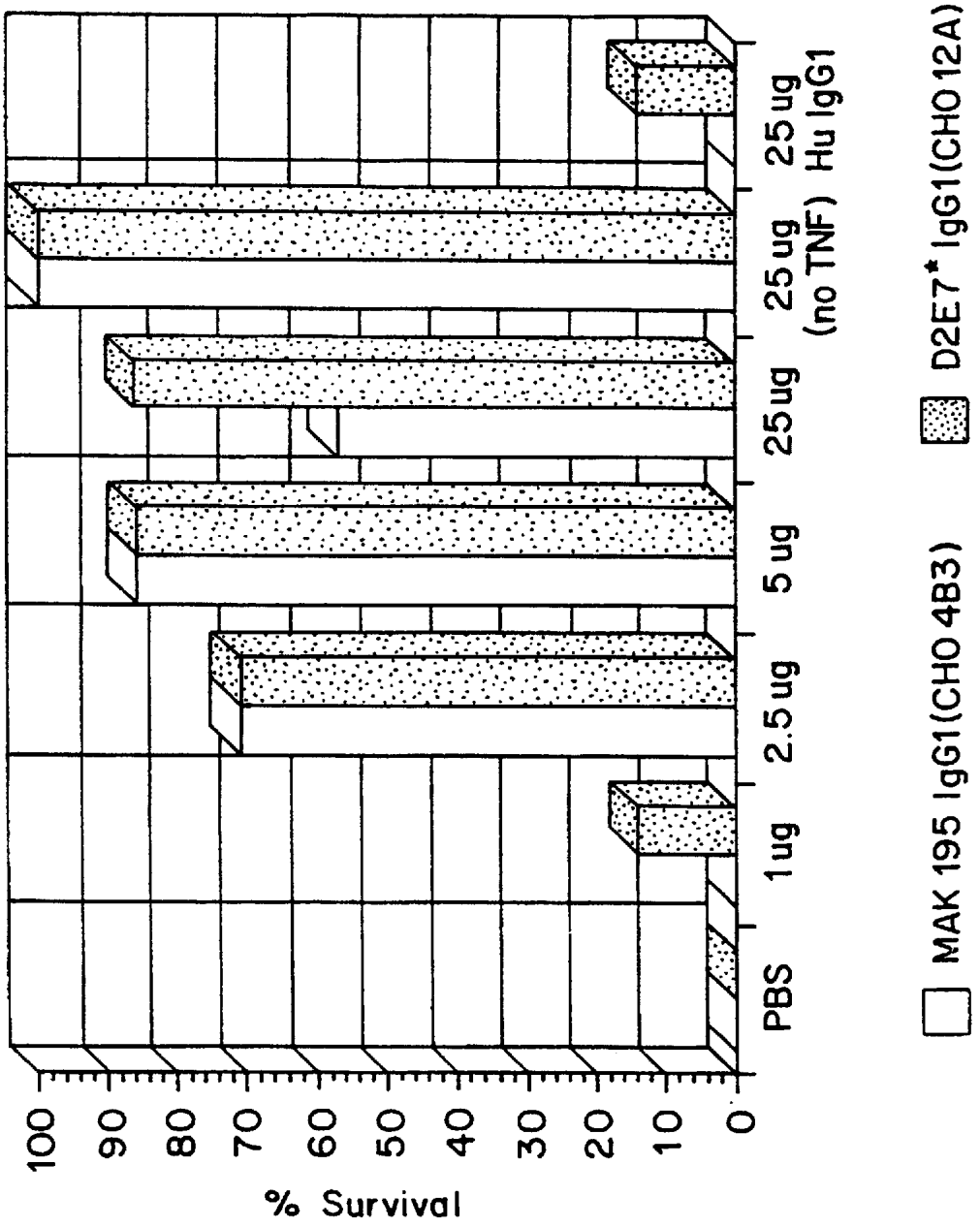

120
100
80
60
40
20
0
-20
% INHIBITION
10^{-15} 10^{-14} 10^{-13} 10^{-12} 10^{-11} 10^{-10} 10^{-9} 10^{-8} 10^{-7}
Antibody Concentration, M
D2E7-IgG4
2SD4-IgG1
MAK195-IgG1
MAK195 F(ab')2

FIG. 6


100
90
80
70
60
50
40
30
20
10
0
% Survival
PBS
1ug
2.5ug
5ug
25ug
25ug (no TNF) Hu IgG1
25ug
MAK 195 IgG1(CHO 4B3)
D2E7* IgG1(CHO 12A)

D2E7 VL

```
GAC ATC CAG ATG ACC CAG TCT CCA TCC TCC CTG TCT GCA TCT GTA
 D   I   Q   M   T   Q   S   P   S   S   L   S   A   S   V

                                                CDR L1
GGG GAC AGA GTC ACC ATC ACT TGT CGG GCA AGT CAG GGC ATC AGA
 G   D   R   V   T   I   T   C   R   A   S   Q   G   I   R

AAT TAC TTA GCC TGG TAT CAG CAA AAA CCA GGG AAA GCC CCT AAG
 N   Y   L   A   W   Y   Q   Q   K   P   G   K   A   P   K

                                CDR L2
CTC CTG ATC TAT GCT GCA TCC ACT TTG CAA TCA GGG GTC CCA TCT
 L   L   I   Y   A   A   S   T   L   Q   S   G   V   P   S

CGG TTC AGT GGC AGT GGA TCT GGG ACA GAT TTC ACT CTC ACC ATC
 R   F   S   G   S   G   S   G   T   D   F   T   L   T   I

AGC AGC CTA CAG CCT GAA GAT GTT GCA ACT TAT TAC TGT CAA AGG
 S   S   L   Q   P   E   D   V   A   T   Y   Y   C   Q   R

  CDR L3
TAT AAC CGT GCA CCG TAT ACT TTT GGC CAG GGG ACC AAG GTG GAA
 Y   N   R   A   P   Y   T   F   G   Q   G   T   K   V   E

ATC AAA
 I   K
```

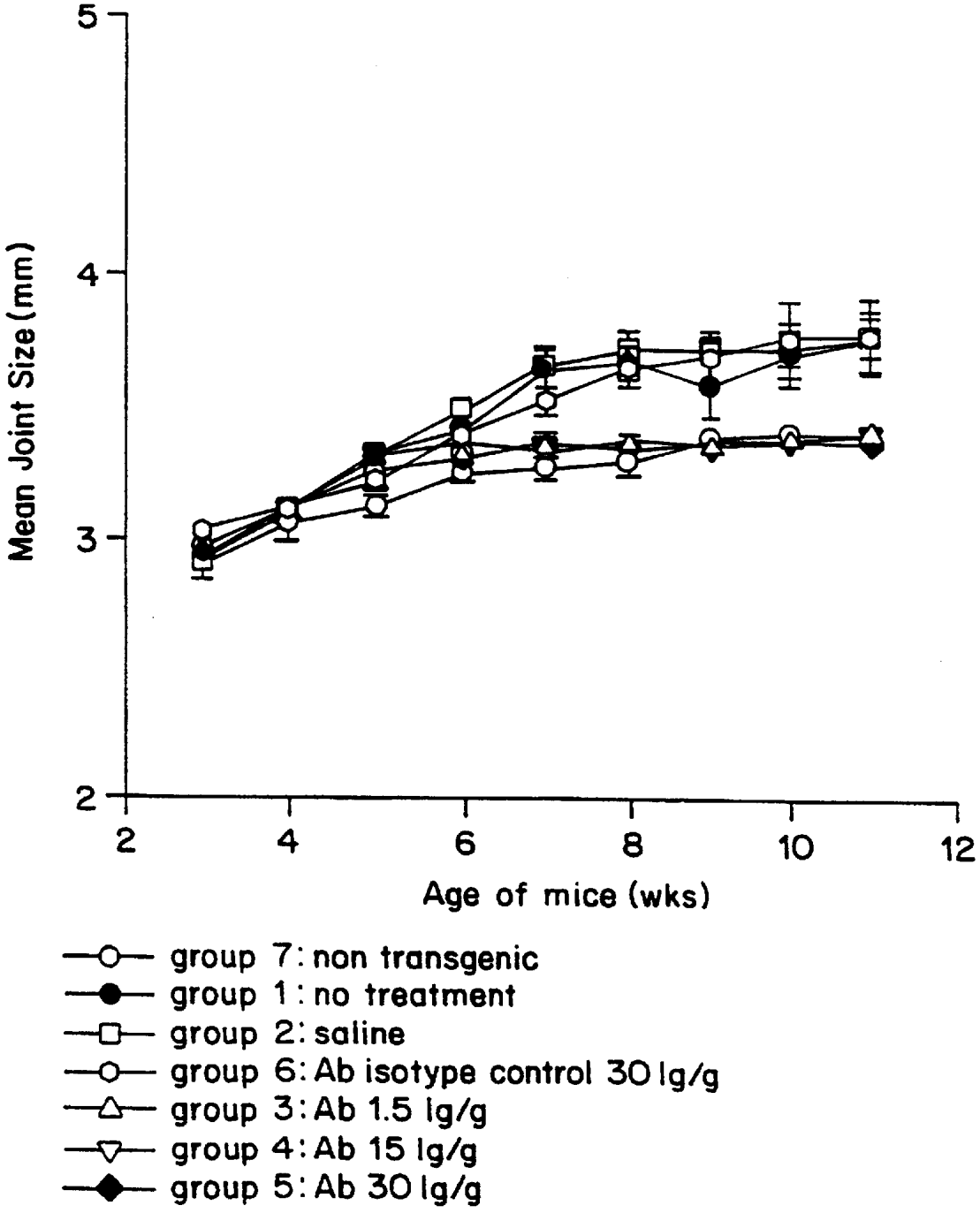
FIGURE 7

D2E7 VH

```
GAG GTG CAG CTG GTG GAG TCT GGG GGA GGC TTG GTA CAG CCC GGC
 E   V   Q   L   V   E   S   G   G   G   L   V   Q   P   G

AGG TCC CTG AGA CTC TCC TGT GCG GCC TCT GGA TTC ACC TTT GAT
 R   S   L   R   L   S   C   A   A   S   G   F   T   F   D

       CDR H1
GAT TAT GCC ATG CAC TGG GTC CGG CAA GCT CCA GGG AAG GGC CTG
 D   Y   A   M   H   W   V   R   Q   A   P   G   K   G   L

                                   CDR H2
GAA TGG GTC TCA GCT ATC ACT TGG AAT AGT GGT CAC ATA GAC TAT
 E   W   V   S   A   I   T   W   N   S   G   H   I   D   Y

GCG GAC TCT GTG GAG GGC CGA TTC ACC ATC TCC AGA GAC AAC GCC
 A   D   S   V   E   G   R   F   T   I   S   R   D   N   A

AAG AAC TCC CTG TAT CTG CAA ATG AAC AGT CTG AGA GCT GAG GAT
 K   N   S   L   Y   L   Q   M   N   S   L   R   A   E   D

                                           CDR H3
ACG GCC GTA TAT TAC TGT GCG AAA GTC TCG TAC CTT AGC ACC GCG
 T   A   V   Y   Y   C   A   K   V   S   Y   L   S   T   A

TCC TCC CTT GAC TAT TGG GGC CAA GGT ACC CTG GTC ACC GTC TCG
 S   S   L   D   Y   W   G   Q   G   T   L   V   T   V   S

AGT
 S
```

FIGURE 8

FIG. 9


Mean Joint Size (mm)
5
4
3
2
2
4
6
8
10
12
Age of mice (wks)
group 7: non transgenic
group 1: no treatment
group 2: saline
group 6: Ab isotype control 30 lg/g
group 3: Ab 1.5 lg/g
group 4: Ab 15 lg/g
group 5: Ab 30 lg/g

HUMAN ANTIBODIES THAT BIND HUMAN TNFα

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a 371 of International Application PCT/US97/02219, which is a CIP of Provisional U.S. application Ser. No. 60/031,476, filed Nov. 25, 1996, which is a CIP of U.S. application Ser. No. 08/599,226, filed Feb. 9, 1996 and now U.S. Pat. No. 6,090,382.

BACKGROUND OF THE INVENTION

Tumor necrosis factor α (TNFα) is a cytokine produced by numerous cell types, including monocytes and macrophages, that was originally identified based on its capacity to induce the necrosis of certain mouse tumors (see e.g., Old, L. (1985) *Science* 230:630–632). Subsequently, a factor termed cachectin, associated with cachexia, was shown to be the same molecule as TNFα. TNFα has been implicated in mediating shock (see e.g., Beutler, B. and Cerami, A. (1988) *Annu. Rev. Biochem.* 57:505–518; Beutler, B. and Cerami, A. (1989) *Annu. Rev. Immunol.* 7:625–655). Furthermore, TNFα has been implicated in the pathophysiology of a variety of other human diseases and disorders, including sepsis, infections, autoimmune diseases, transplant rejection and graft-versus-host disease (see e.g., Moeller, A., et al. (1990) *Cytokine* 2:162–169; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A., et al. Vasilli, P. (1992) *Annu. Rev. Immunol.* 10:411–452; Tracey, K. J. and Cerami, A. (1994) *Annu. Rev. Med.* 45:491–503).

Because of the harmful role of human TNFα (hTNFα) in a variety of human disorders, therapeutic strategies have been designed to inhibit or counteract hTNFα activity. In particular, antibodies that bind to, and neutralize, hTNFα have been sought as a means to inhibit hTNFα activity. Some of the earliest of such antibodies were mouse monoclonal antibodies (mAbs), secreted by hybridomas prepared from lymphocytes of mice immunized with hTNFα (see e.g., Hahn T; et al., (1985) *Proc Natl Acad Sci USA* 82: 3814–3818; Liang, C-M., et al. (1986) *Biochem. Biophys. Res. Commun.* 137:847–854; Hirai, M., et al. (1987) *J Immunol. Methods* 96:57–62; Fendly, B. M., et al. (1987) *Hybridoma* 6:359–370; Moeller, A.. et al. (1990) *Cytokine* 2:162–169; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 186 833 B1 by Wallach, D.; European Patent Application Publication No. 218 868 A1 by Old et al.; European Patent Publication No. 260 610 B1 by Moeller, A., et al.). While these mouse anti-hTNFα antibodies often displayed high affinity for hTNFα (e.g., Kd≦10^{-9}M) and were able to neutralize hTNFα activity, their use in vivo may be limited by problems associated with administration of mouse antibodies to humans, such as short a serum half life, an inability to trigger certain human effector functions and elicitation of an unwanted immune response against the mouse antibody in a human (the "human anti-mouse antibody" (HAMA) reaction).

In an attempt to overcome the problems associated with use of fully-murine antibodies in humans, murine anti-hTNFα antibodies have been genetically engineered to be more "human-like." For example, chimeric antibodies, in which the variable regions of the antibody chains are murine-derived and the constant regions of the antibody chains are human-derived, have been prepared (Knight, D. M, et a. (1993) *Mol. Immunol.* 30:1443–1453; PCT Publication No. WO 92/16553 by Daddona, P. E., et al.). Additionally, humanized antibodies, in which the hypervariable domains of the antibody variable regions are murine-derived but the remainder of the variable regions and the antibody constant regions are human-derived, have also been prepared (PCT Publication No. WO 92/11383 by Adair, J. R., et al.). However, because these chimeric and humanized antibodies still retain some murine sequences, they still may elicit an unwanted immune reaction, the human anti-chimeric antibody (HACA) reaction, especially when administered for prolonged periods, e.g., for chronic indications, such as rheumatoid arthritis (see e.g., Elliott, M. J., et al. (1994) *Lancet* 344:1125–1127; Elliot, M. J., et al., (1994) *Lancet* 344:1105–1110).

A preferred hTNFα inhibitory agent to murine mAbs or derivatives thereof (e.g., chimeric or humanized antibodies) would be an entirely human anti-hTNFα antibody, since such an agent should not elicit the HAMA reaction, even if used for prolonged periods. Human monoclonal autoantibodies against hTNFα have been prepared using human hybridoma techniques (Boyle, P., et al. (1993) *Cell. Immunol.* 152:556–568; Boyle, P., et al. (1993) *Cell. Immunol.* 152:569–581; European Patent Application Publication No. 614 984 A2 by Boyle, et al.). However, these hybridoma-derived monoclonal autoantibodies were reported to have an affinity for hTNFα that was too low to calculate by conventional methods, were unable to bind soluble hTNFα and were unable to neutralize hTNFα-induced cytotoxicity (see Boyle, et al.; supra). Moreover, the success of the human hybridoma technique depends upon the natural presence in human peripheral blood of lymphocytes producing autoantibodies specific for hTNFα. Certain studies have detected serum autoantibodies against hTNFα in human subjects (Fomsgaard, A., et al. (1989) *Scand. J Immunol.* 30:219–223; Bendtzen, K., et al. (1990) *Prog. Leukocyte Biol* 10B:447–452), whereas others have not (Leusch, H-G., et al. (1991) *J. Immunol. Methods* 139:145–147).

Alternative to naturally-occurring human anti-hTNFα antibodies would be a recombinant hTNFα antibody. Recombinant human antibodies that bind hTNFα with relatively low affinity (i.e., K_d~10^{-7}M) and a fast off rate (i.e., K_{off}~10^{-2} sec^{-1}) have been described (Griffiths, A. D., et al. (1993) *EMBO J.* 12:725–734). However, because of their relatively fast dissociation kinetics, these antibodies may not be suitable for therapeutic use. Additionally, a recombinant human anti-hTNFα has been described that does not neutralize hTNFα activity, but rather enhances binding of hTNFα to the surface of cells and enhances internalization of hTNFα (Lidbury, A., et a. (1994) *Biotechnol. Ther.* 5:27–45; PCT Publication No. WO 92103145 by Aston, R. et al)

Accordingly, human antibodies, such as recombinant human antibodies, that bind soluble hTNFα with high affinity and slow dissociation kinetics and that have the capacity to neutralize hTNFα activity, including hTNFα-induced cytotoxicity (in vitro and in vivo) and hTNFα-induced cell activation, are still needed.

SUMMARY OF THE INVENTION

This invention provides human antibodies, preferably recombinant human antibodies, that specifically bind to human TNFα. The antibodies of the invention are characterized by binding to hTNFα with high affinity and slow dissociation kinetics and by neutralizing hTNFα activity, including hTNFα-induced cytotoxicity (in vitro and in vivo) and hTNFα-induced cellular activation. Antibodies of the invention are further characterized by binding to hTNFα but not hTNFβ (lymphotoxin) and by having the ability to bind

to other primate TNFαs and non-primate TNFαs in addition to human TNFα.

The antibodies of the invention can be fill-length (e.g., an IgG1 or IgG4 antibody) or can comprise only an antigen-binding portion (e.g., a Fab, $F(ab')_2$ or scFv fragment). The most preferred recombinant antibody of the invention, termed D2E7, has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3 and a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4. Preferably, the D2E7 antibody has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} s^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-7} M or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5×10^{-4} s^{-1} or less, or even more preferably, with a K_{off} of 1×10^{-4} s^{-1} or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-8} M or less, even more preferably with an IC_{50} of 1×10^{-9} M or less and still more preferably with an IC_{50} of 5×10^{-10} M or less.

In another embodiment, the invention provides a human antibody, or antigen-binding portion thereof, with the following characteristics:

a) dissociates from human TNFα with a K_{off} of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5×10^{-4} s^{-1} or less. Still more preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 1×10^{-4} s^{-1} or less.

In yet another embodiment, the invention provides a human antibody, or an antigen-binding portion thereof, with an LCVR having CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and with an HCVR having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. More preferably, the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5 and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6. Still more preferably, the LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7 and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8.

In still another embodiment, the invention provides an isolated human antibody, or an antigen binding portion thereof, with an LCVR comprising the amino acid sequence of SEQ ID NO: 1 and an HCVR comprising the amino acid sequence of SEQ ID NO: 2. In certain embodiments, the antibody has an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. In yet other embodiments, the antibody is a Fab fragment, an $F(ab')_2$ fragment or a single chain Fv fragment.

In still other embodiments, the invention provides antibodies, or antigen-binding portions thereof, with an LCVR having CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14. SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26 or with an HCVR having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35.

In yet another embodiment, the invention provides an isolated human antibody, or antigen-binding portion thereof, that neutralizes the activity of human TNFα but not human TNFβ (lymphotoxin). In a preferred embodiment, the human antibody, or antigen-binding portion thereof, neutralizes the activity of human TNFα, chimpanzee TNFα and at least one additional primate TNFα selected from the group consisting of baboon TNFα, marmoset TNFα, cynomolgus TNFα and rhesus TNFα. Preferably, the antibody also neutralizes the activity of at least one non-primate TNFα. For example, in one subembodiment, the isolated human antibody, or antigen-binding portion thereof, also neutralizes the activity of canine TNFα. In another subembodiment, the isolated human antibody, or antigen-binding portion thereof, also neutralizes the activity of pig TNFα. In yet another subembodiment, the isolated human antibody, or antigen-binding portion thereof, also neutralizes the activity of mouse TNFα.

Another aspect of the invention pertains to nucleic acid molecules encoding the antibodies, or antigen-binding portions, of the invention. A preferred nucleic acid of the invention, encoding a D2E7 LCVR, has the nucleotide sequence shown in FIG. **7** and SEQ ID NO 36. Another preferred nucleic acid of the invention, encoding a D2E7 HCVR, has the nucleotide sequence shown in FIG. **8** and SEQ ID NO 37. Recombinant expression vectors carrying the antibody-encoding nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of making the antibodies of the invention by culturing the host cells of the invention.

Yet another aspect of the invention pertains to methods for inhibiting human TNFα activity using an antibody, or antigen-binding portion thereof, of the invention. In one embodiment, the method comprises contacting human TNFα with the antibody of the invention, or antigen-binding portion thereof, such that human TNFα activity is inhibited. In another embodiment, the method comprises administering an antibody of the invention, or antigen-binding portion thereof, to a human subject suffering from a disorder in which TNFα activity is detrimental such that human TNFα activity in the human subject is inhibited. The disorder can be, for example, sepsis, an autoimmune disease (e.g., rheumatoid arthritis, allergy, multiple sclerosis, autoimmune

diabetes, autoimmune uveitis and nephrotic syndrome), an infectious disease, a malignancy, transplant rejection or graft-versus-host disease, a pulmonary disorder, a bone disorder, an intestinal disorder or a cardiac disorder.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGS. **1**A and **1**B show the amino acid sequences of the light chain variable region of D2E7 (D2E7 VL; also shown in SEQ ID NO: 1), alanine-scan mutants of D2E7 VL (LD2E7*.AI, LD2E7*.A3, LD2E7*.A4, LD2E7*.A5, LD2E7*.A7 and LD2E7*.A8), the light chain variable region of the D2E7-related antibody 2SD4 (2SD4 VL; also shown in SEQ ID NO: 9) and other D2E7-related light chain variable regions (EP B12, VLIOE4, VL10OA9, VLIOOD2, VLIOF4, LOE5, VLLOF9, VLLOF10, VLLOG7, VLLOG9, VLLOH1, VLLOH10, VLIB7, VLlCl, VLlC7, VL0.1F4, VL0.1H8, LOE7, LOE7.A and LOE7.T). FIG. **1**A shows the FR1, CDR1, FR2 and CDR2 domains. FIG. **1**B shows the FR3, CDR3 and FR4 domains. The light chain CDR1 ("CDR L1"), CDR2 ("CDR L2") and CDR3 ("CDR L3") domains are boxed.

FIGS. **2**A and **2**B show the amino acid sequences of the heavy chain variable region of D2E7 (D2E7 VH; also shown in SEQ ID NO: 2), alanine-scan mutants of D2E7 VH (HD2E7*.A1, HD2E7*.A2, HD2E7*.A3, HD2E7*.A4, HD2E7*.A5, HD2E7*.A6, HD2E7*.A7, HD2E7*A8 and HD2E7*.A9), the heavy chain variable region of the D2E7-related antibody 2SD4 (2SD4 VH; also shown in SEQ ID NO: 10) and other D2E7-related heavy chain variable regions (VH1B11, VHID8, VH1A11, VH1B12, VH1-D2, VH1E4, VH1F6, VH1G1, 3C-H2, VH1-D2.N and VH1-D2.Y). FIG. **2**A shows the FR1, CDR1, FR2 and CDR2 domains. FIG. **2**B shows the FR3, CDR3 and FR4 domains. The heavy chain CDR1 ("CDR HI"), CDR2 ("CDR H2") and CDR3 ("CDR H3") domains are boxed.

FIG. **3** is a graph depicting the inhibition of TNFα-induced L929 cytotoxicity by the human anti-hTNFα antibody D2E7, as compared to the murine anti-hTNFα antibody MAK 195.

FIG. **4** is a graph depicting the inhibition of rhTNFα binding to hTNFα receptors on U-937 cells by the human anti-hTNFα antibody D2E7, as compared to the murine anti-hTNFα antibody MAK 195.

FIG. **5** is a graph depicting the inhibition of TNFα-induced ELAM-1 expression on HUVEC by the human anti-hTNFα antibody D2E7, as compared to the murine anti-hTNFα antibody MAK 195.

FIG. **6** is a bar graph depicting protection from TNFα-induced lethality in D-galactosamine-sensitized mice by administration of the human anti-hTNFα antibody D2E7 (black bars), as compared to the murine anti-hTNFα antibody MAK 195 (hatched bars).

FIG. **7** shows the nucleotide sequence of the light chain variable region of D2E7, with the predicted amino acid sequence below the nucleotide sequence. The CDR L1, CDR L2 and CDR L3 regions are underlined.

FIG. **8** shows the nucleotide sequence of the heavy chain variable region of D2E7, with the predicted amino acid sequence below the nucleotide sequence. The CDR H1, CDR H2 and CDR H3 regions are underlined.

FIG. **9** is a graph depicting the effect of D2E7 antibody treatment on the mean joint size of Tg197 transgenic mice as a polyarthritis model.

DETAILED DESCRIPTION OF THE INVENTION

This invention pertains to isolated human antibodies, or antigen-binding portions thereof, that bind to human TNFα with high affinity, a low off rate and high neutralizing capacity. Various aspects of the invention relate to antibodies and antibody fragments, and pharmaceutical compositions thereof, as well as nucleic acids, recombinant expression vectors and host cells for making such antibodies and fragments. Methods of using the antibodies of the invention to detect human TNFα or to inhibit human TNFα activity, either in vitro or in vivo, are also encompassed by the invention.

In order that the present invention may be more readily understood, certain terms are first defined.

The term "human TNFα" (abbreviated herein as hTNFα, or simply hTNF), as used herein, is intended to refer to a human cytokine that exists as a 17 kD secreted form and a 26 kD membrane associated form, the biologically active form of which is composed of a trimer of noncovalently bound 17 kD molecules. The structure of hTNFα is described further in, for example, Pennica, D., et al. (1984) *Nature* 312:724–729; Davis, J. M., et al. (1987) *Biochemistry* 26:1322–1326; and Jones, E. Y., et al. (1989) *Nature* 338:225–228. The term human TNFα is intended to include recombinant human TNFα (rhTNFα), which can be prepared by standard recombinant expression methods or purchased commercially (R & D Systems, Catalog No. 210-TA, Minneapolis, Minn.).

The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds. Each heavy chain is comprised of a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region is comprised of three domains. CH1, CH2 and CH3. Each light chain is comprised of a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region is comprised of one domain, CL. The VH and VL regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs. arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR1, CDR2, FR3, CDR3, FR4.

The term "antigen-binding portion" of an antibody (or simply "antibody portion"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to an antigen (e.g., hTNFα). It has been shown that the antigen-binding function of an antibody can be performed by fragments of a full-length antibody. Examples of binding fragments encompassed within the term "antigen-binding portion" of an antibody include (i) a Fab fragment, a monovalent fragment consisting of the VL, VH, CL and CH1 domains; (ii) a $F(ab')_2$ fragment, a bivalent fragment comprising two Fab fragments linked by a disulfide bridge at the hinge region; (iii) a Fd fragment consisting of the VH and CH1 domains; (iv) a Fv fragment consisting of the VL and VH domains of a single arm of an antibody, (v) a dAb fragment (Ward et al., (1989) *Nature* 341:544–546), which consists of a VH domain; and (vi) an isolated complementarity determining region (CDR). Furthermore, although the two domains of the Fv fragment, VL and VH, are coded for by separate genes, they can be joined. using recombinant methods, by a synthetic linker that enables them to be made as a single protein chain in which the VL and VH regions pair to form monovalent molecules (known as single chain Fv (scFv); see e.g., Bird et al. (1988) *Science* 242:423–426; and Huston et al. (1988)

Proc. Natl. Acad. Sci. USA 85:5879–5883). Such single chain antibodies are also intended to be encompassed within the term "antigen-binding portion" of an antibody. Other forms of single chain antibodies, such as diabodies are also encompassed. Diabodies are bivalent, bispecific antibodies in which VH and VL domains are expressed on a single polypeptide chain, but using a linker that is too short to allow for pairing between the two domains on the same chain, thereby forcing the domains to pair with complementary domains of another chain and creating two antigen binding sites (see e.g., Holliger, P., et al. (1993) *Proc. Natl. Acad Sci. USA* 90:6444–6448; Poljak, R. J., et al. (1994) *Structure* 2:1121–1123).

Still further, an antibody or antigen-binding portion thereof may be part of a larger immunoadhesion molecules, formed by covalent or noncovalent association of the antibody or antibody portion with one or more other proteins or peptides. Examples of such immunoadhesion molecules include use of the streptavidin core region to make a tetrameric scFv molecule (Kipriyanov, S. M., et al. (1995) *Human Antibodies and Hybridomas* 6:93–101) and use of a cysteine residue, a marker peptide and a C-terminal polyhistidine tag to make bivalent and biotinylated scFv molecules (Kipriyanov, S. M., et al. (1994) *Mol. Immunol.* 31:1047–1058). Antibody portions, such as Fab and $F(ab')_2$ fragments, can be prepared from whole antibodies using conventional techniques, such as papain or pepsin digestion, respectively, of whole antibodies. Moreover, antibodies, antibody portions and immunoadhesion molecules can be obtained using standard recombinant DNA techniques, as described herein.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human antibodies of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include antibodies in which CDR sequences derived from the germline of another mammalian species, such as a mouse, have been grafted onto human framework sequences.

The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further in Section II. below), antibodies isolated from a recombinant, combinatorial human antibody library (described further in Section III, below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor, L. D.. et al. (1992) *Nucl. Acids Res.* 20:6287–6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the VH and VL regions of the recombinant antibodies are sequences that, while derived from and related to human germline VH and VL sequences, may not naturally exist within the human antibody germline repertoire in vivo.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds hTNFα is substantially free of antibodies that specifically bind antigens other than hTNFα). An isolated antibody that specifically binds hTNFα may, however, have cross-reactivity to other antigens, such as TNFα molecules from other species (discussed in further detail below). Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

A "neutralizing antibody", as used herein (or an "antibody that neutralized hTNFα activity"), is intended to refer to an antibody whose binding to hTNFα results in inhibition of the biological activity of hTNFα. This inhibition of the biological activity of hTNFα can be assessed by measuring one or more indicators of hTNFα biological activity, such as hTNFα-induced cytotoxicity (either in vitro or in vivo), hTNFα-induced cellular activation and hTNFα binding to hTNFα receptors. These indicators of hTNFα biological activity can be assessed by one or more of several standard in vitro or in vivo assays known in the art (see Example 4). Preferably, the ability of an antibody to neutralize hTNFα activity is assessed by inhibition of hTNFα-induced cytotoxicity of L929 cells. As an additional or alternative parameter of hTNFα activity, the ability of an antibody to inhibit hTNFα-induced expression of ELAM-1 on HUVEC, as a measure of hTNFα-induced cellular activation, can be assessed.

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biospecific interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIAcore system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.). For further descriptions, see Example 1 and Jönsson, U., et al. (1993) *Ann. Biol. Clin.* 51:19–26; Jönsson, U., et al. (1991) *Biotechniques* 11:620–627; Johnsson, B., et al. (1995) *J. Mol. Recognit.* 8:125–131; and Johnnson, B., et al. (1991) *Anal. Biochem.* 198:268–277.

The term "K_{off}", as used herein, is intended to refer to the off rate constant for dissociation of an antibody from the antibody/antigen complex.

The term "K_d", as used herein, is intended to refer to the dissociation constant of a particular antibody-antigen interaction.

The term "nucleic acid molecule", as used herein, is intended to include DNA molecules and RNA molecules. A nucleic acid molecule may be single-stranded or double-stranded, but preferably is double-stranded DNA.

The term "isolated nucleic acid molecule", as used herein in reference to nucleic acids encoding antibodies or antibody portions (e.g., VH, VL, CDR3) that bind hTNFα, is intended to refer to a nucleic acid molecule in which the nucleotide sequences encoding the antibody or antibody portion are free of other nucleotide sequences encoding antibodies or antibody portions that bind antigens other than hTNFα, which other sequences may naturally flank the nucleic acid in human genomic DNA. Thus, for example, an isolated nucleic acid of the invention encoding a VH region of an anti-TNFα antibody contains no other sequences encoding other VH regions that bind antigens other than TNFα.

The term "vector", as used herein, is intended to refer to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded

DNA loop into which additional DNA segments may be ligated. Another type of vector is a viral vector, wherein additional DNA segments may be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (e.g., bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (e.g., non-episomal mammalian vectors) can be integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors are capable of directing the expression of genes to which they are operatively linked. Such vectors are referred to herein as "recombinant expression vectors" (or simply, "expression vectors"). In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. In the present specification, "plasmid" and "vector" may be used interchangeably as the plasmid is the most commonly used form of vector. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (e.g., replication defective retroviruses, adenoviruses and adeno-associated viruses), which serve equivalent functions.

The term "recombinant host cell" (or simply "host cell"), as used herein, is intended to refer to a cell into which a recombinant expression vector has been introduced. It should be understood that such terms are intended to refer not only to the particular subject cell but to the progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term "host cell" as used herein.

Various aspects of the invention are described in further detail in the following subsections.

I. Human Antibodies that Bind Human TNFα

This invention provides isolated human antibodies, or antigen-binding portions thereof, that bind to human TNFα with high affinity, a low off rate and high neutralizing capacity. Preferably, the human antibodies of the invention are recombinant, neutralizing human anti-hTNFα antibodies. The most preferred recombinant, neutralizing antibody of the invention is referred to herein as D2E7 and has VL and VH sequences as shown in FIG. **1**A, **1**B and FIG. **2**A, **2**B, respectively (the amino acid sequence of the D2E7 VL region is also shown in SEQ ID NO: 1; the amino acid sequence of the D2E7 VH region is also shown in SEQ ID NO: 2). The binding properties of D2E7, as compared to the murine anti-hTNFα MAK 195 mAb that exhibits high affinity and slow dissociation kinetics and another human anti-hTNhFα antibody related in sequence to D2E7, 2SD4, are summarized below:

Antibody	K_{off} sec^{-1}	k_{on} M^{-1} sec^{-1}	K_d M	Stoichiometry
D2E7 IgG1	8.81×10^{-5}	1.91×10^{5}	6.09×10^{-10}	1.2
2SD4 IgG4	8.4×10^{-3}	4.20×10^{5}	2.00×10^{-8}	0.8
MAK 195 $F(ab')_2$	8.70×10^{-5}	1.90×10^{5}	4.60×10^{-10}	1.4

The D2E7 antibody, and related antibodies, also exhibit a strong capacity to neutralize hTNFα activity, as assessed by several in vitro and in vivo assays (see Example 4). For example, these antibodies neutralize hTNFα-induced cytotoxicity of L929 cells with IC_{50} values in the range of about 10^{-7} M to about 10^{-10} M. D2E7, when expressed as a full-length IgG1 antibody, neutralizes hTNFα-induced cytotoxicity of L929 cells with IC_{50} of about 1.25×10^{-10} M. Moreover, the neutralizing capacity of D2E7 is maintained when the antibody is expressed as a Fab, $F(ab')_2$ or scFv fragment. D2E7 also inhibits TNFα-induced cellular activation, as measured by hTNFα-induced ELAM-1 expression on HUVEC (IC_{50}=about 1.85×10^{-10} M), and binding of hTNFα to hTNFα receptors on U-937 cells (IC_{50}=about 1.56×10^{-10} M). Regarding the latter, D2E7 inhibits the binding of hTNFα to both the p55 and p75 hTNFα receptors. Furthermore, the antibody inhibits hTNFα-induced lethality in vivo in mice (ED_{50}=1–2.5 μg/mouse).

Regarding the binding specificity of D2E7, this antibody binds to human TNFα in various forms, including soluble hTNFα, transmembrane hTNFα and hTNFα bound to cellular receptors. D2E7 does not specifically bind to other cytokines, such as lymphotoxin (TNFβ), IL-1α, IL-1β, IL-2, IL4, IL-6, IL-8, IFNγ and TGFβ. However, D2E7 does exhibit crossreactivity to tumor necrosis factors from other species. For example, the antibody neutralizes the activity of at least five primate TNFαs (chimpanzee, baboon, marmoset, cynomolgus and rhesus) with approximately equivalent IC_{50} values as for neutralization of hTNFα (see Example 4, subsection E). D2E7 also neutralizes the activity of mouse TNFα, although approximately 1 000-fold less well than human TNFα (see Example 4, subsection E). D2E7 also binds to canine and porcine TNFα.

In one aspect, the invention pertains to D2E7 antibodies and antibody portions, D2E7-related antibodies and antibody portions, and other human antibodies and antibody portions with equivalent properties to D2E7, such as high affinity binding to hTNFα with low dissociation kinetics and high neutralizing capacity. In one embodiment, the invention provides an isolated human antibody, or an antigen-binding portion thereof, that dissociates from human TNFα with a Kd Of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} S^{-1} or less, both determined by surface plasmon resonance, and neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-7} M or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5×10^{-4} s^{-1} or less, or even more preferably, with a K_{off} of 1×10^{-4} s^{-1} or less. More preferably, the isolated human antibody, or antigen-binding portion thereof, neutralizes human TNFα cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-8} M or less, even more preferably with an IC_{50} of 1×10^{-9} M or less and still more preferably with an IC_{50} of 5×10^{-10} M or less. In a preferred embodiment, the antibody is an isolated human recombinant antibody, or an antigen-binding portion thereof. In another preferred embodiment, the antibody also neutralizes TNFα-induced cellular activation, as assessed using a standard in vitro assay for TNFα-induced ELAM-1 expression on human umbilical vein endothelial cells (HUVEC).

Surface plasmon resonance analysis for determining K_d and K_{off} can be performed as described in Example 1. A standard in vitro L929 assay for determining IC_{50} values is described in Example 4, subsection A. A standard in vitro assay for TNFα-induced ELAM-1 expression on human umbilical vein endothelial cells (HUVEC) is described in Example 4, subsection C. Examples of recombinant human antibodies that meet, or are predicted to meet, the aforementioned kinetic and neutralization criteria include antibodies having the following [VHIVL] pairs, the sequences of which are shown in FIGS. **1**A, **1**B, **2**A and **2**B (see also Examples 2, 3 and 4 for kinetic and neutralization analyses):

[D2E7 VH/D2E7 VL]; [HD2E7*.A1/D2E7 VL], [HD2E7*.A2/D2E7 VL], [HD2E7*.A3/D2E7 VL], [HD2E7*.A4/D2E7 VL], [D2E7*.A5/D2E7 VL], [HD2E7*.A6/D2E7 VL], [HD2E7*.A7/D2E7 VL], [HD2E7*.A8/D2E7 VL], [HD2E7*.A9/D2E7 VL], [D2E7 VH/LD2E7*.A1], [D2E7 VH/LD2E7*.A4], [D2E7 VH/LD2E7*.A5], [D2E7 VH/LD2E7*.A7], [D2E7 VH/LD2E7*.A8], [HD2E7* A9/LD2E7* .A 1], [VH1-D2/LOE7], [VH1-D2.N/LOE7.T], [VH-D2.Y/LOE7.A], [VH1-D2.N/LOE7.A], [VH1-D2/EP B12] and [3C-H2/LOE7].

It is well known in the art that antibody heavy and light chain CDR3 domains play an important role in the binding specificity/affinity of an antibody for an antigen. Accordingly, in another aspect, the invention pertains to human antibodies that have slow dissociation kinetics for association with hTNFα and that have light and heavy chain CDR3 domains that structurally are identical to or related to those of D2E7. As demonstrated in Example 3, position 9 of the D2E7 VL CDR3 can be occupied by Ala or Thr without substantially affecting the K_{off}. Accordingly, a consensus motif for the 92E7 VL CDR3 comprises the amino acid sequence: Q-R-Y-N-R-A-P-Y-(T/A) (SEQ ID NO: 3). Additionally, position 12 of the D2E7 VH CDR3 can be occupied by Tyr or Asn, without substantially affecting the K_{off}. Accordingly, a consensus motif for the D2E7 VH CDR3 comprises the amino acid sequence: V-S-Y-L-S-T-A-S-S-L-D-(Y/N) (SEQ ID NO: 4). Moreover, as demonstrated in Example 2, the CDR3 domain of the D2E7 heavy and light chains is amenable to substitution with a single alanine residue (at position 1, 4, 5, 7 or 8 within the VL CDR3 or at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 within the VH CDR3) without substantially affecting the K_{off}. Still further, the skilled artisan will appreciate that, given the amenability of the D2E7 VL and VH CDR3 domains to substitutions by alanine, substitution of other amino acids within the CDR3 domains may be possible while still retaining the low off rate constant of the antibody, in particular substitutions with conservative amino acids. A "conservative amino acid substitution", as used herein, is one in which one amino acid residue is replaced with another amino acid residue having a similar side chain. Families of amino acid residues having similar side chains have been defined in the art, including basic side chains (e.g., lysine, arginine, histidine), acidic side chains (e.g., aspartic acid, glutamic acid), uncharged polar side chains (e.g., glycine, asparagine, glutamine, serine, threonine, tyrosine, cysteine), nonpolar side chains (eg., alanine, valine, leucine, isoleucine, proline, phenylalanine, methionine, tryptophan), beta-branched side chains (e.g., threonine, valine, isoleucine) and aromatic side chains (e.g., tyrosine, phenylalanine, tryptophan, histidine). Preferably, no more than one to five conservative amino acid substitutions are made within the D2E7 VL and/or VH CDR3 domains. More preferably, no more than one to three conservative amino acid substitutions are made within the D2E7 VL and/or VH CDR3 domains. Additionally, conservative amino acid substitutions should not be made at amino acid positions critical for binding to hTNFα. As shown in Example 3, positions 2 and 5 of the D2E7 VL CDR3 and positions 1 and 7 of the D2E7 VH CDR3 appear to be critical for interaction with hTNFα and thus, conservative amino acid substitutions preferably are not made at these positions (although an alanine substitution at position 5 of the D2E7 VL CDR3 is acceptable, as described above).

Accordingly, in another embodiment, the invention provides an isolated human antibody, or antigen-binding portion thereof, with the following characteristics:

a) dissociates from human TNFα with a K_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1. 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

More preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 5×10^{-4} s^{-1} or less. Even more preferably, the antibody, or antigen-binding portion thereof, dissociates from human TNFα with a K_{off} of 1×10^{-4} s^{-1} or less.

In yet another embodiment, the invention provides an isolated human antibody, or an antigen-binding portion thereof, with a light chain variable region (LCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO. 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, and with a heavy chain variable region (HCVR) having a CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. Preferably, the LCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5 (i.e., the D2E7 VL CDR2) and the HCVR further has a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6 (i.e., the D2E7 VH CDR2). Even more preferably, the LCVR further has CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7 (i.e., the D2E7 VL CDR1) and the HCVR has a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8 (i.e., the D2E7 VH CDR1). The framework regions for VL preferably are from the V_KI human germline family, more preferably from the A20 human germline Vk gene and most preferably from the D2E7 VL framework sequences shown in FIGS. **1**A and **1**B. The framework regions for VH preferably are from the V_H**3** human germline family, more preferably from the DP-31 human germline VH gene and most preferably from the D2E7 VH framework sequences shown in FIGS. **2**A and **2**B.

In still another embodiment, the invention provides an isolated human antibody, or an antigen binding portion thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO:1 (i.e., the D2E7 VL) and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2 (i.e., the D2E7 VH). In certain embodiments, the antibody comprises a heavy chain constant region, such as an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region. Preferably, the heavy chain constant region is an IgG1 heavy chain constant region or an IgG4 heavy chain constant region. Furthermore, the antibody can comprise a light chain constant region, either a kappa light chain constant region or a lambda light chain constant region. Preferably, the antibody comprises a kappa light chain constant region. Alternatively, the antibody portion can be, for example, a Fab fragment or a single chain Fv fragment.

In still other embodiments, the invention provides an isolated human antibody, or an antigen-binding portions thereof, having D2E7-related VL and VH CDR3 domains, for example, antibodies, or antigen-binding portions thereof,

with a light chain variable region (LCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 3, SEQ ID NO: 11, SEQ ID NO: 12. SEQ ID NO: 13. SEQ ID NO: 14. SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25 and SEQ ID NO: 26 or with a heavy chain variable region (HCVR) having a CDR3 domain comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 4, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35.

In yet another embodiment the invention provides a recombinant human antibody, or antigen-binding portion thereof, that neutralizes the activity of human TNFα but not human TNFβ. Preferably, antibody, or antigen-binding portion thereof, also neutralizes the activity of chimpanzee TNFα and at least one additional primate TNFα selected from the group consisting of baboon TNFα, marmoset TNFα, cynomoigus TNFα and rhesus TNFα. Preferably, the antibody, or antigen-binding portion thereof, neutralizes the human, chimpanzee and/or additional primate TNFα in a standard in vitro L929 assay with an IC_{50} of 1×10^{-8} M or less, more preferably 1×10^{-9} M or less, and even more preferably 5×10^{-10} M or less. In one subembodiment, the antibody also neutralizes the activity of canine TNFα, preferably in a standard in vitro L929 assay with an IC_{50} of 1×10^{-7} M or less, more preferably 1×10^{-8} M or less and even more preferably 5×10^{-9} M or less. In another subembodiment, the antibody also neutralizes the activity of pig TNFα, preferably with an IC_{50} of 1×10^{-5} M or less, more preferably 1×10^{-6} M or less and even more preferably 5×10^{-7} M or less. In yet another embodiment, the antibody also neutralizes the activity of mouse TNFα, preferably with an IC_{50} of 11×10^{-4} M or less, more preferably 1×10^{-5} M or less and even more preferably 5×10^{-6} M or less.

An antibody or antibody portion of the invention can be derivatized or linked to another functional molecule (e.g., another peptide or protein). Accordingly, the antibodies and antibody portions of the invention are intended to include derivatized and otherwise modified forms of the human anti-hTNFα antibodies described herein, including immunoadhesion molecules. For example, an antibody or antibody portion of the invention can be functionally linked (by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody (e.g., a bispecific antibody or a diabody), a detectable agent, a cytotoxic agent, a pharmaceutical agent, and/or a protein or peptide that can mediate associate of the antibody or antibody portion with another molecule (such as a streptavidin core region or a polyhistidine tag).

One type of derivatized antibody is produced by crosslinking two or more antibodies (of the same type or of different types, e.g., to create bispecific antibodies). Suitable crosslinkers include those that are heterobifunctional, having two distinctly reactive groups separated by an appropriate spacer (e.g., m-maleimidobenzoyl-N-hydroxysuccinimide ester) or homobifunctional (eg., disuccinimidyl suberate). Such linkers are available from Pierce Chemical Company, Rockford, Ill.

Useful detectable agents with which an antibody or antibody portion of the invention may be derivatized include fluorescent compounds. Exemplary fluorescent detectable agents include fluorescein, fluorescein isothiocyanate, rhodamine, 5-dimethylamine-1-napthalenesulfonyl chloride, phycoerythrin and the like. An antibody may also be derivatized with detectable enzymes, such as alkaline phosphatase, horseradish peroxidase, glucose oxidase and the like. When an antibody is derivatized with a detectable enzyme, it is detected by adding additional reagents that the enzyme uses to produce a detectable reaction product. For example, when the detectable agent horseradish peroxidase is present, the addition of hydrogen peroxide and diaminobenzidine leads to a colored reaction product, which is detectable. An antibody may also be derivatized with biotin, and detected through indirect measurement of avidin or streptavidin binding.

II. Expression of Antibodies

An antibody, or antibody portion, of the invention can be prepared by recombinant expression of immunoglobulin light and heavy chain genes in a host cell. To express an antibody recombinantly, a host cell is transfected with one or more recombinant expression vectors carrying DNA fragments encoding the immunoglobulin light and heavy chains of the antibody such that the light and heavy chains are expressed in the host cell and, preferably, secreted into the medium in which the host cells are cultured, from which medium the antibodies can be recovered. Standard recombinant DNA methodologies are used obtain antibody heavy and light chain genes, incorporate these genes into recombinant expression vectors and introduce the vectors into host cells, such as those described in Sambrook, Fritsch and Maniatis (eds), *Molecular Cloning; A Laboratory Manual, Second Edition,* Cold Spring Harbor, N.Y., (1989), Ausubel, F. M. et al. (eds.) *Current Protocols in Molecular Biology,* Greene Publishing Associates, (1989) and in U.S. Pat. No. 4,816,397 by Boss et al.

To express D2E7 or a D2E7-related antibody, DNA fragments encoding the light and heavy chain variable regions are first obtained. These DNAs can be obtained by amplification and modification of germline light and heavy chain variable sequences using the polymerase chain reaction (PCR). Germline DNA sequences for human heavy and light chain variable region genes are known in the art (see e.g., the "Vbase" human germline sequence database; see also Kabat, E. A., el al. (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition,* U.S. Department of Health and Human Services, NIH Publication No. 91–3242; Tomlinson, I. M., et al. (1992) "The Repertoire of Human Germline V_H Sequences Reveals about Fifty Groups of V_H Segments with Different Hypervariable Loops" *J. Mol. Biol.* 227:776–798; and Cox, J. P. L. et al. (1994) "A Directory of Human Germ-line V_K Segments Reveals a Strong Bias in their Usage" *Eur. J. Immunol.* 24:827–836; the contents of each of which are expressly incorporated herein by reference). To obtain a DNA fragment encoding the heavy chain variable region of D2E7, or a D2E7-related antibody, a member of the V_H**3** family of human germline VH genes is amplified by standard PCR Most preferably, the DP-3 1 VH germline sequence is amplified. To obtain a DNA fragment encoding the light chain variable region of D2E7, or a D2E7-related antibody, a member of the V_KI family of human germline VL genes is amplified by standard PCR. Most preferably, the A20 VL germline sequence is amplified. PCR primers suitable for use in amplifying the DP-31 germline VH and A20 germline VL sequences can be designed based on the nucleotide sequences disclosed in the references cited supra, using standard methods.

Once the germline VH and VL fragments are obtained, these sequences can be mutated to encode the D2E7 or D2E7-related amino acid sequences disclosed herein. The amino acid sequences encoded by the germline VH and VL

DNA sequences are first compared to the D2E7 or D2E7-related VH and VL amino acid sequences to identify amino acid residues in the D2E7 or D2E7-related sequence that differ from germline. Then the appropriate nucleotides of the germline DNA sequences are mutated such that the mutated germline sequence encodes the D2E7 or D2E7-related amino acid sequence, using the genetic code to determine which nucleotide changes should be made. Mutagenesis of the germline sequences is carried out by standard methods, such as PCR-mediated mutagenesis (in which the mutated nucleotides are incorporated into the PCR primers such that the PCR product contains the mutations) or site-directed mutagenesis.

Moreover, it should be noted that if the "germline" sequences obtained by PCR amplification encode amino acid differences in the framework regions from the true germline configuration (i.e., differences in the amplified sequence as compared to the true germline sequence, for example as a result of somatic mutation), it may be desireable to change these amino acid differences back to the true germline sequences (i.e., "backmutation" of framework residues to the germline configuration).

Once DNA fragments encoding D2E7 or D2E7-related VH and VL segments are obtained (by amplification and mutagenesis of germline VH and VL genes, as described above), these DNA fragments can be further manipulated by standard recombinant DNA techniques, for example to convert the variable region genes to full-length antibody chain genes, to Fab fragment genes or to a scFv gene. In these manipulations, a VL- or VH-encoding DNA fragment is operatively linked to another DNA fragment encoding another protein, such as an antibody constant region or a flexible linker. The term "operatively linked", as used in this context, is intended to mean that the two DNA fragments are joined such that the amino acid sequences encoded by the two DNA fragments remain in-frame.

The isolated DNA encoding the VH region can be converted to a full-length heavy chain gene by operatively linking the VH-encoding DNA to another DNA molecule encoding heavy chain constant regions (CH1, CH2 and CH3). The sequences of human heavy chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of Immunological Interest, Fifth Edition,* U.S. Department of Health and Human Services, NIH Publication No. 91–3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The heavy chain constant region can be an IgG1, IgG2, IgG3, IgG4, IgA, IgE, IgM or IgD constant region, but most preferably is an IgG1 or IgG4 constant region. For a Fab fragment heavy chain gene, the VH-encoding DNA can be operatively linked to another DNA molecule encoding only the heavy chain CH1 constant region.

The isolated DNA encoding the VL region can be converted to a full-length light chain gene (as well as a Fab light chain gene) by operatively linking the VL-encoding DNA to another DNA molecule encoding the light chain constant region, CL. The sequences of human light chain constant region genes are known in the art (see e.g., Kabat, E. A., et al. (1991) *Sequences of Proteins of immunological Interest, Fifth Edition,* U.S. Department of Health and Human Services. NIH Publication No. 91–3242) and DNA fragments encompassing these regions can be obtained by standard PCR amplification. The light chain constant region can be a kappa or lambda constant region, but most preferably is a kappa constant region.

To create a scFv gene, the VH- and VL-encoding DNA fragments are operatively linked to another fragment encoding a flexible linker, e.g., encoding the amino acid sequence $(Gly_4\text{-}Ser)_3$, such that the VH and VL sequences can be expressed as a contiguous single-chain protein, with the VL and VH regions joined by the flexible linker (see e.g., Bird et al. (1988) *Science* 242:423–426; Huston et al. (1988) *Proc. Natl. Acad Sci. USA* 85:5879–5883; McCafferty et al., *Nature* (1990) 348:552–554).

To express the antibodies, or antibody portions of the invention, DNAs encoding partial or full-length light and heavy chains, obtained as described above, are inserted into expression vectors such that the genes are operatively linked to transcriptional and translational control sequences. In this context, the term "operatively linked" is intended to mean that an antibody gene is ligated into a vector such that transcriptional and translational control sequences within the vector serve their intended function of regulating the transcription and translation of the antibody gene. The expression vector and expression control sequences are chosen to be compatible with the expression host cell used. The antibody light chain gene and the antibody heavy chain gene can be inserted into separate vector or, more typically, both genes are inserted into the same expression vector. The antibody genes are inserted into the expression vector by standard methods (e.g., ligation of complementary restriction sites on the antibody gene fragment and vector, or blunt end ligation if no restriction sites are present). Prior to insertion of the D2E7 or D2E7-related light or heavy chain sequences, the expression vector may already carry antibody constant region sequences. For example, one approach to converting the D2E7 or D2E7-related VH and VL sequences to full-length antibody genes is to insert them into expression vectors already encoding heavy chain constant and light chain constant regions, respectively, such that the VH segment is operatively linked to the CH segment(s) within the vector and the VL segment is operatively linked to the CL segment within the vector. Additionally or alternatively, the recombinant expression vector can encode a signal peptide that facilitates secretion of the antibody chain from a host cell. The antibody chain gene can be cloned into the vector such that the signal peptide is linked in-frame to the amino terminus of the antibody chain gene. The signal peptide can be an immunoglobulin signal peptide or a heterologous signal peptide (i.e., a signal peptide from a non-immunoglobulin protein).

In addition to the antibody chain genes, the recombinant expression vectors of the invention carry regulatory sequences that control the expression of the antibody chain genes in a host cell. The term "regulatory sequence" is intended to includes promoters, enhancers and other expression control elements (e.g., polyadenylation signals) that control the transcription or translation of the antibody chain genes. Such regulatory sequences are described, for example, in Goeddel; *Gene Expression Technology: Methods in Enzymology* 185, Academic Press, San Diego, Calif. (1990). It will be appreciated by those skilled in the art that the design of the expression vector, including the selection of regulatory sequences may depend on such factors as the choice of the host cell to be transformed, the level of expression of protein desired, etc. Preferred regulatory sequences for mammalian host cell expression include viral elements that direct high levels of protein expression in mammalian cells, such as promoters and/or enhancers derived from cytomegalovirus (CMV) (such as the CMV promoter/enhancer), Simian Virus 40 (SV40) (such as the SV40 promoter/enhancer), adenovirus, (e.g., the adenovirus major late promoter (AdMLP)) and polyoma. For further description of viral regulatory elements, and sequences

thereof, see e.g., U.S. Pat. No. 5,168,062 by Stinski, U.S. Pat. No. 4,510,245 by Bell et al. and U.S. Pat. No. 4,968,615 by Schaffner et al.

In addition to the antibody chain genes and regulatory sequences, the recombinant expression vectors of the invention may carry additional sequences, such as sequences that regulate replication of the vector in host cells (e.g., origins of replication) and selectable marker genes. The selectable marker gene facilitates selection of host cells into which the vector has been introduced (see e.g., U.S. Pat. Nos. 4,399, 216, 4,634.665 and 5,179,017, all by Axel et al.). For example, typically the selectable marker gene confers resistance to drugs, such as G418, hygromycin or methotrexate, on a host cell into which the vector has been introduced. Preferred selectable marker genes include the dihydrofolate reductase (DHFR) gene (for use in dhfr- host cells with methotrexate selection/amplification) and the neo gene (for G418 selection).

For expression of the light and heavy chains, the expression vector(s) encoding the heavy and light chains is transfected into a host cell by standard techniques. The various forms of the term "transfection" are intended to encompass a wide variety of techniques commonly used for the introduction of exogenous DNA into a prokaryotic or eukaryotic host cell, e.g., electroporation, calcium-phosphate precipitation, DEAE-dextran transfection and the like. Although it is theoretically possible to express the antibodies of the invention in either prokaryotic or eukaryotic host cells, expression of antibodies in eukaryotic cells, and most preferably mammalian host cells, is the most preferred because such eukaryotic cells, and in particular mammalian cells, are more likely than prokaryotic cells to assemble and secrete a properly folded and immunologically active antibody. Prokaryotic expression of antibody genes has been reported to be ineffective for production of high yields of active antibody (Boss, M. A. and Wood, C. R. (1985) *Immunology Today* 6:12–13).

Preferred mammalian host cells for expressing the recombinant antibodies of the invention include Chinese Hamster Ovary (CHO cells) (including dhfr- CHO cells, described in Urlaub and Chasin, (1980) *Proc. Natl. Acad Sci. USA* 77:4216–4220, used with a DHFR selectable marker, e.g., as described in R. J. Kaufman and P. A. Sharp (1982) *Mol. Biol.* 159:601–621), NSO myeloma cells, COS cells and SP2 cells. When recombinant expression vectors encoding antibody genes are introduced into mammalian host cells, the antibodies are produced by culturing the host cells for a period of time sufficient to allow for expression of the antibody in the host cells or, more preferably, secretion of the antibody into the culture medium in which the host cells are grown. Antibodies can be recovered from the culture medium using standard protein purification methods.

Host cells can also be used to produce portions of intact antibodies, such as Fab fragments or scFv molecules. It will be understood that variations on the above procedure are within the scope of the present invention. For example, it may be desirable to transfect a host cell with DNA encoding either the light chain or the heavy chain (but not both) of an antibody of this invention. Recombinant DNA technology may also be used to remove some or all of the DNA encoding either or both of the light and heavy chains that is not necessary for binding to hTNFα. The molecules expressed from such truncated DNA molecules are also encompassed by the antibodies of the invention. In addition, bifunctional antibodies may be produced in which one heavy and one light chain are an antibody of the invention and the other heavy and light chain are specific for an antigen other than hTNFα by crosslinking an antibody of the invention to a second antibody by standard chemical crosslinking methods.

In a preferred system for recombinant expression of an antibody, or antigen-binding portion thereof, of the invention, a recombinant expression vector encoding both the antibody heavy chain and the antibody light chain is introduced into dhfr- CHO cells by calcium phosphate-mediated transfection. Within the recombinant expression vector, the antibody heavy and light chain genes are each operatively linked to enhancer/promoter regulatory elements (e.g., derived from SV40, CMV, adenovirus and the like, such as a CMV enhancer/AdMLP promoter regulatory element or an SV40 enhancer/AdMLP promoter regulatory element) to drive high levels of transcription of the genes. The recombinant expression vector also carries a DHFR gene, which allows for selection of CHO cells that have been transfected with the vector using methotrexate selection/amplification. The selected transformant host cells are culture to allow for expression of the antibody heavy and light chains and intact antibody is recovered from the culture medium. Standard molecular biology techniques are used to prepare the recombinant expression vector, transfect the host cells, select for transformants, culture the host cells and recover the antibody from the culture medium.

In view of the foregoing, another aspect of the invention pertains to nucleic acid, vector and host cell compositions that can be used for recombinant expression of the antibodies and antibody portions of the invention. The nucleotide sequence encoding the D2E7 light chain variable region is shown in FIG. **7** and SEQ ID NO: 36. The CDR1 domain of the LCVR encompasses nucleotides 70–102, the CDR2 domain encompasses nucleotides 148–168 and the CDR3 domain encompasses nucleotides 265–291. The nucleotide sequence encoding the D2E7 heavy chain variable region is shown in FIG. **8** and SEQ ID NO: 37. The CDR1 domain of the HCVR encompasses nucleotides 91–105, the CDR2 domain encompasses nucleotides 148–198 and the CDR3 domain encompasses nucleotides 295–330. It will be appreciated by the skilled artisan that nucleotide sequences encoding D2E7-related antibodies, or portions thereof (e.g., a CDR domain, such as a CDR3 domain), can be derived from the nucleotide sequences encoding the D2E7 LCVR and HCVR using the genetic code and standard molecular biology techniques.

In one embodiment, the invention provides an isolated nucleic acid encoding a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3 (i.e., the D2E7 VL CDR3), or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9. This nucleic acid can encode only the CDR3 region or, more preferably, encodes an entire antibody light chain variable region (LCVR). For example, the nucleic acid can encode an LCVR having a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 5 (i.e., the D2E7 VL CDR2) and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 7 (i.e., the D2E7 VL CDR1).

In another embodiment, the invention provides an isolated nucleic acid encoding a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4 (i.e., the D2E7 VH CDR3), or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12. This nucleic acid can encode only the CDR3 region or, more preferably,

encodes an entire antibody heavy chain variable region (HCVR). For example, the nucleic acid can encode a HCVR having a CDR2 domain comprising the amino acid sequence of SEQ ID NO: 6 (i.e., the D2E7 VH CDR2) and a CDR1 domain comprising the amino acid sequence of SEQ ID NO: 8 (i.e., the D2E7 VH CDR1).

In yet another embodiment, the invention provides isolated nucleic acids encoding a D2E7-related CDR3 domain, e.g., comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: 3, SEQ ID NO 4, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33, SEQ ID NO: 34 and SEQ ID NO: 35.

In still another embodiment, the invention provides an isolated nucleic acid encoding an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 1 (i.e., the D2E7 LCVR). Preferably this nucleic acid comprises the nucleotide sequence of SEQ ID NO: 36, although the skilled artisan will appreciate that due to the degeneracy of the genetic code, other nucleotide sequences can encode the amino acid sequence of SEQ ID NO: 1. The nucleic acid can encode only the LCVR or can also encode an antibody light chain constant region, operatively linked to the LCVR. In one embodiment, this nucleic acid is in a recombinant expression vector.

In still another embodiment, the invention provides an isolated nucleic acid encoding an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2 (i.e., the D2E7 HCVR). Preferably this nucleic acid comprises the nucleotide sequence of SEQ ID NO: 37, although the skilled artisan will appreciate that due to the degeneracy of the genetic code, other nucleotide sequences can encode the amino acid sequence of SEQ ID NO: 2. The nucleic acid can encode only the HCVR or can also encode a heavy chain constant region, operatively linked to the HCVR. For example, the nucleic acid can comprise an IgG1 or lgG4 constant region. In one embodiment, this nucleic acid is in a recombinant expression vector.

The invention also provides recombinant expression vectors encoding both an antibody heavy chain and an antibody light chain. For example, in one embodiment, the invention provides a recombinant expression vector encoding:

a) an antibody light chain having a variable region comprising the amino acid sequence of SEQ ID NO: 1 (i.e., the D2E7 LCVR); and

b) an antibody heavy chain having a variable region comprising the amino acid sequence of SEQ ID NO: 2 (i.e., the D2E7 HCVR).

The invention also provides host cells into which one or more of the recombinant expression vectors of the invention have been introduced. Preferably, the host cell is a mammalian host cell, more preferably the host cell is a CHO cell, an NSO cell or a COS cell.

Still further the invention provides a method of synthesizing a recombinant human antibody of the invention by culturing a host cell of the invention in a suitable culture medium until a recombinant human antibody of the invention is synthesized. The method can further comprise isolating the recombinant human antibody from the culture medium.

III. Selection of Recombinant Human Antibodies

Recombinant human antibodies of the invention in addition to the D2E7 or D2E7-related antibodies disclosed herein can be isolated by screening of a recombinant combinatorial antibody library, preferably a scFv phage display library, prepared using human VL and VH cDNAs prepared from mRNA derived from human lymphocytes. Methodologies for preparing and screening such libraries are known in the art. In addition to commercially available kits for generating phage display libraries (e.g., the Pharmacia *Recombinant Phage Antibody System,* catalog no. 27–9400-01; and the Stratagene *SurfZAP™ phage display kit, catalog no.* 240612), examples of methods and reagents particularly amenable for use in generating and screening antibody display libraries can be found in, for example, Ladner et al. U.S. Pat. No. 5,223,409; Kang et al. PCT Publication No. WO 92/18619; Dower et al. PCT Publication No. WO 91/17271; Winter et al. PCT Publication No. WO 92120791; Markland et al. PCT Publication No. WO 92/15679; Breitling et al. PCT Publication No. WO 93/01288; McCafferty et al. PCT Publication No. WO 92/01047; Garrard et al. PCT Publication No. WO 92/09690; Fuchs et al. (1991) *Bio/Technology* 9:1370–1372; Hay et al (1992) *Hum Antibod Hybridomas* 3:81–85; Huse et al (1989) *Science* 246:1275–1281; McCafferty et al., *Nature* (1990) 348:552–554; Griffiths et al. (1993) *EMBO J* 12:725–734; Hawkins et al. (1992) *J Mol Biol* 226:889–896; Clackson et al. (1991) *Nature* 352:624–628; Gram el al. (1992) *PNAS* 89:3576–3580; Garrad et al. (1991) *Bio/Technology* 9:1373–1377; Hoogenboom et al. (1991) *Nuc Acid Res* 19:4133–4137; and Barbas et al. (1991) *PNAS* 88:7978–7982.

In a preferred embodiment, to isolate human antibodies with high affinity and a low off rate constant for hTNFα, a murine anti-hTNFα antibody having high affinity and a low off rate constant for hTNFα (e.g., MAK 195, the hybridoma for which has deposit number ECACC 87 050801) is first used to select human heavy and light chain sequences having similar binding activity toward hTNFα, using the epitope imprinting, or guided selection, methods described in Hoogenboom et al., PCT Publication No. WO 93/06213. The antibody libraries used in this method are preferably scFv libraries prepared and screened as described in McCafferty et al., PCT Publication No. WO 92/01047, McCafferty et al., *Nature* (1990) 348:552–554; and Griffiths et al., (1993) *EMBO J* 12:725–734. The scFv antibody libraries preferably are screened using recombinant human TNFα as the antigen.

Once initial human VL and VH segments are selected, "mix and match" experiments, in which different pairs of the initially selected VL and VH segments are screened for hTNFα binding, are performed to select preferred VL/VH pair combinations. Additionally, to further improve the affinity and/or lower the off rate constant for hTNFα binding, the VL and VH segments of the preferred VL/VH pair(s) can be randomly mutated, preferably within the CDR3 region of VH and/or VL, in a process analogous to the in vivo somatic mutation process responsible for affinity maturation of antibodies during a natural immune response. This in vitro affinity maturation can be accomplished by amplifying VH and VL regions using PCR primers complimentary to the VH CDR3 or VL CDR3, respectively, which primers have been "spiked" with a random mixture of the four nucleotide bases at certain positions such that the resultant PCR products encode VH and VL segments into which random mutations have been introduced into the VH and/or VL CDR3 regions. These randomly mutated VH and

VL segments can be rescreened for binding to hTNFα and sequences that exhibit high affinity and a low off rate for hTNFα binding can be selected.

The amino acid sequences of selected antibody heavy and light chains can be compared to germline heavy and light chain amino acid sequences. In cases where certain framework residues of the selected VL and/or VH chains differ from the germline configuration (eg., as a result of somatic mutation of the immunoglobulin genes used to prepare the phage library). it may be desireable to "backmutate" the altered framework residues of the selected antibodies to the germline configuration (i.e., change the framework amino acid sequences of the selected antibodies so that they are the same as the germline framework amino acid sequences). Such "backmutation" (or "germlining") of framework residues can be accomplished by standard molecular biology methods for introducing specific mutations (e.g., site-directed mutagenesis; PCR-mediated mutagenesis, and the like).

Following screening and isolation of an anti-hTNFα antibody of the invention from a recombinant immunoglobulin display library, nucleic acid encoding the selected antibody can be recovered from the display package (e.g., from the phage genome) and subcloned into other expression vectors by standard recombinant DNA techniques. If desired, the nucleic acid can be further manipulated to create other antibody forms of the invention (e.g., linked to nucleic acid encoding additional immunoglobulin domains, such as additional constant regions). To express a recombinant human antibody isolated by screening of a combinatorial library, the DNA encoding the antibody is cloned into a recombinant expression vector and introduced into a mammalian host cells, as described in further detail in Section II above.

IV. Pharmaceutical Compositions and Pharmaceutical Administration

The antibodies and antibody-portions of the invention can be incorporated into pharmaceutical compositions suitable for administration to a subject. Typically, the pharmaceutical composition comprises an antibody or antibody portion of the invention and a pharmaceutically acceptable carrier. As used herein, "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like that are physiologically compatible. Examples of pharmaceutically acceptable carriers include one or more of water, saline, phosphate buffered saline, dextrose, glycerol, ethanol and the like, as well as combinations thereof. In many cases, it will be preferable to include isotonic agents, for example, sugars, polyalcohols such as mannitol, sorbitol, or sodium chloride in the composition. Pharmaceutically acceptable carriers may further comprise minor amounts of auxiliary substances such as wetting or emulsifying agents, preservatives or buffers, which enhance the shelf life or effectiveness of the antibody or antibody portion.

The compositions of this invention may be in a variety of forms. These include, for example, liquid, semi-solid and solid dosage forms, such as liquid solutions (e.g., injectable and infusible solutions), dispersions or suspensions, tablets, pills, powders, liposomes and suppositories. The preferred form depends on the intended mode of administration and therapeutic application. Typical preferred compositions are in the form of injectable or infusible solutions, such as compositions similar to those used for passive immunization of humans with other antibodies. The preferred mode of administration is parenteral (e.g., intravenous, subcutaneous, intraperitoneal, intramuscular). In a preferred embodiment, the antibody is administered by intravenous infusion or injection. In another preferred embodiment, the antibody is administered by intramuscular or subcutaneous injection.

Therapeutic compositions typically must be sterile and stable under the conditions of manufacture and storage. The composition can be formulated as a solution, microemulsion, dispersion, liposome, or other ordered structure suitable to high drug concentration. Sterile injectable solutions can be prepared by incorporating the active compound (i.e., antibody or antibody portion) in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and freeze-drying that yields a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. The proper fluidity of a solution can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prolonged absorption of injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, monostearate salts and gelatin.

The antibodies and antibody-portions of the present invention can be administered by a variety of methods known in the art, although for many therapeutic applications, the preferred route/mode of administration is intravenous injection or infusion. As will be appreciated by the skilled artisan, the route and/or mode of administration will vary depending upon the desired results. In certain embodiments, the active compound may be prepared with a carrier that will protect the compound against rapid release, such as a controlled release formulation, including implants, transdermal patches, and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Many methods for the preparation of such formulations are patented or generally known to those skilled in the art. See, e.g., *Sustained and Controlled Release Drug Delivery Systems,* J. R. Robinson. ed., Marcel Dekker, Inc., New York, 1978.

In certain embodiments, an antibody or antibody portion of the invention may be orally administered, for example, with an inert diluent or an assimilable edible carrier. The compound (and other ingredients, if desired) may also be enclosed in a hard or soft shell gelatin capsule, compressed into tablets, or incorporated directly into the subject's diet. For oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. To administer a compound of the invention by other than parenteral administration, it may be necessary to coat the compound with, or co-administer the compound with, a material to prevent its inactivation.

Supplementary active compounds can also be incorporated into the compositions. In certain embodiments, an antibody or antibody portion of the invention is coformulated with and/or coadministered with one or more addi-

tional therapeutic agents that are useful for treating disorders in which TNFα activity is detrimental. For example, an anti-hTNFα antibody or antibody portion of the invention may be coformulated and/or coadministered with one or more additional antibodies that bind other targets (e.g., antibodies that bind other cytokines or that bind cell surface molecules), one or more cytokines, soluble TNFα receptor (see e.g., PCT Publication No. WO 94/06476) and/or one or more chemical agents that inhibit hTNFα production or activity (such as cyclohexane-ylidene derivatives as described in PCT Publication No. WO 93119751). Furthermore, one or more antibodies of the invention may be used in combination with two or more of the foregoing therapeutic agents. Such combination therapies may advantageously utilize lower dosages of the administered therapeutic agents, thus avoiding possible toxicities or complications associated with the various monotherapies.

Nonlimiting examples of therapeutic agents for rheumatoid arthritis with which an antibody, or antibody portion, of the invention can be combined include the following: non-steroidal anti-inflammatory drug(s) (NSAIDs); cytokine suppressive anti-inflammatory drug(s) (CSAIDs); CDP-57111BAY-10–3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2 (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein; Immunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 37. S295; *J. Invest Med.* (1996) Vol. 44 235A); 55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IDEC-CE9.I/SB 210396 (non-depleting primatized anti-CD4 antibody; IDEC/SmithKline; see e.g., *Arthritis & Rheumatism* (1995) Vol. 38, S185); DAB 486-IL-2 and/or DAB 389-IL-2 (IL-2 fusion proteins; Seragen; see e.g., *Arthritis & Rheumatism* (1993) Vol. 36, 1223); Anti-Tac (humanized anti-IL-2Rα; Protein Design Labs/Roche); IL4 (anti-inflammatory cytokine; DNAX/Schering); IL-10 (SCH 52000; recombinant IL-10, anti-inflammatory cytokine; DNAX/Schering); IL-4; IL-10 and/or IL-4 agonists (e.g., agonist antibodies); IL-1 RA (IL-1 receptor antagonist; Synergen/Amgen); TNF-bp/s-TNFR (soluble TNF binding protein; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39 No. 9 (supplement), S284; *Amer. J. Physiol.—Heart and Circulatory Physiology* (1995) Vol. 268, pp. 3742); R973401 (phosphodiesterase Type IV inhibitor; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39. No. 9 (supplement), S282); MK-966 (COX-2 Inhibitor; see e.g., *Arthritis & Rheumatism* (1996) Vol. 3, No. 9 (supplement), S81); Iloprost (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39. No. 9 (supplement), S82); methotrexate: thalidomide (see e.g., *Arthritis & Rheumatism* (1996) Vol. 9, No. 9 (supplement), S282) and thalidomide-related drugs (e.g., Celgen); leflunomide (anti-inflammatory and cytokine inhibitor; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39 No. 9 (supplement), S131; *Inflammation Research* (1996) Vol. 4, pp. 103–107); tranexamic acid (inhibitor of plasminogen activation; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S284); T614 (cytokine inhibitor; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39 No. 9 (supplement), S282); prostaglandin E1 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S282); Tenidap (non-steroidal anti-inflammatory drug; see e.g., *Arthritis & Rheumatism* (1996) Vol. 39 No. 9 (supplement), S280); Naproxen (non-steroidal anti-inflammatory drug; see e.g., *Neuro Report* (1996) Vol. 7, pp. 1209–1213); Meloxicam (non-steroidal anti-inflammatory drug); Ibuprofen (non-steroidal anti-inflammatory drug); Piroxicam (non-steroidal anti-inflammatory drug); Diclofenac (non-steroidal anti-inflammatory drug); Indomethacin (non-steroidal anti-inflammatory drug); Sulfasalazine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 9, No. 9 (supplement), S281); Azathioprine (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39 No. 9 (supplement), S281); ICE inhibitor (inhibitor of the enzyme interleukin-1β converting enzyme); zap-70 and/or Ick inhibitor (inhibitor of the tyrosine kinase zap-70 or Ick); VEGF inhibitor and/or VEGF-R inhibitor (inhibitos of vascular endothelial cell growth factor or vascular endothelial cell growth factor receptor; inhibitors of angiogenesis); corticosteroid anti-inflammatory drugs (e.g., SB203580); TNF-convertase inhibitors; anti-IL-12 antibodies; interleukin-11 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S296); interleukin-13 (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39, No. 9 (supplement), S308); interleukin-17 inhibitors (see e.g., *Arthritis & Rheumatism* (1996) Vol. 39. No. 9 (supplement), S120); gold; penicillamine; chloroquine; hydroxychloroquine; chlorambucil; cyclophosphamide; cyclosporine; total lymphoid irradiation; anti-thymocyte globulin; anti-CD4 antibodies; CD5-toxins; orally-administered peptides and collagen; lobenzarit disodium; Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); prednisone. orgotein; glycosaninoglycan polysulphate; minocycline; anti-IL2R antibodies; marine and botanical lipids (fish and plant seed fatty acids; see e.g., DeLuca et al. (1995) *Rheum. Dis. Clin. North Am.* 21:759–777); auranofm; phenylbutazone; meclofenamic acid; flufenamic acid; intravenous immune globulin; zileuton; mycophenolic acid (RS-61443); tacrolimus (FK-506); sirolimus (rapamycin); amiprilose (therafectin); cladribine (2-chlorodeoxyadenosine); and azaribine.

Nonlimiting examples of therapeutic agents for inflammatory bowel disease with which an antibody, or antibody portion, of the invention can be combined include the following: budenoside; epidermal growth factor; corticosteroids; cyclosporin, sulfasalazine; aminosalicylates; 6-mercaptopurine; azathioprine; metronidazole; lipoxygenase inhibitors; mesalamine; olsalazine; balsalazide; antioxidants; thromboxane inhibitors; IL-1 receptor antagonists; anti-IL-1β monoclonal antibodies; anti-IL-6 monoclonal antibodies; growth factors; elastase inhibitors; pyridinyl-imidazole compounds; CDP-571/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2 (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG (75 kD TNF receptorIgG fusion protein; Immunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 7, S295; *J. Invest. Med.* (1996) Vol. 44 235A); 55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); interleukin- 10 (SCH 52000; Schering Plough); IL4; IL-10 and/or IL4 agonists (e.g., agonist antibodies); interleukin-11; glucuronide- or dextran-conjugated prodrugs of prednisolone, dexamethasone or budesonide; ICAM-1 antisense phosphorothioate oligodeoxynucleotides (ISIS 2302; Isis Pharmaceuticals, Inc.); soluble complement receptor 1 (TP10; T Cell Sciences, Inc.); slow-release mesalazine; methotrexate; antagonists of Platelet Activating Factor (PAF); ciprofloxacin; and lignocaine.

Nonlimiting examples of therapeutic agents for multiple sclerosis with which an antibody, or antibody portion, of the invention can be combined include the following: corticosteroids; prednisolone; methylprednisolone; azathioprine; cyclophosphamide; cyclosporine; methotrexate; 4-aminopyridine; tizanidine; interferon-β1a (Avonex™; Biogen); interferon-β1b (Betaseron™; Chiron/Berlex); Copolymer 1 (Cop1; Copaxone™; Teva Pharmaceutical

Industries, Inc.); hyperbaric oxygen; intravenous immunoglobulin; clabribine; CDP-571/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2 (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein; Immunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J Invest. Med.* (1996) Vol. 44, 235A); 55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); IL-10; IL-4; and IL-10 and/or IL-4 agonists (e.g., agonist antibodies).

Nonlimiting examples of therapeutic agents for sepsis with which an antibody, or antibody portion, of the invention can be combined include the following: hypertonic saline solutions; antibiotics; intravenous gamma globulin; continuous hemofiltration; carbapenems (e.g., meropenem); antagonists of cytokines such as TNFα, IL-β, IL-6 and/or IL-8; CDP-571BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2 (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein; lmmunex; see e.g., *Arthritis & Rheumatism* (1994) Vol. 37, S295; *J Invest. Med.* (1996) Vol. 44, 235A); 55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche); Cytokine Regulating Agents (CRAs) HP228 and HP466 (Houghten Pharmaceuticals, Inc.); SK&F 107647 (low molecular peptide; SmithKline Beecham); tetravalent guanylhydrazone CNI-1493 (Picower Institute); Tissue Factor Pathway Inhibitor (TFPI; Chiron); PHP (chemically modified hemoglobin; APEX Bioscience); iron chelators and chelates, including diethylenetriamine pentaacetic acid—iron (III) complex (DTPA iron (III); Molichem Medicines); lisofylline (synthetic small molecule methylxanthine; Cell Therapeutics, Inc.); PGG-Glucan (aqeuous soluble β1,3glucan; Alpha-Beta Technology); apolipoprotein A-1 reconstituted with lipids; chiral hydroxamic acids (synthetic antibacterials that inhibit lipid A biosynthesis); anti-endotoxin antibodies; E5531 (synthetic lipid A antagonist; Eisai America, Inc.); $rBPI_{21}$ (recombinant N-terminal fragment of human Bactericidal/Permeability-Increasing Protein); and Synthetic Anti-Endotoxin Peptides (SAEP; Bios Ynth Research Laboratories);

Nonlimiting examples of therapeutic agents for adult respiratory distress syndrome (ARDS) with which an antibody, or antibody portion, of the invention can be combined include the following: anti-IL-8 antibodies; surfactant replacement therapy; CDP-571/BAY-10-3356 (humanized anti-TNFα antibody; Celltech/Bayer); cA2 (chimeric anti-TNFα antibody; Centocor); 75 kdTNFR-IgG (75 kD TNF receptor-IgG fusion protein; Immunex; see e.g., *Arthritis & Rheumatism* (1 994) Vol. 3.7 S295; *J. Invest. Med.* (1996) Vol. 44, 235A); and 55 kdTNFR-IgG (55 kD TNF receptor-IgG fusion protein; Hoffmann-LaRoche).

The use of the antibodies, or antibody portions, of the invention in combination with other therapeutic agents is discussed further in subsection IV.

The pharmaceutical compositions of the invention may include a "therapeutically effective amount" or a "prophylactically effective amount" of an antibody or antibody portion of the invention. A "therapeutically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired therapeutic result. A therapeutically effective amount of the antibody or antibody portion may vary according to factors such as the disease state, age, sex, and weight of the individual, and the ability of the antibody or antibody portion to elicit a desired response in the individual. A therapeutically effective amount is also one in which any toxic or detrimental effects of the antibody or antibody portion are outweighed by the therapeutically beneficial effects. A "prophylactically effective amount" refers to an amount effective, at dosages and for periods of time necessary, to achieve the desired prophylactic result. Typically, since a prophylactic dose is used in subjects prior to or at an earlier stage of disease, the prophylactically effective amount will be less than the therapeutically effective amount.

Dosage regimens may be adjusted to provide the optimum desired response (e g., a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active compound and the particular therapeutic or prophylactic effect to be achieved, and (b) the limitations inherent in the art of compounding such an active compound for the treatment of sensitivity in individuals.

An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody or antibody portion of the invention is 0.1–20 mg/kg, more preferably 1–10 mg/kg. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that dosage ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition.

IV. Uses of the Antibodies of the Invention

Given their ability to bind to hTNFα, the anti-hTNFα antibodies, or portions thereof, of the invention can be used to detect hTNFα (e.g., in a biological sample, such as serum or plasma), using a conventional immunoassay, such as an enzyme linked immunosorbent assays (ELISA), an radioimmunoassay (RIA) or tissue immunohistochemistry. The invention provides a method for detecting hTNFα in a biological sample comprising contacting a biological sample with an antibody, or antibody portion, of the invention and detecting either the antibody (or antibody portion) bound to hTNFα or unbound antibody (or antibody portion), to thereby detect hTNFα in the biological sample. The antibody is directly or indirectly labeled with a detectable substance to facilitate detection of the bound or unbound antibody. Suitable detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, β-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

Alternative to labeling the antibody, hTNFα can be assayed in biological fluids by a competition immunoassay

utilizing rhTNFα standards labeled with a detectable substance and an unlabeled anti-hTNFα antibody. In this assay, the biological sample, the labeled rhTNFα standards and the anti-hTNFα antibody are combined and the amount of labeled rhTNFα standard bound to the unlabeled antibody is determined. The amount of hTNFα in the biological sample is inversely proportional to the amount of labeled rhTNFα standard bound to the anti-hTNFα antibody.

A D2E7 antibody of the invention can also be used to detect TNFαs from species other than humans, in particular TNFαs from primates (e.g., chimpanzee, baboon, marmoset, cynomolgus and rhesus), pig and mouse, since D2E7 can bind to each of these TNFαs (discussed further in Example 4, subsection E).

The antibodies and antibody portions of the invention are capable of neutralizing hTNFα activity both in vitro and in vivo (see Example 4). Moreover, at least some of the antibodies of the invention, such as D2E7. can neutralize TNFα activity from other species. Accordingly, the antibodies and antibody portions of the invention can be used to inhibit TNFα activity, e.g., in a cell culture containing hTNFα. in human subjects or in other mammalian subjects having TNFαs with which an antibody of the invention cross-reacts (e.g. chimpanzee, baboon, marmoset, cynomolgus and rhesus, pig or mouse). In one embodiment, the invention provides a method for inhibiting TNFα activity comprising contacting TNFα with an antibody or antibody portion of the invention such that TNFα activity is inhibited. Preferably, the TNFα is human TNFα. For example, in a cell culture containing, or suspected of containing hTNFα, an antibody or antibody portion of the invention can be added to the culture medium to inhibit hTNFα activity in the culture.

In another embodiment, the invention provides a method for inhibiting TNFα activity in a subject suffering from a disorder in which TNFα activity is detrimental. TNFα has been implicated in the pathophysiology of a wide variety of disorders (see e.g., Moeller, A., et al. (1990) *Cytokine* 2:162–169; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A.). The invention provides methods for TNFα activity in a subject suffering from such a disorder, which method comprises administering to the subject an antibody or antibody portion of the invention such that TNFα activity in the subject is inhibited. Preferably, the TNFα is human TNFα and the subject is a human subject. Alternatively, the subject can be a mammal expressing a TNFα with which an antibody of the invention cross-reacts. Still further the subject can be a mammal into which has been introduced hTNFα (e.g., by administration of hTNFα or by expression of an hTNFα transgene). An antibody of the invention can be administered to a human subject for therapeutic purposes (discussed further below). Moreover, an antibody of the invention can be administered to a non-human mammal expressing a TNFα with which the antibody cross-reacts (e.g., a primate, pig or mouse) for veterinary purposes or as an animal model of human disease. Regarding the latter, such animal models may be useful for evaluating the therapeutic efficacy of antibodies of the invention (e.g., testing of dosages and time courses of administration).

As used herein, the term "a disorder in which TNFα activity is detrimental" is intended to include diseases and other disorders in which the presence of TNFα in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, a disorder in which TNFα activity is detrimental is a disorder in which inhibition of TNFα activity is expected to alleviate the symptoms and/or progression of the disorder. Such disorders may be evidenced, for example, by an increase in the concentration of TNFα in a biological fluid of a subject suffering from the disorder (e.g., an increase in the concentration of TNFα in serum, plasma, synovial fluid, etc. of the subject), which can be detected, for example, using an anti-TNFα antibody as described above. There are numerous examples of disorders in which TNFα activity is detrimental. The use of the antibodies and antibody portions of the invention in the treatment of specific disorders is discussed further below:

A. Sepsis

Tumor necrosis factor has an established role in the pathophysiology of sepsis, with biological effects that include hypotension, myocardial suppression, vascular leakage syndrome, organ necrosis, stimulation of the release of toxic secondary mediators and activation of the clotting cascade (see e.g., Moeller, A.. et al. (1990) *Cytokine* 2:162–169; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B1 by Moeller, A.; Tracey, K. J. and Cerami, A. (1994) *Annu. Rev. Med.* 45:491–503; Russell, D and Thompson, R. C. (1993) *Curr. Opin. Biotech.* 4:714–721). Accordingly, the human antibodies, and antibody portions, of the invention can be used to treat sepsis in any of its clinical settings, including septic shock, endotoxic shock, gram negative sepsis and toxic shock syndrome.

Furthermore, to treat sepsis, an anti-hTNFα antibody, or antibody portion, of the invention can be coadministered with one or more additional therapeutic agents that may further alleviate sepsis, such as an interleukin- I inhibitor (such as those described in PCT Publication Nos. WO 92/16221 and WO 92/17583), the cytokine interleukin-6 (see e.g., PCT Publication No. WO 93/11793) or an antagonist of platelet activating factor (see e.g., European Patent Application Publication No. EP 374 510). Other combination therapies for the treatment of sepsis are discussed further in subsection Ill.

Additionally, in a preferred embodiment, an anti-TNFα antibody or antibody portion of the invention is administered to a human subject within a subgroup of sepsis patients having a serum or plasma concentration of IL-6 above 500 pg/ml. and more preferably 1000 μg/ml, at the time of treatment (see PCT Publication No. WO 95/20978 by Daum, L., et al.).

B. Autoimmune Diseases

Tumor necrosis factor has been implicated in playing a role in the pathophysiology of a variety of autoimmune diseases. For example, TNFα has been implicated in activating tissue inflammation and causing joint destruction in rheumatoid arthritis (see e.g., Moeller, A., et al. (1990) *Cytokine* 2:162–169; U.S. Pat. No. 5,231,024 to Moeller et al.; European Patent Publication No. 260 610 B 1 by Moeller, A.; Tracey and Cerami, supra; Arend, W. P. and Dayer, J-M. (1995) *Arth. Rheum.* 38:151–160; Fava, R. A., et al. (1993) *Clin. Exp. Immunol.* 94:261–266). TNFα also has been implicated in promoting the death of islet cells and in mediating insulin resistance in diabetes (see e.g., Tracey and Cerami, supra; PCT Publication No. WO 94/08609). TNFα also has been implicated in mediating cytotoxicity to oligodendrocytes and induction of inflammatory plaques in multiple sclerosis (see e.g, Tracey and Cerami, supra). Chimeric and humanized murine anti-hTNFα antibodies have undergone clinical testing for treatment of rheumatoid arthritis (see e.g., Elliott, M. J., et al. (1994) *Lancet*

344:1125–1127; Elliot, M. J., et al. (1994) *Lancet* 344:1105–1110; Rankin, E. C., et al. (1995) *Br. J. Rheumatol.* 34:334–342).

The human antibodies, and antibody portions of the invention can be used to treat autoimmune diseases, in particular those associated with inflammation, including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis and gouty arthritis, allergy, multiple sclerosis, autoimmune diabetes, autoinunune uveitis and nephrotic syndrome. Typically, the antibody, or antibody portion, is administered systemically, although for certain disorders, local administration of the antibody or antibody portion at a site of inflammation may be beneficial (e.g., local administration in the joints in rheumatoid arthritis or topical application to diabetic ulcers, alone or in combination with a cyclohexanylidene derivative as described in PCT Publication No. WO 93/19751). An antibody, or antibody portion, of the invention also can be administered with one or more additional therapeutic agents useful in the treatment of autoimmune diseases, as discussed further in subsection III.

C. Infectious Diseases

Tumor necrosis factor has been implicated in mediating biological effects observed in a variety of infectious diseases. For example, TNFα has been implicated in mediating brain inflammation and capillary thrombosis and infarction in malaria TNFα also has been implicated in mediating brain inflammation, inducing breakdown of the blood-brain barrier, triggering septic shock syndrome and activating venous infarction in meningitis. TNFα also has been implicated in inducing cachexia, stimulating viral proliferation and mediating central nervous system injury in acquired immune deficiency syndrome (AIDS). Accordingly, the antibodies, and antibody portions, of the invention, can be used in the treatment of infectious diseases, including bacterial meningitis (see e.g., European Patent Application Publication No. EP 585 705), cerebral malaria, AIDS and AIDS-related complex (ARC) (see e.g., European Patent Application Publication No. EP 230 574), as well as cytomegalovirus infection secondary to transplantation (see e.g., Fietze, E., et al. (1994) *Transplantation* 58:675–680). The antibodies, and antibody portions, of the invention, also can be used to alleviate symptoms associated with infectious diseases, including fever and myalgias due to infection (such as influenza) and cachexia secondary to infection (e.g., secondary to AIDS or ARC).

D. Transplantation

Tumor necrosis factor has been implicated as a key mediator of allograft rejection and graft versus host disease (GVHD) and in mediating an adverse reaction that has been observed when the rat antibody OKT3, directed against the T cell receptor CD3 complex, is used to inhibit rejection of renal transplants (see e.g, Eason, J. D., et al. (1995) *Transplantation* 59:300–305; Suthanthiran, M. and Strom, T. B. (1994) *New Engl. J. Med.* 331:365–375). Accordingly, the antibodies, and antibody portions, of the invention, can be used to inhibit transplant rejection, including rejections of allografts and xenografts and to inhibit GVHD. Although the antibody or antibody portion may be used alone, more preferably it is used in combination with one or more other agents that inhibit the immune response against the allograft or inhibit GVHD. For example, in one embodiment, an antibody or antibody portion of the invention is used in combination with OKT3 to inhibit OKT3-induced reactions. In another embodiment, an antibody or antibody portion of the invention is used in combination with one or more antibodies directed at other targets involved in regulating immune responses, such as the cell surface molecules CD25 (interleukin-2 receptor-a), CD11a (LFA-1), CD54 (ICAM-1), CD4, CD45, CD28/CTLA4, CD80 (B7-1) and/or CD86 (B7-2). In yet another embodiment, an antibody or antibody portion of the invention is used in combination with one or more general immunosuppressive agents, such as cyclosporin A or FK506.

E. Malignancy

Tumor necrosis factor has been implicated in inducing cachexia, stimulating tumor growth, enhancing metastatic potential and mediating cytotoxicity in malignancies. Accordingly, the antibodies, and antibody portions, of the invention, can be used in the treatment of malignancies, to inhibit tumor growth or metastasis and/or to alleviate cachexia secondary to malignancy. The antibody, or antibody portion, may be administered systemically or locally to the tumor site.

F. Pulmonary Disorders

Tumor necrosis factor has been implicated in the pathophysiology of adult respiratory distress syndrome (ARDS), including stimulating leukocyte-endothelial activation, directing cytotoxicity to pneumocytes and inducing vascular leakage syndrome. Accordingly, the antibodies, and antibody portions, of the invention, can be used to treat various pulmonary disorders, including adult respiratory distress syndrome (see e.g., PCT Publication No. WO 91/04054), shock lung, chronic pulmonary inflammatory disease, pulmonary sarcoidosis, pulmonary fibrosis and silicosis. The antibody, or antibody portion, may be administered systemically or locally to the lung surface, for example as an aerosol. An antibody, or antibody portion, of the invention also can be administered with one or more additional therapeutic agents useful in the treatment of pulmonary disorders, as discussed further in subsection III.

G. Intestinal Disorders

Tumor necrosis factor has been implicated in the pathophysiology of inflammatory bowel disorders (see eg., Tracy, K. J., et al. (1986) *Science* 234:470–474; Sun, X-M., et al. (1988) *J. Clin. Invest* 81:1328–1331; MacDonald, T. T., et al. (1990) *Clin. Exp. Immunol.* 81:301–305). Chimeric murine anti-hTNFα antibodies have undergone clinical testing for treatment of Crohn's disease (van Dullemen, H. M., et al. (1995) *Gastroenterology* 109:129–135). The human antibodies, and antibody portions, of the invention, also can be used to treat intestinal disorders, such as idiopathic inflammatory bowel disease, which includes two syndromes. Crohn's disease and ulcerative colitis. An antibody, or antibody portion, of the invention also can be administered with one or more additional therapeutic agents useful in the treatment of intestinal disorders, as discussed further in subsection III.

H. Cardiac Disorders

The antibodies, and antibody portions, of the invention, also can be used to treat various cardiac disorders, including ischemia of the heart (see e.g., European Patent Application Publication No. EP 453 898) and heart insufficiency (weakness of the heart muscle)(see e.g., PCT Publication No. WO 94/20139).

I. Others

The antibodies, and antibody portions, of the invention, also can be used to treat various other disorders in which TNFα activity is detrimental. Examples of other diseases and disorders in which TNFα activity has been implicated in the pathophysiology, and thus which can be treated using an antibody, or antibody portion, of the invention, include

inflammatory bone disorders and bone resorption disease (see e.g., Bertolini. D. R., et al. (1986) *Nature* 319:516–518; Konig, A.. et al. (1988) *J. Bone Miner. Res.* 3:621–627; Lerner, U. H. and Ohlin, A. (1993) *J. Bone Miner. Res.* 8:147–155; and Shanlar. G. and Stem, P. H. (1993) *Bone* 14:871–876), hepatitis, including alcoholic hepatitis (see e g., McClain, C. J. and Cohen, D. A. (1989) *Hepatology* 9:349–351; Felver, M. E., el al. (1990) *Alcohol. Clin. Exp. Res.* 14:255–259; and Hansen, J., el al. (1994) *Hepatology* 20:461–474), viral hepatitis (Sheron, N., et al. (1991) *J. Hepatol.* 12:241–245; and Hussain, M. J., et al. (1994) *J. Clin. Pathol.* 47:1112–1115), and fulminant hepatitis; coagulation disturbances (see e.g., van der Poll, T., el al. (1990) *N. Engl. J. Med.* 322:1622–1627; and van der Poll, T., et al. (1991) *Prog. Clin. Biol. Res.* 367:55–60), bums (see eg., Giroir, B. P., el al. (1994) *Am. J. Physiol.* 267:H 118–124; and Liu. X. S., el al. (1994) *Burns* 20:40–44), reperfusion injury (see e.g., Scales. W. E., et al. (1994) *Am. J Physiol.* 267:G1122–1127; Serrick, C., el al. (1994) *Transplantation* 58:1158–1162; and Yao, Y. M., et al. (1995) *Resuscitation* 29:157–168), keloid formation (see e.g., McCauley, R. L., et al. (1992) *J. Clin. Immunol.* 12:300–308), scar tissue formation; pyrexia; periodontal disease; obesity and radiation toxicity.

This invention is further illustrated by the following examples which should not be construed as limiting. The contents of all references, patents and published patent applications cited throughout this application are hereby incorporated by reference.

EXAMPLE 1

Kinetic Analysis of Binding of Human Antibodies to hTNFα

Real-time binding interactions between ligand (biotinylated recombinant human TNFα (rhTNJFα) immobilized on a biosensor matrix) and analyte (antibodies in solution) were measured by surface plasmon resonance (SPR) using the BlAcore system (Pharmacia Biosensor, Piscataway, N.J.). The system utilizes the optical properties of SPR to detect alterations in protein concentrations within a dextran biosensor matrix. Proteins are covalently bound to the dextran matrix at known concentrations. Antibodies are injected through the dextran matrix and specific binding between injected antibodies and immobilized ligand results in an increased matrix protein concentration and resultant change in the SPR signal. These changes in SPR signal are recorded as resonance units (RU) and are displayed with respect to time along the y-axis of a sensorgram.

To facilitate immobilization of biotinylated rhTNFα on the biosensor matrix, streptavidin is covalently linked via free amine groups to the dextran matrix by first activating carboxyl groups on the matrix with 100 mM N-hydroxysuccinimide (NHS) and 400 mM N-ethyl-N'-(3-diethylaminopropyl) carbodiimide hydrochloride (EDC). Next, streptavidin is injected across the activated matrix. Thirty-five microliters of streptavidin (25 μg/ml), diluted in sodium acetate, pH 4.5, is injected across the activated biosensor and free amines on the protein are bound directly to the activated carboxyl groups. Unreacted matrix EDC-esters are deactivated by an injection of 1 M ethanolamine. Streptavidin-coupled biosensor chips also are commercially available (Pharmacia BR-1000-16, Pharmacia Biosensor, Piscataway, N.J.).

Biotinylated rhTNFα was prepared by first dissolving 5.0 mg of biotin (D-biotinyl-ε-aminocaproic acid N-hydroxysuccinimide ester; Boehringer Mannheim Cat. No. 1008 960) in 500 oil dimethylsulfoxide to make a 10 mg/ml solution. Ten microliters of biotin was added per ml of rhTNFα (at 2.65 mg/ml) for a 2:1 molar ratio of biotin to rhTNFα. The reaction was mixed gently and incubated for two hours at room temperature in the dark. A PD-10 column, Sephadex G-25M (Pharmacia Catalog No. 17-0851-01) was equilibrated with 25 ml of cold PBS and loaded with 2 ml of rhTNFα-biotin per column. The column was eluted with 10×1 ml cold PBS. Fractions were collected and read at OD280 (1.0 OD=1.25 mg/ml). The appropriate fractions were pooled and stored at −80° C. until use. Biotinylated rhTNFα also is commercially available (R & D Systems Catalog No. FTA00, Minneapolis, Minn.).

Biotinylated rhTNFα to be immobilized on the matrix via streptavidin was diluted in PBS running buffer (Gibco Cat. No. 14190–144, Gibco BRL, Grand Island, N.Y.) supplemented with 0.05% (BIAcore) surfactant P20 (Pharmacia BR-1000-54, Pharmacia Biosensor, Piscataway, N.J.). To determine the capacity of rhTNFα-specific antibodies to bind immobilized rhTNFα, a binding assay was conducted as follows. Aliquots of biotinylated rhTNFα (25 nM; 10 μl aliquots) were injected through the streptavidin-coupled dextran matrix at a flow rate of 5 μl/min. Before injection of the protein and immediately afterward, PBS buffer alone flowed through each flow cell. The net difference in signal between baseline and approximately 30 sec. after completion of biotinylated rhTNFα injection was taken to represent the binding value (approximately 500 RU). Direct rhTNFα-specific antibody binding to immobilized biotinylated rhTNFα was measured. Antibodies (20 μg/ml) were diluted in PBS running buffer and 25 μl aliquots were injected through the immobilized protein matrices at a flow rate of 5 μl/min. Prior to injection of antibody, and immediately afterwards, PBS buffer alone flowed through each flow cell. The net difference in baseline signal after completion of antibody injection was taken to represent the binding value particular sample. Biosensor matrices were regenerated using 100 mM HCl before injection of the next sample. To determine the off rate (K_{off}), on rate (K_{on}), association rate (K_a) and dissociation rate (K_d) constants, BIAcore kinetic evaluation software (version 2.1) was used.

Representative results of D2E7 (IgG4 full-length antibody) binding to biotinylated rhTNFα, as compared to the mouse mAb MAK 195 ($F(ab')_2$ fragment), are shown below in Table 1.

TABLE 1

Binding of D2E7 IgG4 or MAK 195 to Biotinylated rhTNFα

Antibody	[Ab], nM	rhTNFα, bound, RUs	Ab, bound, RUs	rhTNFα/ Ab	K_{off}, sec^{-1}, (Avg)
D2E7	267	373	1215	1.14	8.45×10^{-5}
	133	420	1569	1.30	5.42×10^{-5}
	67	434	1633	1.31	4.75×10^{-5}
	33	450	1532	1.19	4.46×10^{-5}
	17	460	1296	0.98	3.47×10^{-5}
	8	486	936	0.67	2.63×10^{-5}
	4	489	536	0.38	2.17×10^{-5}
	2	470	244	0.18	3.68×10^{-5}
					(4.38×10^{-5})
MAK 195	400	375	881	1.20	5.38×10^{-5}
	200	400	1080	1.38	4.54×10^{-5}
	100	419	1141	1.39	3.54×10^{-5}
	50	427	1106	1.32	3.67×10^{-5}
	25	446	957	1.09	4.41×10^{-5}

TABLE 1-continued

Binding of D2E7 IgG4 or MAK 195 to Biotinylated rhTNFα

Antibody	[Ab], nM	rhTNFα, bound, RUs	Ab, bound, RUs	rhTNFα/ Ab	K_{off}, sec^{-1}, (Avg)
	13	464	708	0.78	3.66×10^{-5}
	6	474	433	0.47	7.37×10^{-5}
	3	451	231	0.26	6.95×10^{-5}
					(4.94×10^{-5})

In a second series of experiments, the molecular kinetic interactions between an IgG1 full-length from of D2E7 and biotinylated rhTNF was quantitatively analyzed using BIAcore technology, as described above, and kinetic rate constants were derived, summarized below in Tables 2, 3 and 4.

TABLE 2

Apparent dissociation rate constants of the interaction between D2E7 and biotinylated rhTNF

Experiment	K_d (s^{-1})
1	9.58×10^{-5}
2	9.26×10^{-5}
3	7.60×10^{-5}
Average	$8.81 \pm 1.06 \times 10^{-5}$

TABLE 3

Apparent association rate constants of the interaction between D2E7 and biotinylated rhTNF

Experiment	K_a (M^{-1}, s^{-1})
1	1.33×10^5
2	1.05×10^5
3	3.36×10^5
Average	$1.91 \pm 1.26 \times 10^5$

TABLE 4

Apparent kinetic reate and affinity constants of D2E7 and biotinylated rhTNF

Experiment	K_a (M^{-1}, s^{-1})	K_d (s^{-1})	K_d (M)
1	1.33×10^5	9.58×10^{-5}	7.20×10^{-10}
2	1.05×10^5	9.26×10^{-5}	8.82×10^{-10}
3	3.36×10^5	7.60×10^{-5}	2.26×10^{-10}
Average	$1.91 \pm 1.26 \times 10^5$	$8.81 \pm 1.06 \times 10^{-5}$	$6.09 \pm 3.42 \times 10^{-10}$

Dissociation and association rate constants were calculated by analyzing the dissociation and association regions of the sensorgrams by BIA analysis software. Conventional chemical reaction kinetics were assumed for the interaction between D2E7 and biotinylated rhTNF molecule: a zero order dissociation and first order association kinetics. For the sake of analysis, interaction only between one arm of the bivalent D2E7 antibody and one unit of the trimeric biotinylated rhTNF was considered in choosing molecular models for the analysis of the kinetic data. Three independent experiments were performed and the results were analyzed separately. The average apparent dissociation rate constant (k_d) of the interaction between D2E7 and biotinylated rhTNF was $8.81 \pm 1.06 \times 10^{-5}$ s^{-1}, and the average apparent association rate constant, k_a was $1.91 \pm 1.26 \times 10^5$ M^{-1} s^{-1}. The apparent intrinsic dissociation constant (K_d) was then calculated by the formula: $K_d = k_d/k_a$. Thus, the mean K_d of D2E7 antibody for rhTNF derived from kinetic parameters was $6.09 \pm 3.42 \times 10^{-10}$ M. Minor differences in the kinetic values for the IgG1 form of D2E7 (presented in Tables 2, 3 and 4) and the IgG4 form of D2E7 (presented in Table 1 and in Examples 2 and 3) are not thought to be true differences resulting from the presence of either an IgG1 or an IgG4 constant regions but rather are thought to be attributable to more accurate antibody concentration measurements used for the IgG1 kinetic analysis. Accoringly, the kinetic values for the IgG1 form of D2E7 presented herein are thought to be the most accurate kinetic parameters for the D2E7 antibody.

EXAMPLE 2

Alanine Scanning Mutagenesis of D2E7 CDR3 Domains

A series of single alanine mutations were introduced by standard methods along the CDR3 domain of the D2E7 VL and the D2E7 VH regions. The light chain mutations are illustrated in FIG. **1**B (LD2E7*.A1, LD2E7*.A3, LD2E7*.A4, LD2E7*.A5, LD2E7*.A7 and LD2E7*.A8, having an alanine mutation at position 1, 3, 4, 5, 7 or 8, respectively, of the D2E7 VL CDR3 domain). The heavy chain mutations are illustrated in FIG. **2**B (HD2E7*.A1, HD2E7*.A2, HD2E7*.A3, HD2E7*.A4, HD2E7*.A5, HD2E7*.A6, HD2E7*.A7, HD2E7*.A8 and HD2E7*.A9, having an alanine mutation at position 2, 3, 4, 5, 6, 8, 9, 10 or 11, respectively, of the D2E7 VH CDR3 domain). The kinetics of rhTNFα interaction with an antibody composed of wild-type D2E7 VL and VH was compared to that of antibodies composed of 1) a wild-type D2E7 VL paired with an alanine-substituted D2E7 VH; 2) a wild-type D2E7 VH paired with an alanine-substituted D2E7 VL; or 3) an alanine-substituted D2E7 VL paired with an alanine-substituted D2E7 VH. All antibodies were tested as full-length, IgG4 molecules.

Kinetics of interaction of antibodies with rhTNFα was determined by surface plasmon resonance as described in Example 1. The K_{off} rates for the different VH/VL pairs are summarized below in Table 5:

TABLE 5

Binding of D2E7 Alanine-Scan Mutants to Biotinylated rhTNFα

VH	VL	K_{off} (sec^{-1})
D2E7 VH	D2E7 VL	9.65×10^{-5}
HD2E7*.A1	D2E7 VL	1.4×10^{-4}
HD2E7*.A2	D2E7 VL	4.6×10^{-4}
HD2E7*.A3	D2E7 VL	8.15×10^{-4}
HD2E7*.A4	D2E7 VL	1.8×10^{-4}
HD2E7*.A5	D2E7 VL	2.35×10^{-4}
HD2E7*.A6	D2E7 VL	2.9×10^{-4}
HD2E7*.A7	S2E7 VL	1.0×10^{-4}
HD2E7*.A8	D2E7 VL	3.1×10^{-4}
HD2E7*.A9	D2E7 VL	8.1×10^{-4}
D2E7 VH	LD2E7*.A1	6.6×10^{-5}
D2E7 VH	LD2E7*.A3	NOT DETECTABLE
D2E7 VH	LD2E7*.A4	1.75×10^{-4}
D2E7 VH	LD2E7*.A5	1.8×10^{-4}
D2E7 VH	LD2E7*.A7	1.4×10^{-4}
D2E7 VH	LD2E7*.A8	3.65×10^{-4}
HD2E7*.A9	LD2E7*.A1	1.05×10^{-4}

These results demonstrate that the majority of positions of the CDR3 domains of the D2E7 VL region and VH region are amenable to substitution with a single alanine residue.

Substitution of a single alanine at position 1, 4, 5, or 7 of the D2E7 VL CDR3 domain or at position 2, 5, 6, 8, 9 or 10 of the D2E7 VH CDR3 domain does not significantly affect the off rate of hTNFα binding as compared to the wild-type parental D2E7 antibody. Substitution of alanine at position 8 of the D2E7 VL CDR3 or at position 3 of the D2E7 VH CDR3 gives a 4-fold faster K_{off} and an alanine substitution at position 4 or 11 of D2E7 VH CDR3 gives an 8-fold faster K_{off}, indicating that these positions are more critical for binding to hTNFα. However, a single alanine substitution at position 1, 4, 5, 7 or 8 of the D2E7 VL CDR3 domain or at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 of the D2E7 VH CDR3 domain still results in an anti-hTNFα antibody having a K_{off} of 1×10^{-3} sec^{-1} or less.

EXAMPLE 3

Binding Analysis of D2E7-Related Antibodies

A series of antibodies related in sequence to D2E7 were analyzed for their binding to rhTNFα, as compared to D2E7, by surface plasmon resonance as described in Example 1. The amino acid sequences of the VL regions tested are shown in FIGS. **1A** and **1B**. The amino acid sequences of the VH regions tested are shown in FIGS. **2A** and **2B**. The K_{off} rates for various VH/VL pairs (in the indicated format, either as a full-length IgG1 or IgG4 antibody or as a scFv) are summarized below in Table 6:

TABLE 6

Binding of D2E7-Related Antibodies to Biotinylated rrhTNFα

VH	VL	Format	K_{off} (sec^{-1})
D2E7 VH	D2E7 VL	IgG1/IgG4	9.65×10^{-5}
VH1-D2	LOE7	IgG1/IgG4	7.7×10^{-5}
VH1-D2	LOE7	scFv	4.6×10^{-4}
VH1-D2.N	LOE7.T	IgG4	2.1×10^{-5}
VH1-D2.Y	LOE7.A	IgG4	2.7×10^{-5}
VH1-D2.N	LOE7.A	IgG4	3.2×10^{-5}
VH1-D2	EP B12	scFv	8.0×10^{-4}
VH1-D2	2SD4 VL	scFv	1.94×10^{-3}
3C-H2	LOE7	scFv	1.5×10^{-3}
2SD4 VH	LOE7	scFv	6.07×10^{-3}
2SD4 VH	2SD4 VL	scFv	1.37×10^{-2}
VH1A11	2SD4 VL	scFv	1.34×10^{-2}
VH1B12	2SD4 VL	scFv	1.01×10^{-2}
VH1B11	2SD4 VL	scFv	9.8×10^{-3}
VH1E4	2SD4 VL	scFv	1.59×10^{-2}
VH1F6	2SD4 VL	scFv	2.29×10^{-2}
VH1D8	2SD4 VL	scFv	9.5×10^{-3}
VH1G1	2SD4 VL	scFv	2.14×10^{-2}
2SD4 VH	EP B12	scFv	6.7×10^{-3}
2SD4 VH	VL10E4	scFv	9.6×10^{-3}
2SD4 VH	VL100A9	scFv	1.33×10^{-2}
2SD4 VH	VL100D2	scFv	1.41×10^{-2}
2SD4 VH	VL10F4	scFv	1.11×10^{-2}
2SD4 VH	VLLOE5	scFv	1.16×10^{-2}
2SD4 VH	VLL0F9	scFv	6.09×10^{-3}
2SD4 VH	VLL0F10	scFv	1.34×10^{-2}
2SD4 VH	VLLOG7	scFv	1.56×10^{-2}
2SD4 VH	VLLOG9	scFv	1.46×10^{-2}
2SD4 VH	VLLOH1	scFv	1.17×10^{-2}
2SD4 VH	VLLOH10	scFv	1.12×10^{-2}
2SD4 VH	VL1B7	scFv	1.3×10^{-2}
2SD4 VH	VL1C1	scFv	1.36×10^{-2}
2SD4 VH	VL1C7	scFv	2.0×10^{-2}
2SD4 VH	VL0.1F4	scFv	1.76×10^{-2}
2SD4 VH	VL0.1H8	scFv	1.14×10^{-2}

The slow off rates (i.e., $K_{off} \leqq 1\times10^{-4}$ sec^{-1}) for full-length antibodies (i.e., IgG format) having a VL selected from D2E7, LOE7, LOE7.T and LOE7.A, which have either a threonine or an alanine at position 9, indicate that position 9 of the D2E7 VL CDR3 can be occupied by either of these two residues without substantially affecting the K_{off}. Accordingly, a consensus motif for the D2E7 VL CDR3 comprises the amino acid sequence: Q-R-Y-N-R-A-P-Y-(T/A) (SEQ ID NO: 3). Furthermore, the slow off rates (i.e., $K_{off} \leqq 1\times10^{-4}$ sec^{-1}) for antibodies having a VH selected from D2E7, VH1-D2.N and VH1-D2.Y, which have either a tyrosine or an asparagine at position 12, indicate that position 12 of the D2E7 VH CDR3 can be occupied by either of these two residues without substantially affecting the Koff. Accordingly, a consensus motif for the D2E7 VH CDR3 comprises the amino acid sequence: V-S-Y-L-S-T-A-S-S-L-D-(Y/N) (SEQ ID NO: 4).

The results shown in Table 6 demonstrate that, in scFv format, antibodies containing the 2SD4 VL or VH CDR3 region exhibit a faster K_{off} (i.e., $K_{off} \geqq 1\times10^{-3}$ sec^{-1}) as compared to antibodies containing the D2E7 VL or VH CDR3 region. Within the VL CDR3, 2SD4 differs from D2E7 at positions 2, 5 and 9. As discussed above, however, position 9 may be occupied by Ala (as in 2SD4) or Thr (as in D2E7) without substantially affecting the K_{off}. Thus, by comparison of 2SD4 and D2E7, positions 2 and 5 of the D2E7 VL CDR3, both arginines, can be identified as being critical for the association of the antibody with hTNFα. These residues could be directly involved as contact residues in the antibody binding site or could contribute critically to maintaining the scaffolding architecture of the antibody molecule in this region. Regarding the importance of position 2, replacement of Arg (in LOE7, which has the same VL CDR3 as D2E7) with Lys (in EP B12) accelerates the off rate by a factor of two. Regarding the importance of position 5, replacement of Arg (in D2E7) with Ala (in LD2E7*.A5), as described in Example 2, also accelerates the off rate two-fold. Furthermore, without either Arg at positions 2 and 5 (in 2SD4), the off rate is five-fold faster. However, it should be noted that although position 5 is important for improved binding to hTNFα, a change at this position can be negated by changes at other positions, as seen in VLLOE4, VLLOH1 or VL0.1H8.

Within the VH CDR3, 2SD4 differs from D2E7 at positions 1, 7 and 12. As discussed above, however, position 12 may be occupied by Asn (as in 2SD4) or Tyr (as in D2E7) without substantially affecting the K_{off}. Thus, by comparison of 2SD4 and D2E7, positions 1 and 7 of the D2E7 VH CDR3 can be identified as being critical for binding to hTNFα. As discussed above, these residues could be directly involved as contact residues in the antibody binding site or could contribute critically to maintaining the scaffolding architecture of the antibody molecule in this region. Both positions are important for binding to hTNFα since when the 3C-H2 VH CDR3 (which has a valine to alanine change at position 1 with respect to the D2E7 VH CDR3) is used, the scFv has a 3-fold faster off rate than when the D2E7 VH CDR3 is used but this off rate is still four times slower than when the 2SD4 VH CDR3 is used (which has changes at both positions 1 and 7 with respect to the D2E7 VH CDR3).

EXAMPLE 4

Functional Activity of D2E7

To examine the functional activity of D2E7, the antibody was used in several assays that measure the ability of the antibody to inhibit hTNFα activity, either in vitro or in vivo.

A. Neutralization of TNFα-Induced Cytotoxicity in L929 Cells

Human recombinant TNFα (rhTNFα) causes cell cytotoxicity to murine L929 cells after an incubation period of 18–24 hours. Human anti-hTNFα antibodies were evaluated in L929 assays by coincubation of antibodies with rhTNFα and the cells as follows. A 96-well microtiter plate contain-

ing 100 μl of anti-hTNFα Abs was serially diluted ⅓ down the plate in duplicates using RPMI medium containing 10% fetal bovine serum (FBS). Fifty microliters of rhTNFα was added for a final concentration of 500 pg/ml in each sample well. The plates were then incubated for 30 minutes at room temperature. Next, 50 μl of TNFα-sensitive L929 mouse fibroblasts cells were added for a final concentration of 5×10^4 cells per well, including 1 μg/ml Actinomycin-D. Controls included medium plus cells and rhTNFα plus cells. These controls, and a TNFα standard curve, ranging from 2 ng/ml to 8.2 pg/ml, were used to determine the quality of the assay and provide a window of neutralization. The plates were then incubated overnight (18–24 hours) at 37° C. in 5% CO_2.

One hundred microliters of medium was removed from each well and 50 μl of 5 mg/ml 3,(4,4-dimethylthiazol-2-yl)2,5-diphenyl-tetrazolium bromide (MTT; commercially available from Sigma Chemical Co., St. Louis, Mo.) in PBS was added. The plates were then incubated for 4 hours at 37° C. Fifty microliters of 20% sodium dodecyl sulfate (SDS) was then added to each well and the plates were incubated overnight at 37° C. The optical density at 570/630 nm was measured, curves were plotted for each sample and IC_{50}s were determined by standard methods.

Representative results for human antibodies having various VL and VH pairs, as compared to the murine MAK 195 mAb, are shown in FIG. **3** and in Table 7 below.

TABLE 7

Neutralization of TNFα-Induced L929 Cytotoxicity

VH	VL	Structure	IC_{50}, M
D2E7	D2E7	scFv	1.1×10^{-10}
D2E7	D2E7	IgG4	4.7×10^{-11}
2SD4	2SD4	scFv/IgG1/IgG4	3.0×10^{-7}
2SD4	LOE7	scFv	4.3×10^{-8}
VH1-D2	2SD4	scFv	1.0×10^{-8}
VH1-D2	LOE7	scFv/IgG1/IgG4	3.4×10^{-10}
VH1.D2.Y	LOE7.T	IgG4	8.1×10^{-11}
VH1-D2.N	LOE7.T	IgG4	1.3×10^{-10}
VH1-D2.Y	LOE7.A	IgG4	2.8×10^{-11}
VH1-D2.N	LOE7.A	IgG4	6.2×10^{-11}
MAK 195	MAK 195	scFv	1.9×10^{-8}
MAK 195	MAK195	$F(ab')_2$	6.2×10^{-11}

The results in FIG. **3** and Table 7 demonstrate that the D2E7 human anti-hTNFα antibody, and various D2E7-related antibodies, neutralize TNFα-induced L929 cytotoxicity with a capacity approximately equivalent to that of the murine anti-hTNFα mAb MAK 195.

In another series of experiments, the ability of the IgG1 form of D2E7 to neutralize TNFα-induced L929 cytotoxicity was examined as described above. The results from three independent experiments, and the average thereof, are summarized below in Table 8:

TABLE 8

Neutralization of TNFα-Induced L929 Cytotoxocity by D2E7 IgG1

Experiment	IC_{50} [M]
1	1.26×10^{-10}
2	1.33×10^{-10}
3	1.15×10^{-10}
Average	$1.25 \times 0.01 \times 10^{-10}$

This series of experiments confirmed that D2E7, in the full-length IgG1 form, neutralizes TNFα-induced L929 cytotoxicity with an average IC_{50} [M] of $1.25\pm0.01\times10^{-10}$.

B. Inhibition of TNFα Binding to TNFα Receptors on U-937 Cells

The ability of human anti-hTNFα antibodies to inhibit the binding of hTNFα to hTNFα receptors on the surface of cells was examined using the U-937 cell line (ATCC No. CRL 1593), a human histiocytic cell line that expresses hTNFα receptors. U-937 cells were grown in RPMI 1640 medium supplemented with 10% fetal bovine serum (Hyclone A-1111, Hyclone Laboratories, Logan, Utah), L-glutamine (4 nM), HEPES buffer solution (10 mM), penicillin (100 μg/ml) and streptomycin (100 μg/ml). To examine the activity of full-length IgG antibodies, U-937 cells were preincubated with PBS supplemented with 1 mg/ml of human IgG (Sigma 1-4506, Sigma Chemical Co., St. Louis, Mo.) for 45 minutes on ice and then cells were washed three times with binding buffer. For the receptor binding assay, U-937 cells (5×10^6 cells/well) were incubated in a binding buffer (PBS supplemented with 0.2% bovine serum albumin) in 96-well microtiter plates (Costar 3799, Costar Corp., Cambridge, Mass.) together with ^{125}I-labeled rhTNFα (3×10^{-10} M; 25 μCi/ml; obtained from NEN Research Products, Wilmington, Del.), with or without anti-hTNFα antibodies, in a total volume of 0.2 ml. The plates were incubated on ice for 1.5 hours. Then, 75 μl of each sample was transferred to 1.0 ml test tubes (Sarstedt 72.700, Sarstedt Corp., Princeton, N.J.) containing dibutylphthalate (Sigma D-2270, Sigma Chemical Co., St. Louis, Mo.) and dinonylphthalate (ICN 210733, ICN, Irvine, Calif.). The test tubes contained a 300 μl mixture of dibutylphthalate and dinonylphthalate, 2:1 volume ratio, respectively. Free (i.e., unbound) ^{125}I-labeled rhTNFα was removed by microcentrifugation for five minutes. Then, each test tube end containing a cell pellet was cut with the aid of a microtube scissor (Bel-Art 210180001, Bel-Art Products, Pequannock, N.J.). The cell pellet contains ^{125}I-labeled rhTNFα bound to the p60 or p80 TNFα receptor, whereas the aqueous phase above the oil mixture contains excess free ^{125}I-labeled rhTNFα. All cell pellets were collected in a counting tube (Falcon 2052, Becton Dickinson Labware, Lincoln Park, N.J.) and counted in a scintillation counter.

Representative results are shown in FIG. **4**. The IC_{50} value for D2E7 inhibition of hTNFα binding to hTNFα receptors on U-937 cells is approximately 3×10^{-10} M in these experiments. These results demonstrate that the D2E7 human anti-hTNFα antibody inhibits rhTNFα binding to hTNFα receptors on U-937 cells at concentrations approximately equivalent to that of the murine anti-hTNFα mAb MAK 195.

In another series of experiments, the ability of the IgG1 form of D2E7 to inhibit rhTNFα binding to hTNFα receptors on U-937 cells was examined as described above. The results from three independent experiments, and the average thereof, are summarized below in Table 9:

TABLE 9

Inhibition of TNF Receptor Binding on U-937 Cells by D2E7 IgG1

Experiment	IC_{50} [M]
1	1.70×10^{-10}
2	1.49×10^{-10}
3	1.50×10^{-10}
Average	$1.56 \pm 0.12 \times 10^{-10}$

This series of experiments confirmed that D2E7, in the full-length IgG1 form, inhibits TNF receptor binding on U-937 cells with an average IC_{50} [M] of $1.56\pm0.12\times10^{-10}$.

To investigate the inhibitory potency of D2E7 in the binding of ^{125}I-rhTNF binding to individual p55 and p75

receptors, a solid phase radioimmunoassay was performed. To measure the IC_{50} values of D2E7 for separate TNF receptors, varying concentrations of the antibody were incubated with 3×10^{-10} concentration of ^{125}I-rhTNF. The mixture was then tested on separate plates containing either the p55 or the p75 TNF receptors in a dose dependent manner. The results are summarized below in Table 10:

TABLE 10

Inhibition of TNF Receptor Binding to p55 and p75 TNFR by D2E7 IgG1

	IC_{50} [M]	
Reagent	p55 TNFR	p75 TNFR
D2E7	1.47×10^{-9}	1.26×10^{-9}
rhTNF	2.31×10^{-9}	2.70×10^{-9}

Inhibition of ^{125}I-rhTNF binding to the p55 and p75 TNF receptors on U937 cells by D2E7 followed a simple sigmoidal curve, indicating similar IC_{50} values for each receptor. In the solid phase radioimmunoassay (RIA) experiments with recombinant TNF receptors, IC_{50} values for inhibition of ^{125}I-rhTNF binding to the p55 and the p75 receptors by D2E7 were calculated as 1.47×10^{-9} and 1.26×10^{-9} M, respectively. The decrease in IC_{50} values in the solid phase was probably due to higher density of receptors in the RIA format as unlabeled rhTNF also inhibited with similar IC_{50} values. The IC_{50} values for inhibition of ^{125}I-rhTNF binding to the p55 and the p75 receptors by unlabeled rhTNF were 2.31×10^{-9} and 2.70×10^{-9} M, respectively

C. Inhibition of ELAM-1 Expression on HUVEC

Human umbilical vein endothelial cells (HUVEC) can be induced to express endothelial cell leukocyte adhesion molecule 1 (ELAM-1) on their cell-surface by treatment with rhTNFα, which can be detected by reacting rhTNFα-treated HUVEC with an mouse anti-human ELAM-1 antibody. The ability of human anti-hTNFα antibodies to inhibit this TNFα-induced expression of ELAM-1 on HUVEC was examined as follows: HUVEC (ATCC No. CRL 1730) were plated in 96-well plates (5×10^4 cells/well) and incubated overnight at 37° C. The following day, serial dilutions of human anti-hTNFα antibody (1:10) were prepared in a microtiter plate, starting with 20–100 μg/ml of antibody. A stock solution of rhTNFα was prepared at 4.5 ng/ml, aliquots of rhTNFα were added to each antibody-containing well and the contents were mixed well. Controls included medium alone, medium plus anti-hTNFα antibody and medium plus rhTNFα. The HUVEC plates were removed from their overnight incubation at 37° C. and the medium gently aspirated from each well. Two hundred microliters of the antibody-rhTNFα mixture were transferred to each well of the HUVEC plates. The HUVEC plates were then further incubated at 37° C. for 4 hours. Next, a murine anti-ELAM-1 antibody stock was diluted 1:1000 in RPMI. The medium in each well of the HUVEC plate was gently aspirated, 50 μl/well of the anti-ELAM-1 antibody solution was added and the HUVEC plates were incubated 60 minutes at room temperature. An ^{125}I-labeled anti-mouse Ig antibody solution was prepared in RPMI (approximately 50,000 cpm in 50 μl). The medium in each well of the HUVEC plates was gently aspirated, the wells were washed twice with RPMI and 50 μl of the ^{125}I-labeled anti-mouse Ig solution was added to each well. The plates were incubated for one hour at room temperature and then each well was washed three times with RPMI. One hundred eighty microliters of 5% SDS was added to each well to lyse the cells. The cell lysate from each well was then transferred to a tube and counted in a scintillation counter.

Representative results are shown in FIG. **5**. The IC_{50} value for D2E7 inhibition of hTNFα-induced expression of ELAM-1 on HUVEC is approximately 6×10^{-11} M in these experiments. These results demonstrate that the D2E7 human anti-hTNFα antibody inhibits the hTNFα-induced expression of ELAM-1 on HUVEC at concentrations approximately equivalent to that of the murine anti-hTNFα mAb MAK 195.

In another series of experiments, the ability of the IgG I form of D2E7 to inhibit hTNFα-induced expression of ELAM-1 on HUVEC was examined as described above. The results from three independent experiments, and the average thereof, are summarized below in Table 11:

TABLE 11

Inhibition of TNFα-Inducted ELAM-1 Expression by D2E7 IgG1 Receptor

Experiment	IC_{50} [M]
1	1.95×10^{-10}
2	1.69×10^{-10}
3	1.90×10^{-10}
Average	$1.85 \pm 0.14 \times 10^{-10}$

This series of experiments confirmed that D2E7, in the full-length IgG1 form inhibits TNFα-induced ELAM-1 expression on HUVEC with an average IC_{50} [M] of $1.85\pm0.14\times10^{-10}$.

The neutralization potency of D2E7 IgG1 was also examined for the rhTNF induced expression of two other adhesion molecules, ICAM-1 and VCAM-1. Since the rhTNF titration curve for ICAM-1 expression at 16 hours was very similar to the curve of ELAM-1 expression, the same concentration of rhTNF was used in the antibody neutralization experiments. The HUVEC were incubated with rhTNF in the presence of varying concentrations of D2E7 in a 37° C. CO_2 incubator for 16 hours, and the ICAM-1 expression was measured by mouse anti-ICAM-1 antibody followed by ^{125}I-labeled sheep anti-mouse antibody. Two independent experiments were performed and the IC_{50} values were calculated. An unrelated human IgG1 antibody did not inhibit the ICAM-1 expression.

The experimental procedure to test inhibition of VCAM-1 expression was the same as the procedure for ELAM-1 expression, except anti-VCAM-1 MAb was used instead of anti-ELAM-1 MAb. Three independent experiments were performed and the IC_{50} values were calculated. An unrelated human IgG1 antibody did not inhibit VCAM-1 expression.

The results are summarized below in Table 12:

TABLE 12

Inhibition of ICAM-1 and VCAM-1 Expression by D2E7 IgG1

ICAM-1 Inhibition		IC_{50} [M]	
Experiment	IC_{50} [M]	Experiment	IC_{50} [M]
1	1.84×10^{-10}	1	1.03×10^{-10}
2	2.49×10^{-10}	2	9.26×10^{-11}
		3	1.06×10^{-10}
Average	$2.17 \pm 0.46 \times 10^{-10}$	Average	$1.01 \pm 0.01 \times 10^{-10}$

These experiments demonstrate that treatment of primary human umbilical vein endothelial cells with rhTNF led to optimum expression of adhesion molecules: ELAM-1 and VCAM-1 at four hours, and the maximum up-regulated expression of ICAM-1 at 16 hours. D2E7 was able to inhibit the expression of the three adhesion molecules in a dose

dependent manner. The IC_{50} values for the inhibition of ELAM-1, ICAM-1 and VCAM-1 were 1.85×10^{-10}, 2.17×10^{-10} and 1.01×10^{-10} M, respectively. These values are very similar, indicating similar requirements for the dose of rhTNF activation signal to induce ELAM-1, ICAM-1 and VCAM-1 expression. Interestingly, D2E7 was similarly effective in the longer inhibition assay of the the ICAM-1 expression. The ICAM-1 inhibition assay required 16 hours of co-incubation of rhTNF and D2E7 with HUVEC as opposed to 4 hours required for the ELAM-1 and the VCAM-1 inhibition assays. Since D2E7 has a slow off-rate for rhTNF, it is conceivable that during the 16 hour co-incubation period there was no significant competition by the TNF receptors on the HUVEC.

D. In Vivo Neutralization of hTNFα

Three different in vivo systems were used to demonstrate that D2E7 is effective at inhibiting hTNFα activity in vivo.

I. Inhibition of TNF-Induced Lethality in D-Galactosamine-Sensitized Mice

Injection of recombinant human TNFα (rhTNFα) to D-galactosamine sensitized mice causes lethality within a 24 hour time period. TNFα neutralizing agents have been shown to prevent lethality in this model. To examine the ability of human anti-hTNFα antibodies to neutralize hTNFα in vivo in this model, C57B1/6 mice were injected with varying concentrations of D2E7-IgG1, or a control protein, in PBS intraperitoneally (i.p.). Mice were challenged 30 minutes later with 1 μg of rhTNFα and 20 mg of D-galactosamine in PBS i.p., and observed 24 hours later. These amount of rhTNFα and D-galactosamine were previously determined to achieve 80–90% lethality in these mice.

Representative results, depicted as a bar graph of % survival versus antibody concentration, are shown in FIG. **6**. The black bars represent D2E7, whereas the hatched bars represent MAK 195. Injection of 2.5–25 μg of D2E7 antibody per mouse protected the animals from TNFα-induced lethality. The ED_{50} value is approximately 1–2.5 μg/mouse. The positive control antibody, MAK 195, was similar in its protective ability. Injection of D2E7 in the absence of rhTNFα did not have any detrimental effect on the mice. Injection of a non-specific human IgG1 antibody did not offer any protection from TNFα-induced lethality.

In a second experiment, forty-nine mice were divided into 7 equal groups. Each group received varying doses of D2E7 thirty minutes prior to receiving an LD_{80} dose of rhTNF/D-galactosamine mixture (1.0 μg rhTNF and 20 mg D-galactosamine per mouse). Control group 7 received normal human IgG1 kappa antibody at 25 μg/mouse dose. The mice were examined 24 hours later. Survival for each group is summarized below in Table 13.

TABLE 13

24 Hour Survival After Treatment with D2E7

Group	Survival (alive/total)	Survival (%)
1 (no antibody)	0/7	0
2 (1 μg)	1/7	14
3 (2.6 μg)	5/7	71
4 (5.2 μg)	6/7	86
5 (26 μg)	6/7	86
6 (26 μg; no rhTNF)	7/7	100
7 (25 μg Hu IgG1)	1/7	14

II. Inhibition of TNF-Induced Rabbit Pyrexia

The efficacy of D2E7 in inhibiting rhTNF-induced pyrexia response in rabbits was examined. Groups of three NZW female rabbits weighing approximately 2.5 kg each were injected intravenously with D2E7, rhTNF, and immune complexes of D2E7 and rhTNF. Rectal temperatures were measured by thermistor probes on a Kaye thermal recorder every minute for approximately 4 hours. Recombinant human TNF in saline, injected at 5 μg/kg, elicted a rise in temperature greater than 0.4° C. at approximately 45 minutes after injection. The antibody preparation by itself, in saline at a dose of 138 μg/kg, did not elicit a rise in temperature in the rabbits up to 140 minutes after administration. In all further experiments, D2E7 or control reagents (human IgG1 or a saline vehicle) were injected i.v. into rabbits followed 15 minutes later by an injection of rhTNF in saline at 5 μg/kg i.v. Representative results of several experiments are summarized below in Table 14:

TABLE 14

Inhibition of rhTNF-induced Pyrexia with D2E7 in Rabbits

	Temp. rise*, ° C.			Molar Ratio	Peak Temp.
D2E7 dose (μg/kg)	rhTNF	rhTNF + D2E7	% Inhib.**	D2E7: rhTNF	minutes post rhTNF
14	0.53	0.25	53	1	60
24	0.43	0.13	70	1.6	40
48	0.53	0.03	94	3.3	50
137	0.53	0.00	100	9.5	60
792	0.80	0.00	100	55	60

* = Peak temperature

** = % inhibition = (1-{temperature rise with rhTNF & D2E7/temperature rise with rhTNF alone}) × 100.

Intravenous pretreatment with D2E7 at a dose of 14 μg/kg partially inhibited the pyrogenic response, compared to rabbits pre-treated with saline alone. D2E7 administered at 137 μg/kg totally suppressed the pyrogenic response of rhTNF in the same experiment. In a second experiment, D2E7 administered at 24 μg/kg also partially suppressed the pyrogenic response, compared to rabbits pretreated with saline alone. The molar ratio of D2E7 to rhTNF was 1/6:1 in this experiment. In a third experiment, D2E7 injected i.v. at 48 μg/kg (molar ratio D2E7:rhTNF=3.3:1) totally suppressed the pyrogenic response, compared to rabbits pretreated with the control human IgG1 in saline at 30 μg/kg. In the final experiment, rabbits pretreated with D2E7 (792 μg/kg) at a very high molar ratio to rhTNF (55:1) did not develop any rise in temperature at any time up to 4 hours of observation. Treatment of rabbits with immune complexes generated from a mixture of D2E7 and rhTNF incubated at 37° C. for 1 hour at a molar ratio of 55:1, without subsequent rhTNF administration, also did not elicit any rise in temperature in the same experiment

III. Prevention of Polyarthritis in Tg197 Transgenic Mice

The effect of D2E7 on disease development was investigated in a transgenic murine model of arthritis. Transgenic mice (Tg197) have been generated that express human wild type TNF (modified in the 3' region beyond the coding sequences) and these mice develop chronic polyarthritis with 100% incidence at 4–7 weeks of age (see EMBO J (1991) 10:40254031 for further description of the Tg197 model of polyarthritis).

Transgenic animals were identified by PCR at 3 days of age Litters of transgenic mice were divided into six groups. Transgenic mice were verified by slot-blot hybridization analysis at 15 days of age. The treatment protocols for the

six groups were as follows: Group I=no treatment; Group 2=saline (vehicle); Group 3=D2E7 at 1.5 μg/g; Group 4=D2E7 at 15 μg/g; Group 5=D2E7 at 30 μg/g; and Group 6=IgG1 isotype control at 30 μg/g. A litter with non transgenic mice was also included in the study to serve as a control (Group 7—nontransgenic; no treatment). Each group received three i.p. injections per week of the indicated treatments. Injections continued for 10 weeks. Each week, macroscopic changes in joint morphology were recorded for each animal. At 10 weeks, all mice were sacrificed and mouse tissue was collected in formalin. Microscopic examination of the tissue was performed.

Animal weight in grams was taken for each mouse at the start of each week. At the same time measurements of joint size (in mm) were also taken, as a measurement of disease severity. Joint size was established as an average of three measurements on the hind right ankle using a micrometer device. Arthritic scores were recorded weekly as follows: 0 =No arthritis, (normal appearence and flexion); +=mild arthritis (joint distortion); ++=moderate arthritis (swelling, joint deformation) and +++=heavy arthritis (ankylosis detected on flexion and severely impaired movement). Histopathological scoring based on haematoxylinleosin staining of joint sections was based as follows; 0=No detectable disease; 1=proliferation of the synovial membrane; 2=heavy synovial thickening 3=cartilage destruction and bone erosion.

The effect of D2E7 treatment on the mean joint size of the Tg197 transgenic arthritic mice is shown in the graph of FIG. **9**. The histopathological and arthritic cores of the Tg197 transgenic mice, at 11 weeks of age, are summarized below in Table

TABLE 15

Effect of D2E7 on Histopathology and Arthritic Score in Tg197 Mice

Group	Treatment	Histopathological Score	Arthritic Score
1	none	3 (7/7)	+++ (7/7)
2	saline	3 (8/8)	+++ (8/8)
6	IgG1 control	3 (9/9)	+++ (7/9)
3	D2E7 at 1.5 μg/g	0 (6/8)	0 (8/8)
4	D2E7 at 15 μg/g	0 (7/8)	0 (8/8)
5	D2E7 at 30 μg/g	0 (8/8)	0 (8/8)

This experiment demonstrated that the D2E7 antibody has a definite beneficial effect on transgenic mice expressing the wild-type human TNF (Tg197) with no arthritis evident after the study period.

E. D2E7 Neutralization of TNFαs from Other Species

The binding specificity of D2E7 was examined by measuring its ability to neutralize tumor necrosis factors from various primate species and from mouse, using an L929 cytotoxicity assay (as described in Example 4, subsection A, above). The results are summarized in Table 16 below:

TABLE 16

Ability of D2E7 to Neutralize TNF from Different Species in the L929 Assay

TNFα*	Source	IC_{50} for D2E7 Neutralization (M)**
Human	Recombinant	7.8×10^{-11}
Chimpanzee	LPS-stimulated PBMC	5.5×10^{-11}
baboon	Recombinant	6.0×10^{-11}
marmoset	LPS-stimulated PBMC	4.0×10^{-10}
cynomolgus	LPS-stimulated PBMC	8.0×10^{-11}
rhesus	LPS-stimulated PBMC	3.0×10^{-11}
canine	LPS-stimulated WBC	2.2×10^{-10}
porcine	Recombinant	1.0×10^{-7}
murine	Recombinant	$>1.0 \times 10^{-7}$

The results in Table 16 demonstrate that D2E7 can neutralize the activity of five primate TNFαs approximately equivalently to human TNFα and, moreover, can neutralize the activity of canine TNFα (about ten-fold less well than human TNFα) and porcine and mouse TNFα (about 1000-fold less well than human TNFα). Moreover, the binding of D2E7 to solution phase rhTNFα was not inhibited by other cytokines, such as lymphotoxin (TNFβ), IL-1α, IL-1β, IL-2, IL4, IL-6, IL-8, IFNγ and TGFβ, indicating that D2E7 is very specific for its ligand TNFα.

F. Lack of Cytokine Release by Human Whole Blood Incubated with D2E7

In this example, the ability of D2E7 to induce, by itself, normal human blood cells to secrete cytokines or shed cell surface molecules was examined. D2E7 was incubated with diluted whole blood from three different normal donors at varying concentrations for 24 hours. An LPS positive control was run at the same time, at a concentration previously determined to stimulate immunocompetent blood cells to secrete cytokines. The supernatants were harvested and tested in a panel of ten soluble cytokine, receptor and adhesion molecule ELISA kits: IL-1α, IL-1β, IL-1 receptor antagonist, IL-6, IL-8, TNFα, soluble TNF receptor I, soluble TNF receptor II, soluble ICAM-1 and soluble E-selectin. No significant amounts of cytokines or shed cell surface molecules were measured as a result of D2E7 antibody co-incubation, at concentrations up to 343 μg/ml. Control cultures without the addition of the antibody also did not yield any measurable amounts of cytokines, whereas the LPS co-culture control yielded elevated values in the high picogram to low nanogram range. These results indicate that D2E7 did not induce whole blood cells to secrete cytokines or shed cell surface proteins above normal levels in ex vivo cultures.

Forming part of the present disclosure is the appended Sequence Listing, the contents of which are summarized in the table below:

SEQ ID NO:	ANTIBODY CHAIN	REGION	SEQUENCE TYPE
1	D2E7	VL	amino acid
2	D2E7	VH	amino acid
3	D2E7	VL CDR3	amino acid
4	D2E7	VH CDR3	amino acid
5	D2E7	VL CDR2	amino acid
6	D2E7	VH CDR2	amino acid
7	D2E7	VL CDR1	amino acid
8	D2E7	VH CDR1	amino acid
9	2SD4	VL	amino acid
10	2SD4	VH	amino acid
11	2SD4	VL CDR3	amino acid
12	EP B12	VL CDR3	amino acid

-continued

SEQ ID NO:	ANTIBODY CHAIN	REGION	SEQUENCE TYPE
13	VL10E4	VL CDR3	amino acid
14	VL100A9	VL CDR3	amino acid
15	VLL100D2	VL CDR3	amino acid
16	VLL0F4	VL CDR3	amino acid
17	LOE5	VL CDR3	amino acid
18	VLLOG7	VL CDR3	amino acid
19	VLLOG9	VL CDR3	amino acid
20	VLLOH1	VL CDR3	amino acid
21	VLLOH10	VL CDR3	amino acid
22	VL1B7	VL CDR3	amino acid
23	VL1C1	VL CDR3	amino acid
24	VL0.1F4	VL CDR3	amino acid
25	VL0.1H8	VL CDR3	amino acid
26	LOE7.A	VL CDR3	amino acid
27	2SD4	VH CDR3	amino acid
28	VH1B11	VH CDR3	amino acid
29	VH1D8	VH CFR3	amino acid
30	VH1A11	VH CDR3	amino acid
31	VH1B12	VH CDR3	amino acid

-continued

SEQ ID NO:	ANTIBODY CHAIN	REGION	SEQUENCE TYPE
32	VH1E4	VH CDR3	amino acid
33	VH1F6	VH CDR3	amino acid
34	3C-H2	VH CDR3	amino acid
35	VH1-D2.N	VH CDR3	amino acid
36	D2E7	VL	nucleic acid
37	D2E7	VH	nucleic acid

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation many equivalents to the specific embodiments of the invention described herein. Such equivalents are intended to be encompassed by the following claims.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(iii) NUMBER OF SEQUENCES: 37

(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

```
Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Arg Tyr Asn Arg Ala Pro Tyr
                85                  90                  95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105
```

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 121 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

-continued

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
    50                  55                  60

Glu Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Lys Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Tyr Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120
```

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 9
(D) OTHER INFORMATION: /note= “Xaa is Thr or Ala”

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

```
Gln Arg Tyr Asn Arg Ala Pro Tyr Xaa
1               5
```

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(ix) FEATURE:
(A) NAME/KEY: Modified-site
(B) LOCATION: 12
(D) OTHER INFORMATION: /note= “Xaa is Tyr or Asn”

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

```
Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Xaa
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 7 amino acids
(B) TYPE: amino acid

-continued

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Ala Ala Ser Thr Leu Gln Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 17 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val Glu
1 5 10 15

Gly

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 11 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Arg Ala Ser Gln Gly Ile Arg Asn Tyr Leu Ala
1 5 10

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Asp Tyr Ala Met His
1 5

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 107 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Ile Gly

-continued

```
1               5                   10                  15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Tyr
            20                  25                  30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45

Tyr Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80

Glu Asp Val Ala Thr Tyr Tyr Cys Gln Lys Tyr Asn Ser Ala Pro Tyr
                85                  90                  95

Ala Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100                 105


(2) INFORMATION FOR SEQ ID NO: 10:

     (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 121 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: peptide

     (v) FRAGMENT TYPE: internal

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1               5                   10                  15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Asp Trp Val
        35                  40                  45

Ser Ala Ile Thr Trp Asn Ser Gly His Ile Asp Tyr Ala Asp Ser Val
    50                  55                  60

Glu Gly Arg Phe Ala Val Ser Arg Asp Asn Ala Lys Asn Ala Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Pro Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Thr Lys Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Asn Trp Gly
            100                 105                 110

Gln Gly Thr Leu Val Thr Val Ser Ser
        115                 120


(2) INFORMATION FOR SEQ ID NO: 11:

     (i) SEQUENCE CHARACTERISTICS:
          (A) LENGTH: 9 amino acids
          (B) TYPE: amino acid
          (D) TOPOLOGY: linear

    (ii) MOLECULE TYPE: peptide

     (v) FRAGMENT TYPE: internal

    (xi) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Gln Lys Tyr Asn Ser Ala Pro Tyr Ala
1               5


(2) INFORMATION FOR SEQ ID NO: 12:

     (i) SEQUENCE CHARACTERISTICS:
```

-continued

(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Gln Lys Tyr Asn Arg Ala Pro Tyr Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Gln Lys Tyr Gln Arg Ala Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Gln Lys Tyr Ser Ser Ala Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Gln Lys Tyr Asn Ser Ala Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Gln Lys Tyr Asn Arg Ala Pro Tyr Thr

-continued

1 5

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Gln Lys Tyr Asn Ser Ala Pro Tyr Tyr
1 5

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Gln Lys Tyr Asn Ser Ala Pro Tyr Asn
1 5

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Gln Lys Tyr Thr Ser Ala Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Gln Lys Tyr Asn Arg Ala Pro Tyr Asn
1 5

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

-continued

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Gln Lys Tyr Asn Ser Ala Ala Tyr Ser
1 5

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Gln Gln Tyr Asn Ser Ala Pro Asp Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Gln Lys Tyr Asn Ser Asp Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Gln Lys Tyr Ile Ser Ala Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Gln Lys Tyr Asn Arg Pro Pro Tyr Thr
1 5

(2) INFORMATION FOR SEQ ID NO: 26:

-continued

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 9 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Gln Arg Tyr Asn Arg Ala Pro Tyr Ala
1 5

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Asn
1 5 10

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Lys
1 5 10

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Tyr
1 5 10

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

-continued

```
Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu Asp Asp
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

```
Ala Ser Tyr Leu Ser Thr Ser Phe Ser Leu Asp Tyr
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

```
Ala Ser Tyr Leu Ser Thr Ser Ser Ser Leu His Tyr
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

```
Ala Ser Phe Leu Ser Thr Ser Ser Ser Leu Glu Tyr
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

```
Ala Ser Tyr Leu Ser Thr Ala Ser Ser Leu Glu Tyr
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 12 amino acids
(B) TYPE: amino acid
(D) TOPOLOGY: linear

-continued

(ii) MOLECULE TYPE: peptide

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

```
Val Ser Tyr Leu Ser Thr Ala Ser Ser Leu Asp Asn
1               5                   10
```

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 321 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

```
GACATCCAGA TGACCCAGTC TCCATCCTCC CTGTCTGCAT CTGTAGGGGA CAGAGTCACC     60

ATCACTTGTC GGGCAAGTCA GGGCATCAGA AATTACTTAG CCTGGTATCA GCAAAAACCA    120

GGGAAAGCCC CTAAGCTCCT GATCTATGCT GCATCCACTT TGCAATCAGG GGTCCCATCT    180

CGGTTCAGTG GCAGTGGATC TGGGACAGAT TTCACTCTCA CCATCAGCAG CCTACAGCCT    240

GAAGATGTTG CAACTTATTA CTGTCAAAGG TATAACCGTG CACCGTATAC TTTTGGCCAG    300

GGGACCAAGG TGGAAATCAA A                                              321
```

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 363 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: cDNA

(xi) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

```
GAGGTGCAGC TGGTGGAGTC TGGGGGAGGC TTGGTACAGC CCGGCAGGTC CCTGAGACTC     60

TCCTGTGCGG CCTCTGGATT CACCTTTGAT GATTATGCCA TGCACTGGGT CCGGCAAGCT    120

CCAGGGAAGG GCCTGGAATG GGTCTCAGCT ATCACTTGGA ATAGTGGTCA CATAGACTAT    180

GCGGACTCTG TGGAGGGCCG ATTCACCATC TCCAGAGACA ACGCCAAGAA CTCCCTGTAT    240

CTGCAAATGA ACAGTCTGAG AGCTGAGGAT ACGGCCGTAT ATTACTGTGC GAAAGTCTCG    300

TACCTTAGCA CCGCGTCCTC CCTTGACTAT TGGGGCCAAG GTACCCTGGT CACCGTCTCG    360

AGT                                                                  363
```

What is claimed is:

1. An isolated nucleic acid encoding a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8, or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9.

2. The isolated nucleic acid of claim **1**, which encodes an antibody light chain variable region (LCVR).

3. The isolated nucleic acid of claim **2**, wherein the CDR2 domain of the antibody LCVR comprises the amino acid sequence of SEQ ID NO: 5.

4. The isolated nucleic acid of claim **3**, wherein the CDR1 domain of the antibody LCVR comprises the amino acid sequence of SEQ ID NO: 7.

5. An isolated nucleic acid encoding a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11. or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12.

6. The isolated nucleic acid of claim **5**, which encodes an antibody heavy chain variable region (HCVR).

7. The isolated nucleic acid of claim **6**, wherein the CDR2 domain of the antibody HCVR comprises the amino acid sequence of SEQ ID NO: 6.

8. The isolated nucleic acid of claim **7**, wherein the CDR 1 domain of the antibody HCVR comprises the amino acid sequence of SEQ ID NO: 8.

9. An isolated nucleic acid encoding a CDR3 domain comprising an amino acid sequence selected from the group consisting of: SEQ ID NO: 3, SEQ ID NO 4, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18. SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 24, SEQ ID NO: 25, SEQ ID NO: 26, SEQ ID NO: 27, SEQ ID NO: 28, SEQ ID NO: 29, SEQ ID NO: 30, SEQ ID NO: 31, SEQ ID NO: 32, SEQ ID NO: 33 and SEQ ID NO: 34.

10. An isolated nucleic acid encoding an antibody light chain variable region comprising the amino acid sequence of SEQ ID NO: 1.

11. The isolated nucleic acid of claim **10**, which encodes the antibody light chain variable region and an antibody light chain constant region.

12. The isolated nucleic acid of claim **11**, which is in a recombinant expression vector.

13. An isolated nucleic acid encoding an antibody heavy chain variable region comprising the amino acid sequence of SEQ ID NO: 2.

14. The isolated nucleic acid of claim **13** which encodes the antibody heavy chain variable region and an antibody heavy chain constant region.

15. The isolated nucleic acid of claim **14**, wherein the antibody heavy chain constant region is an IgG1 constant region.

16. The isolated nucleic acid of claim **14**, wherein the antibody heavy chain constant region is an IgG4 constant region.

17. The isolated nucleic acid of claim **14**, which is in a recombinant expression vector.

18. A recombinant expression vector encoding:

a) an antibody light chain having a variable region comprising the amino acid sequence of SEQ ID NO: 1; and

b) an antibody heavy chain having a variable region comprising the amino acid sequence of SEQ ID NO: 2.

19. A host cell into which the recombinant expression vector of claim **18** has been introduced.

20. A method of synthesizing a human antibody that binds human TNFα, comprising culturing the host cell of claim **19** in a culture medium until a human antibody that binds human TNFα is synthesized by the cell.

* * * * *

ABSTRACT NUMBER: 1427

Discovery and Characterization Of ABT-122, An Anti-TNF/IL-17 DVD-Ig™ Molecule As a Potential Therapeutic Candidate For Rheumatoid Arthritis

Chung-Ming Hsieh[1], Carolyn Cuff[2], Edit Tarcsa[3] and Margaret Hugunin[4], [1]Biologics, AbbVie Pharmaceuticals, Worcester, MA, [2]Immunology, AbbVie, Inc, Worcester, MA, [3]Immunology, AbbVie Bioresearch Center, Worcester, MA, [4]Molecular and Cellular Pharmacology, AbbVie Bioresearch Center, Worcester, MA

Meeting: 2013 ACR/ARHP Annual Meeting

Keywords: Biologics, rheumatoid arthritis (RA) and tumor necrosis factor (TNF)

SESSION INFORMATION

Session Title: Rheumatoid Arthritis Treatment - Small Molecules, Biologics and Gene Therapy II

Session Type: Abstract Submissions (ACR)

Background/Purpose: Rheumatoid arthritis (RA) is a serious autoimmune disease that significantly impacts patients' quality of life. Several approved biologic drugs targeting tumor necrosis factor (TNF) and other immune targets are efficacious treatments for RA, and newer drug candidates, including antibodies to interleukin-17 (IL-17), are at various stages of clinical development. Previous and current studies have demonstrated that in a preclinical mouse model of arthritis treatment with antibodies to TNF and IL-17 is significantly more efficacious than treatment with either antibody alone. We therefore generated a novel bispecific dual variable domain immunoglobulin (DVD-Ig™) molecule to both TNF and IL-17 as a potential drug candidate for RA.

Methods: An *in vitro* PROfusion™ mRNA display technology was used to screen for fully human antibodies against human IL-17. The identified IL-17 antibodies were further engineered to improve affinity. We inserted the variable domain of several affinity-matured IL-17 antibodies between an available anti-TNF variable domain and the human IgG1/κ constant region to obtain a panel of novel DVD-Ig™ molecules. These DVD-Ig™ molecules differ from each other in the anti-IL-17 variable domains and the peptide linkers (lengths and sequences) connecting the two variable domains. We characterized the DVD-Ig™ activities by ELISA, surface plasmon resonance, and cell-based potency assays. To demonstrate the activities of these DVD-Ig™ molecules *in vivo*, we studied the pharmacokinetic profiles of the top three candidates in rat. The *in vivo* pharmacologic activity was assessed in mouse models by inhibition of recombinant human TNF-*D*gal-induced lethality and recombinant human IL-17-induced KC production.

Results: Fully human antibodies with sub-nM affinity to human IL-17 were selected from human antibody libraries. Their affinities were enhanced by molecular engineering to low pM range. The affinity-matured IL-17 antibodies were combined with an antibody to TNF into a panel of DVD-Ig™ molecules, and screened for optimal activities in antigen binding and neutralization assays. Three drug candidates with strong affinities and potencies (K_D and IC_{50} in the low pM range) were selected for further characterization. In rat pharmacokinetic studies these DVD-Ig™ molecules had 9 to 13 day circulating half-lives upon intravenous injection. In acute mouse models *in vivo*, these DVD-Ig™ molecules also demonstrated potent inhibition of human TNF and IL-17 activity. The DVD-Ig™

molecule with the best affinity and potency, as well as the longest half-life in rat was designated ABT-122 for further development.

Conclusion: ABT-122 is a novel DVD-Ig™ molecule that is engineered to have high affinity and neutralizing potency to both human TNF and IL-17 cytokines. Based on the combined efficacy in a preclinical mouse arthritis model, the demonstrated efficacy of TNF-targeted therapy in RA patients, and encouraging response to IL-17 antibodies in RA clinical trials, we will be evaluating the efficacy and safety profile of the anti-TNF/IL-17 DVD-Ig™ molecule in human RA clinical trials.

Disclosure:

C. M. Hsieh,

AbbVie,

3,

AbbVie,

1;

C. Cuff,

AbbVie,

3,

AbbVie,

1;

E. Tarcsa,

AbbVie,

3,

AbbVie,

1;

M. Hugunin,

Abbvie,

3,

Abbvie,

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ACR Meeting Abstracts - http://acrabstracts.org/abstract/discovery-and-characterization-of-abt-122-an-anti-tnfil-17-dvd-ig-molecule-as-a-potential-therapeutic-candidate-for-rheumatoid-arthritis/

US009447173B2

(12) **United States Patent**
Gurnett-Bander et al.

(10) **Patent No.: US 9,447,173 B2**
(45) **Date of Patent: Sep. 20, 2016**

(54) **HUMAN ANTIBODIES TO RESPIRATORY SYNCYTIAL VIRUS F PROTEIN AND METHODS OF USE THEREOF**

(71) Applicant: **Regeneron Pharmaceuticals, Inc.**, Tarrytown, NY (US)

(72) Inventors: **Anne Gurnett-Bander**, Carmel, NY (US); **David Perez-Caballero**, Briarwood, NY (US); **Sumathi Sivapalasingam**, Brooklyn, NY (US); **Xunbao Duan**, Maple Glen, PA (US); **Douglas MacDonald**, New York, NY (US)

(73) Assignee: **Regeneron Pharmaceuticals, Inc.**, Tarrytown, NY (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/207,797**

(22) Filed: **Mar. 13, 2014**

(65) **Prior Publication Data**

US 2014/0271653 A1 Sep. 18, 2014

Related U.S. Application Data

(60) Provisional application No. 61/911,093, filed on Dec. 3, 2013, provisional application No. 61/782,215, filed on Mar. 14, 2013.

(51) **Int. Cl.**

C07K 16/10	(2006.01)
A61K 39/42	(2006.01)
A61K 39/155	(2006.01)
A61K 45/06	(2006.01)
G01N 33/569	(2006.01)

(52) **U.S. Cl.**

CPC ***C07K 16/1027*** (2013.01); ***A61K 39/155*** (2013.01); ***A61K 45/06*** (2013.01); ***G01N 33/56983*** (2013.01); *C07K 2317/21* (2013.01); *C07K 2317/24* (2013.01); *C07K 2317/76* (2013.01); *C07K 2317/92* (2013.01); *C12N 2760/18521* (2013.01); *G01N 2333/135* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(Continued)

Primary Examiner — Shanon A Foley
Assistant Examiner — Myron Hill
(74) *Attorney, Agent, or Firm* — Alston & Bird LLP; Veronica Mallon

(57) **ABSTRACT**

The present invention provides fully human antibodies that bind to respiratory syncytial virus F protein, compositions comprising the antibodies and methods of use. The antibodies of the invention are useful for preventing fusion of the virus with the cell membrane and preventing cell to cell spread of the virus, thereby providing a means of preventing the infection, or treating a patient suffering from the infection and ameliorating one or more symptoms or complications associated with the viral infection. The antibodies may also be useful for diagnosis of an infection by RSV.

46 Claims, 2 Drawing Sheets

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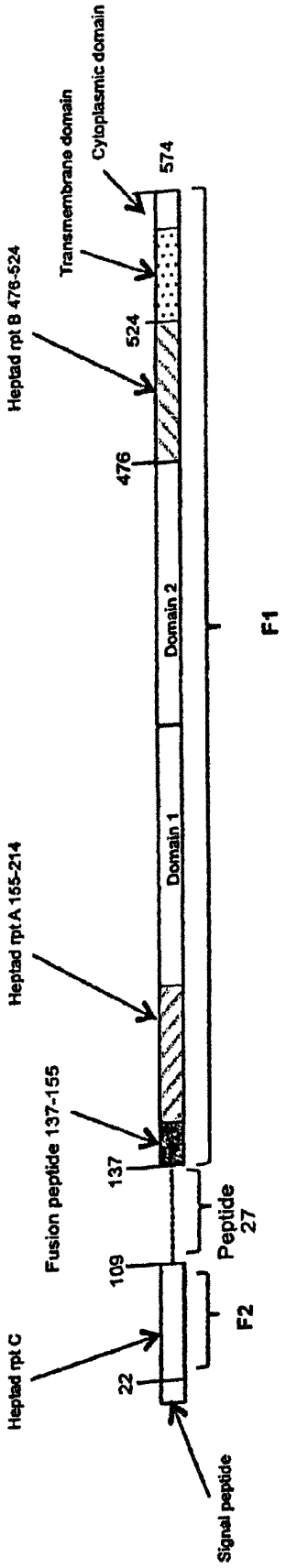
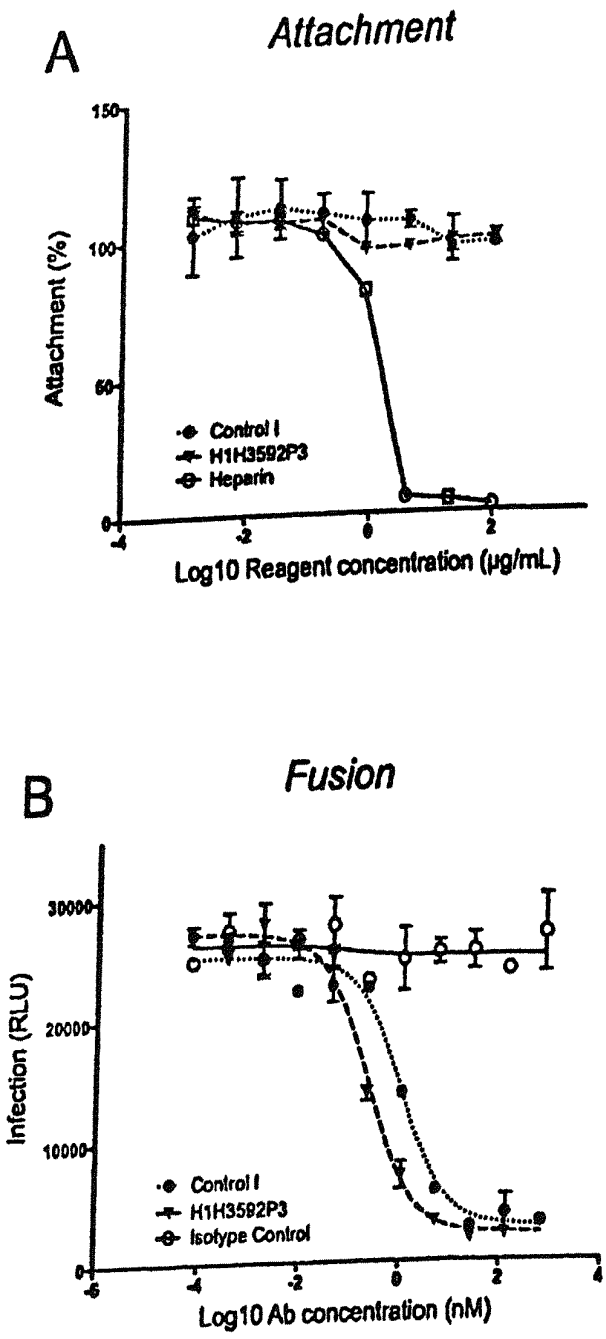

Cytoplasmic domain
Transmembrane domain
574
524
476
Heptad rpt B 476-524
Domain 2
Domain 1
F1
Heptad rpt A 155-214
Fusion peptide 137-155
137
109
Peptide
27
F2
22
Heptad rpt C
Signal peptide

Figure 1

Figure 2


A
Attachment
Attachment (%)
150
100
50
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-4
-2
0
2
Control I
H1H3592P3
Heparin
Log10 Reagent concentration (µg/mL)
B
Fusion
Infection (RLU)
30000
20000
10000
0
-6
-4
-2
0
2
4
Control I
H1H3592P3
Isotype Control
Log10 Ab concentration (nM)

HUMAN ANTIBODIES TO RESPIRATORY SYNCYTIAL VIRUS F PROTEIN AND METHODS OF USE THEREOF

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit under 35 U.S.C. §119 (e) of U.S. provisional application Nos. 61/782,215, filed Mar. 14, 2013 and 61/911,093, filed Dec. 3, 2013, both of which are herein specifically incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention is related to human antibodies and antigen-binding fragments of human antibodies that specifically bind to Respiratory Syncytial Virus F protein (RSV-F), compositions comprising these antibodies and methods of using these antibodies.

STATEMENT OF RELATED ART

Respiratory syncytial virus (RSV) is a negative sense, single stranded RNA virus that is the leading cause of serious respiratory tract infections in infants and children, with the primary infection occurring in children from 6 weeks to 2 years of age and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall et al., 1979, New Engl. J. Med. 300:393-396). (Feigen et al., eds., 1987, In: Textbook of Pediatric Infectious Diseases, W B Saunders, Philadelphia at pages 1653-1675; New Vaccine Development, Establishing Priorities, Vol. 1, 1985, National Academy Press, Washington D.C. at pages 397-409; Ruuskanen et al., 1993, Curr. Probl. Pediatr. 23:50-79; Hall et al., 1979, New Engl. J. Med. 300:393-396). Certain populations of children are at risk for developing an RSV infection and these include preterm infants (Hall et al., 1979, New Engl. J. Med. 300:393-396), children with congenital malformations of the airway, children with bronchopulmonary dysplasia (Groothuis et al., 1988, Pediatrics 82:199-203), children with congenital heart disease (MacDonald et al., New Engl. J. Med. 307:397-400), and children with congenital or acquired immunodeficiency (Ogra et al., 1988, Pediatr. Infect. Dis. J. 7:246-249; and Pohl et al., 1992, J. Infect. Dis. 165:166-169), and cystic fibrosis (Abman et al., 1988, J. Pediatr. 113:826-830).

RSV can infect the adult population as well. In this population, RSV causes primarily an upper respiratory tract disease, although elderly patients may be at greater risk for a serious infection and pneumonia (Evans, A. S., eds., 1989, Viral Infections of Humans. Epidemiology and Control, 3rd ed., Plenum Medical Book, New York at pages 525-544), as well as adults who are immunosuppressed, particularly bone marrow transplant patients (Hertz et al., 1989, Medicine 68:269-281). Other at risk patients include those suffering from congestive heart failure and those suffering from chronic obstructive pulmonary disease (ie. COPD). There have also been reports of epidemics among nursing home patients and institutionalized young adults (Falsey, A. R., 1991, Infect. Control Hosp. Epidemiol. 12:602-608; and Garvie et al., 1980, Br. Med. J. 281:1253-1254).

While treatment options for established RSV disease are limited, more severe forms of the disease of the lower respiratory tract often require considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields et al., eds, 1990, Fields Virology, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072).

Ribavirin, which is the only drug approved for treatment of infection, has been shown to be effective in the treatment of pneumonia and bronchiolitis associated with RSV infection, and has been shown to modify the course of severe RSV disease in immunocompetent children (Smith et al., 1991, New Engl. J. Med. 325:24-29). The use of ribavirin is limited due to concerns surrounding its potential risk to pregnant women who may be exposed to the aerosolized drug while it is being administered in a hospital environment.

Similarly, while a vaccine may be useful, no commercially available vaccine has been developed to date. Several vaccine candidates have been abandoned and others are under development (Murphy et al., 1994, Virus Res. 32:13-36). The development of a vaccine has proven to be problematic. In particular, immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. However, it is known that the neonatal immune response is immature at that time. Plus, the infant at that point in time still has high titers of maternally acquired RSV antibody, which might reduce vaccine immunogenicity (Murphy et al., 1988, J. Virol. 62:3907-3910; and Murphy et al., 1991, Vaccine 9:185-189).

Two glycoproteins, F and G, on the surface of RSV have been shown to be targets of neutralizing antibodies (Fields et al., 1990, supra; and Murphy et al., 1994, supra). These two proteins are also primarily responsible for viral recognition and entry into target cells; G protein binds to a specific cellular receptor and the F protein promotes fusion of the virus with the cell. The F protein is also expressed on the surface of infected cells and is responsible for subsequent fusion with other cells leading to syncytia formation and cell to cell virus spread.

Currently, the only approved approach to prophylaxis of RSV disease is passive immunization. For example, the humanized antibody, palivizumab (SYNAGIS®), which is specific for an epitope on the F protein, is approved for intramuscular administration to pediatric patients for prevention of serious lower respiratory tract disease caused by RSV at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is a composite of human (95%) and murine (5%) antibody sequences. See, Johnson et al., (1997), J. Infect. Diseases 176:1215-1224 and U.S. Pat. No. 5,824,307, the entire contents of which are incorporated herein by reference.

Although SYNAGIS® has been successfully used for the prevention of RSV infection in pediatric patients, multiple intramuscular doses of 15 mg/kg of SYNAGIS® are required to achieve a prophylactic effect. The necessity for the administration of multiple intramuscular doses of antibody requires repeated visits to the doctor's office, which is not only inconvenient for the patient but can also result in missed doses.

Efforts were made to improve on the therapeutic profile of an anti-RSV-F antibody, and this lead to the identification and development of motavizumab, also referred to as NUMAX™. However, clinical testing revealed that certain of the patients being administered motavizumab were having severe hypersensitivity reactions. Further development of this humanized anti-RSV-F antibody was then discontinued.

Other antibodies to RSV-F protein have been described and can be found in U.S. Pat. No. 6,656,467; U.S. Pat. No.

5,824,307, U.S. Pat. No. 7,786,273; U.S. Pat. No. 7,670,600; U.S. Pat. No. 7,083,784; U.S. Pat. No. 6,818,216; U.S. Pat. No. 7,700,735; U.S. Pat. No. 7,553,489; U.S. Pat. No. 7,323,172; U.S. Pat. No. 7,229,619; U.S. Pat. No. 7,425,618; U.S. Pat. No. 7,740,851; U.S. Pat. No. 7,658,921; U.S. Pat. No. 7,704,505; U.S. Pat. No. 7,635,568; U.S. Pat. No. 6,855,493; U.S. Pat. No. 6,565,849; U.S. Pat. No. 7,582,297; U.S. Pat. No. 7,208,162; U.S. Pat. No. 7,700,720; U.S. Pat. No. 6,413,771; U.S. Pat. No. 5,811,524; U.S. Pat. No. 6,537,809; U.S. Pat. No. 5,762,905; U.S. Pat. No. 7,070,786; U.S. Pat. No. 7,364,742; U.S. Pat. No. 7,879,329; U.S. Pat. No. 7,488,477; U.S. Pat. No. 7,867,497; U.S. Pat. No. 5,534,411; U.S. Pat. No. 6,835,372; U.S. Pat. No. 7,482,024; U.S. Pat. No. 7,691,603; U.S. Pat. No. 8,562,996; U.S. Pat. No. 8,568,726; US20100015596; WO2009088159A1. To date, none other than SYNAGIS® has been approved by a regulatory agency for use in preventing an RSV infection.

Thus, a need still exists for antibodies that specifically bind to an RSV antigen, such as RSV-F, which are highly potent and which produce no adverse effects that would preclude approval for clinical use.

BRIEF SUMMARY OF THE INVENTION

The invention provides isolated fully human monoclonal antibodies (mAbs) and antigen-binding fragments thereof that bind specifically to Respiratory Syncytial Virus F protein (RSV-F). Given the role that the F protein plays in fusion of the virus with the cell and in cell to cell transmission of the virus, the antibodies described herein provide a method of inhibiting that process and as such, may be used for preventing infection of a patient exposed to, or at risk for acquiring an infection with RSV, or for treating and/or ameliorating one or more symptoms associated with RSV infection in a patient exposed to, or at risk for acquiring an infection with RSV, or suffering from infection with RSV. The antibodies described herein may also be used to prevent or to treat an RSV infection in a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition. A patient who may benefit from treatment with an antibody of the invention may be a pre-term infant, a full-term infant born during RSV season (approximately late fall (November) through early spring (April)) that is at risk because of other pre-existing or underlying medical conditions including congenital heart disease or chronic lung disease, a child greater than one year of age with or without an underlying medical condition, an institutionalized or hospitalized patient, or an elderly adult (>65 years of age) with or without an underlying medical condition, such as congestive heart failure (CHF), or chronic obstructive pulmonary disease (COPD). A patient who may benefit from such therapy may suffer from a medical condition resulting from a compromised pulmonary, cardiovascular, neuromuscular, or immune system. For example, the patient may suffer from an abnormality of the airway, or an airway malfunction, a chronic lung disease, a chronic or congenital heart disease, a neuromuscular disease that compromises the handling of respiratory secretions, or the patient may be immunosuppressed due to severe combined immunodeficiency disease or severe acquired immunodeficiency disease, or from any other underlying infectious disease or cancerous condition that results in immunosuppression, or the patient may be immunosuppressed due to treatment with an immunosuppressive drug (e.g. any drug used for treating a transplant patient) or radiation therapy. A patient who may benefit from the antibodies of the invention may be a patient that suffers from chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), bronchopulmonary dysplasia, congestive heart failure (CHF), or congenital heart disease.

Because the antibodies of the invention are more effective at neutralization of RSV compared to known antibodies, lower doses of the antibodies or antibody fragments could be used to achieve a greater level of protection against infection with RSV, and more effective treatment and/or amelioration of symptoms associated with an RSV infection. Accordingly, the use of lower doses of antibodies or fragments thereof which immunospecifically bind to RSV-F antigen may result in fewer or less severe adverse events. Likewise, the use of more effective neutralizing antibodies may result in a diminished need for frequent administration of the antibodies or antibody fragments than previously envisioned as necessary for the prevention of infection, or for virus neutralization, or for treatment or amelioration of one or more symptoms associated with an RSV infection. Symptoms of RSV infection may include a bluish skin color due to lack of oxygen (hypoxia), breathing difficulty (rapid breathing or shortness of breath), cough, croupy cough ("seal bark" cough), fever, nasal flaring, nasal congestion (stuffy nose), apnea, decreased appetite, dehydration, poor feeding, altered mental status, or wheezing.

Such antibodies may be useful when administered prophylactically (prior to exposure to the virus and infection with the virus) to lessen the severity, or duration of a primary infection with RSV, or ameliorate at least one symptom associated with the infection. The antibodies may be used alone or in conjunction with a second agent useful for treating an RSV infection. In certain embodiments, the antibodies may be given therapeutically (after exposure to and infection with the virus) either alone, or in conjunction with a second agent to lessen the severity or duration of the primary infection, or to ameliorate at least one symptom associated with the infection. In certain embodiments, the antibodies may be used prophylactically as stand-alone therapy to protect patients who are at risk for acquiring an infection with RSV, such as those described above. Any of these patient populations may benefit from treatment with the antibodies of the invention, when given alone or in conjunction with a second agent, including for example, an anti-viral therapy, such as ribavirin, or other anti-viral vaccines.

The antibodies of the invention can be full-length (for example, an IgG1 or IgG4 antibody) or may comprise only an antigen-binding portion (for example, a Fab, $F(ab')_2$ or scFv fragment), and may be modified to affect functionality, e.g., to eliminate residual effector functions (Reddy et al., (2000), J. Immunol. 164:1925-1933).

Accordingly, in a first aspect, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F).

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody has one or more of the following characteristics:

(a) is a fully human monoclonal antibody;

(b) interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354;

(c) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID

NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354;

(d) is capable of neutralizing respiratory syncytial virus subtype A and subtype B strains in vitro;

(e) demonstrates the ability to significantly reduce the nasal and/or lung viral load in vivo in an animal model of RSV infection; or

(f) inhibits fusion of the virus to the cell.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354.

In one embodiment, the antibody is a fully human monoclonal antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or an antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354, and wherein the antibody neutralizes respiratory syncytial virus subtype A and/or subtype B strains in vitro and in vivo.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates the ability to significantly reduce the lung viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers as compared to palivizumab in a cotton rat model of RSV infection when administered at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 0.15 mg/kg or less when administered in a mouse model of RSV subtype A infection.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection.

In one embodiment, the invention provides an isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates an ED_{99} that is about 2 to 3 fold lower than the ED_{99} for palivizumab or motavizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a half maximal inhibitory concentration (IC_{50}) of about 2 pM to about 600 pM in a microneutralization assay specific for RSV subtype A strains of RSV.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a half maximal inhibitory concentration (IC_{50}) of about 6 pM to about 100 pM in a microneutralization assay specific for RSV subtype B strains of RSV.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to RSV-F protein demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about a 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about 10 to 22 fold improvement over palivizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2 to 5 fold improvement over palivizumab.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about a 0.5 to 2 fold improvement over AM-22.

In one embodiment, the isolated antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22.

In one embodiment, the isolated human antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), exhibits a K_D ranging from 1×10^{-7}M to 6×10^{-10} M, as measured by surface plasmon resonance.

In one embodiment, the isolated human antibody or an antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), exhibits a K_D ranging from 1×10^{-7}M to 9×10^{-9}M, as measured by surface plasmon resonance.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises the three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within a HCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within a LCVR amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

Methods and techniques for identifying CDRs within HCVR and LCVR amino acid sequences are well known in the art and can be used to identify CDRs within the specified HCVR and/or LCVR amino acid sequences disclosed herein. Exemplary conventions that can be used to identify the boundaries of CDRs include, e.g., the Kabat definition,

the Chothia definition, and the AbM definition. In general terms, the Kabat definition is based on sequence variability, the Chothia definition is based on the location of the structural loop regions, and the AbM definition is a compromise between the Kabat and Chothia approaches. See, e.g., Kabat, "Sequences of Proteins of Immunological Interest," National Institutes of Health, Bethesda, Md. (1991); Al-Lazikani et al., (1997), *J. Mol. Biol.* 273:927-948; and Martin et al., (1989), *Proc. Natl. Acad. Sci. USA* 86:9268-9272. Public databases are also available for identifying CDR sequences within an antibody.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises the heavy chain amino acid sequence of SEQ ID NO: 363 and the light chain amino acid sequence of SEQ ID NO: 364.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: SEQ ID NO: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), comprises:

(a) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344; and

(b) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), further comprises:

(c) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340;

(d) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342;

(e) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348; and

(f) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) comprises:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 276 and 340;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 278 and 342;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 280 and 344;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 284 and 348;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 286 and 350; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 288 and 352.

In one embodiment, the isolated human antibody or antigen binding fragment thereof that specifically binds to RSV-F comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NOs: 276, 278 and 280, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 284, 286 and 288, respectively.

In one embodiment, the isolated human antibody or antigen binding fragment thereof that specifically binds to RSV-F comprises the HCDR1, HCDR2 and HCDR3 amino acid sequences of SEQ ID NOs: 340, 342 and 344, respectively and LCDR1, LCDR2 and LCDR3 amino acid sequences of SEQ ID NOs: 348, 350 and 352, respectively.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) competes for specific binding to RSV-F with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof, which comprises heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, and which specifically binds to Respiratory Syncytial Virus F protein (RSV-F), does not compete for specific binding to RSV-F with palivizumab, motavizumab, or AM-22.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F) binds the same epitope on RSV-F that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

In one embodiment, the isolated human antibody or antigen-binding fragment thereof, which comprises heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, and which specifically binds to Respiratory Syncytial Virus F protein (RSV-F), does not bind the same epitope on RSV-F as palivizumab or motavizumab.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds to RSV-F, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a K_D ranging from about 1×10^{-7}M to about 6×10^{-10} M as measured by surface plasmon resonance; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg; (xi) demonstrates a 1 to 2 logs greater reduction of nasal and/or lung viral titers in a cotton rat model of RSV infection at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg when compared to palivizumab; (xii) demonstrates an effective dose 99 (ED_{99}) ranging from about 0.15 mg/kg to about 2.5 mg/kg when administered in an animal model of RSV infection (e.g. a mouse model or a cotton rat model); or (xiii) demonstrates a half maximal inhibitory concentration (IC_{50}) of about 2 pM to about 15 pM in a microneutralization assay specific for RSV subtype A strains of RSV and a half maximal inhibitory concentration (IC_{50}) of about 6 pM to about 100 pM in a microneutralization assay.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds to RSV-F, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%,

at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a K_D ranging from about 1×10^{-7}M to about 6×10^{-10} M; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in an animal model of RSV infection (e.g. a mouse model) when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg; (xi) demonstrates a 1 to 2 logs greater reduction of nasal and/or lung viral titers in an animal model of RSV infection (e.g. a cotton rat model) at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg when compared to palivizumab; (xii) demonstrates an effective dose 99 (ED_{99}) ranging from about 0.05 mg/kg to about 2.5 mg/kg when administered in an animal model of RSV infection (e.g. a mouse model or a cotton rat model); (xiii) demonstrates an ED_{99} that is about 2 to 3 fold lower than the ED_{99} for palivizumab or motavizumab; (xiv) demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about a 10-22 fold improvement over palivizumab; (xv) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2 to 5 fold improvement over palivizumab; (xvi) demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about 0.5 to 2 fold improvement over AM-22; (xvii) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that specifically binds to RSV-F, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (i) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (ii) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iii) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (iv) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (v) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vi) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (vii) and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (viii) exhibits a K_D ranging from about 1×10^{-7}M to about 6×10^{-10} M; (ix) is capable of neutralizing respiratory syncytial virus subtype A and/or subtype B strains in vitro; (x) demonstrates the ability to significantly reduce the viral load in an mammal having an RSV infection; (xi) interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354; (xii) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354, and the threonine at position 174 of SEQ ID NO:

354; (xiii) inhibits fusion of RSV to the host cell; (xiv) does not cross-compete with palivizumab or AM-22 for binding to RSV-F.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds Respiratory Syncytial Virus F protein (RSV-F), or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within SEQ ID NO: 355 or SEQ ID NO:356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354, and wherein the antibody or antigen-binding fragment thereof comprises three heavy chain CDRs (HCDR1, HCDR2 and HCDR3) contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282.

In one embodiment, the invention provides an isolated human monoclonal antibody or antigen-binding fragment thereof that specifically binds to Respiratory Syncytial Virus F protein (RSV-F), wherein the antibody or antigen-binding fragment thereof comprises:

(a) a HCDR1 domain comprising the amino acid sequence of SEQ ID NO: 276;

(b) a HCDR2 domain comprising the amino acid sequence of SEQ ID NO: 278;

(c) a HCDR3 domain comprising the amino acid sequence of SEQ ID NO: 280;

(d) a LCDR1 domain comprising the amino acid sequence of SEQ ID NO: 284;

(e) a LCDR2 domain comprising the amino acid sequence of SEQ ID NO: 286; and

(f) a LCDR3 domain comprising the amino acid sequence of SEQ ID NO: 288.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282 and wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within SEQ ID NO: 355 or SEQ ID NO:356.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof, that binds specifically to RSV-F, wherein the antibody comprises the three HCDRs contained within the heavy chain variable region (HCVR) amino acid sequence of SEQ ID NO: 274; and the three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within the light chain variable region (LCVR) amino acid sequence of SEQ ID NO: 282, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not cross-compete for binding to RSV-F with palivizumab, or motavizumab.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not cross-compete for binding to RSV-F with AM-22.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not bind the same epitope on RSV-F as palivizumab.

In one embodiment, the invention provides an isolated human antibody, or an antigen-binding fragment thereof that does not bind the same epitope on RSV-F as motavizumab.

In one embodiment, the invention provides an isolated human monoclonal antibody, or an antigen-binding fragment thereof that does not bind to an epitope on RSV-F

ranging from about amino acid residue 255 to about amino acid residue 276 of SEQ ID NO: 354.

In one embodiment, the isolated human monoclonal antibody, or an antigen-binding fragment thereof does not bind to the same epitope on RSV-F as palivizumab, wherein the epitope ranges from about amino acid residue 255 to about amino acid residue 276 of SEQ ID NO: 354.

In a second aspect, the invention provides nucleic acid molecules encoding antibodies or fragments thereof that specifically bind to RSV-F. Recombinant expression vectors carrying the nucleic acids of the invention, and host cells into which such vectors have been introduced, are also encompassed by the invention, as are methods of producing the antibodies by culturing the host cells under conditions permitting production of the antibodies, and recovering the antibodies produced.

In one embodiment, the invention provides an antibody or fragment thereof comprising a HCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1, 17, 33, 49, 65, 81, 97, 113, 129, 145, 161, 177, 193, 209, 225, 241, 257, 273, 289, 305, 321, and 337 or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

In one embodiment, the HCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 273 and 337.

In one embodiment, the antibody or fragment thereof further comprises a LCVR encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 9, 25, 41, 57, 73, 89, 105, 121, 137, 153, 169, 185, 201, 217, 233, 249, 265, 281, 297, 313, 329, and 345, or a substantially identical sequence having at least 90%, at least 95%, at least 98%, or at least 99% homology thereof.

In one embodiment, the LCVR is encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO: 281 and 345.

In one embodiment, the invention also provides an antibody or antigen-binding fragment of an antibody comprising a HCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 7, 23, 39, 55, 71, 87, 103, 119, 135, 151, 167, 183, 199, 215, 231, 247, 263, 279, 295, 311, 327, and 343 or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR3 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 15, 31, 47, 63, 79, 95, 111, 127, 143, 159, 175, 191, 207, 223, 239, 255, 271, 287, 303, 319, 335, and 351, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

In one embodiment, the invention provides an antibody or fragment thereof further comprising a HCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 3, 19, 35, 51, 67, 83, 99, 115, 131, 147, 163, 179, 195, 211, 227, 243, 259, 275, 291, 307, 323, and 339, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 5, 21, 37, 53, 69, 85, 101, 117, 133, 149, 165, 181, 197, 213, 229, 245, 261, 277, 293, 309, 325, and 341, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 11, 27, 43, 59, 75, 91, 107, 123, 139, 155, 171, 187, 203, 219, 235, 251, 267, 283, 299, 315, 331, and 347, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain encoded by a nucleotide sequence selected from the group consisting of SEQ ID NO: 13, 29, 45, 61, 77, 93, 109, 125, 141, 157, 173, 189, 205, 221, 237, 253, 269, 285, 301, 317, 333, and 349, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity.

In a third aspect, the invention features a human antibody or antigen-binding fragment specific for RSV-F comprising a HCVR encoded by nucleotide sequence segments derived from V_H, D_H and J_H germline sequences, and a LCVR encoded by nucleotide sequence segments derived from V_K and J_K germline sequences.

The invention encompasses antibodies having a modified glycosylation pattern. In some applications, modification to remove undesirable glycosylation sites may be useful, or e.g., removal of a fucose moiety to increase antibody dependent cellular cytotoxicity (ADCC) function (see Shield et al. (2002) JBC 277:26733). In other applications, modification of galactosylation can be made in order to modify complement dependent cytotoxicity (CDC).

In a fourth aspect, the invention provides a pharmaceutical composition comprising at least one isolated fully human monoclonal antibody or antigen-binding fragment thereof that binds to RSV-F and a pharmaceutically acceptable carrier or diluent. In one embodiment, the invention provides a pharmaceutical composition comprising two fully human monoclonal antibodies or antigen-binding fragments thereof, which either bind to the same epitope or bind to two different epitopes on RSV-F and a pharmaceutically acceptable carrier or diluent. It is to be understood that any combination of antibodies as described herein may be used in a pharmaceutical composition to achieve the desired results in the patient population in need of such therapy. For example, two antibodies that recognize and/or bind RSV-F may be used in a composition. Alternatively, two antibodies, one that recognizes and/or binds RSV-F and a second antibody that binds to another antigen on RSV (e.g. RSV-G) may be used in a composition. In one embodiment, two antibodies, one that recognizes and/or binds RSV-F and a second antibody that binds to a metapneumovirus antigen may be used in a composition. Alternatively, two or more antibodies may be used in a composition, one that recognizes and/or binds to RSV-F, one that binds to a metapneumovirus antigen and one that binds to an influenza virus antigen or to any other virus that causes respiratory diseases.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 274/282.

In one embodiment, the pharmaceutical composition comprises an antibody that binds RSV-F and has a HCVR/LCVR amino acid sequence pair consisting of SEQ ID NOs: 338/346.

In one embodiment, the pharmaceutical composition comprises at least one antibody that binds RSV-F, wherein the antibody comprises the three heavy chain complementarity determining regions (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 274 and 338; and the three light chain complementarity determining regions (LCDR1,

LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 282 and 346.

In one embodiment, the antibodies of the invention, or compositions containing one or more antibodies of the invention may be used to neutralize RSV from any subtype A or subtype B strain of RSV.

In one embodiment, the invention features a composition, which is a combination of an antibody or antigen-binding fragment of an antibody of the invention, and a second therapeutic agent.

The second therapeutic agent may be a small molecule drug, a protein/polypeptide, an antibody, a nucleic acid molecule, such as an anti-sense molecule, or a siRNA. The second therapeutic agent may be synthetic or naturally derived.

The second therapeutic agent may be any agent that is advantageously combined with the antibody or fragment thereof of the invention, for example, an antiviral agent (e.g. ribavirin), a vaccine specific for RSV, or a vaccine specific for influenza virus, or a vaccine specific for metapneumovirus (MPV), an siRNA specific for an RSV antigen, an siRNA specific for an influenza virus antigen, an siRNA specific for a metapneumovirus (MPV) antigen, a second antibody specific for an RSV antigen, or a metapneumovirus (MPV) antigen, or an influenza antigen, an anti-IL4R antibody, an anti-RSV-G antibody or a NSAID. In certain embodiments, the second therapeutic agent may be an agent that helps to counteract or reduce any possible side effect(s) associated with the antibody or antigen-binding fragment of an antibody of the invention, if such side effect(s) should occur.

It will also be appreciated that the antibodies and pharmaceutically acceptable compositions of the present invention can be employed in combination therapies, that is, the antibodies and pharmaceutically acceptable compositions can be administered concurrently with, prior to, or subsequent to, one or more other desired therapeutics or medical procedures. The particular combination of therapies (therapeutics or procedures) to employ in a combination regimen will take into account compatibility of the desired therapeutics and/or procedures and the desired therapeutic effect to be achieved. It will also be appreciated that the therapies employed may achieve a desired effect for the same disorder (for example, an antibody may be administered concurrently with another agent used to treat the same disorder), or they may achieve different effects (e.g., control of any adverse effects). As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease, or condition, are appropriate for the disease, or condition, being treated.

When multiple therapeutics are co-administered, dosages may be adjusted accordingly, as is recognized in the pertinent art.

A fifth aspect of the invention provides a method for preventing infection with respiratory syncytial virus in a patient in need thereof, or for treating a patient suffering from an infection with RSV, or for ameliorating at least one symptom or complication associated with the RSV infection, the method comprising administering one or more antibodies or antigen-binding fragments thereof as described herein, or a pharmaceutical composition comprising one or more antibodies of the invention or fragments thereof, as described herein, to a patient in need thereof, such that the RSV infection is prevented, or at least one symptom or complication associated with the infection is ameliorated, alleviated or reduced in severity and/or duration.

In a related embodiment, the invention provides a pharmaceutical composition comprising one or more antibodies of the invention, alone or in combination with a second therapeutic agent, for use in preventing a respiratory syncytial virus (RSV) infection in a patient in need thereof, or for treating a patient suffering from an RSV infection, or for ameliorating at least one symptom or complication associated with the infection, wherein the infection is either prevented, or at least one symptom or complication associated with the infection is prevented, ameliorated, or lessened in severity and/or duration.

In one embodiment, the invention provides a pharmaceutical composition comprising one or more antibodies of the invention, alone or in combination with a second therapeutic agent in the manufacture of a medicament for preventing a respiratory syncytial virus (RSV) infection in a patient in need thereof, or for treating a patient suffering from an RSV infection, or for ameliorating at least one symptom or complication associated with the infection, wherein the infection is either prevented, or at least one symptom or complication associated with the infection is prevented, ameliorated, or lessened in severity and/or duration.

In one embodiment, a patient in need of treatment with an antibody of the invention, or an antigen-binding fragment thereof is a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition. In one embodiment, the method provides for preventing the development of infection with RSV in a patient at risk thereof, the method comprising administering to the patient an effective amount of an antibody or an antigen-binding fragment thereof that binds to the F protein of RSV, or a pharmaceutical composition comprising an effective amount of an antibody or an antigen-binding fragment thereof that binds to the F protein of RSV such that the infection is either prevented, ameliorated, or lessened in severity and/or duration, or at least one symptom or complication associated with the infection is prevented, or ameliorated, or lessened in severity or duration. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of recurrent wheezing in the patient. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of RSV-associated asthma in a child. In one embodiment, the administering of the isolated human RSV-F antibody or an antigen-binding fragment thereof results in prevention of an RSV infection caused by a subtype A or a subtype B respiratory syncytial virus.

In one embodiment, the at least one symptom or complication associated with the RSV infection that may be treated with an antibody of the invention, or an antigen-binding fragment thereof, may be selected from the group consisting of hypoxia, a bluish skin color due to lack of oxygen, breathing difficulty (e.g., rapid breathing or shortness of breath), cough, croupy cough ("seal bark" cough), fever, nasal flaring, stuffy nose, wheezing, pneumonia, apnea, dehydration, poor feeding, altered mental status, decreased appetite, or bronchiolitis.

In one embodiment, the patient at risk of developing an RSV infection, who may benefit from treatment with the antibodies of the invention, or with a composition comprising one or more antibodies of the invention, may be selected from the group consisting of a pre-term infant, a full term infant who is compromised due to some other underlying medical condition and/or is exposed during the peak season

for RSV, a child greater than or equal to one year of age with or without an underlying medical condition (e.g. congenital heart disease, chronic lung disease, cystic fibrosis, immunodeficiency, a neuromuscular disorder), an institutionalized or hospitalized patient, an elderly patient 65 years of age) with or without an underlying medical condition such as congestive heart failure or chronic obstructive pulmonary disease), a patient who is immunocompromised due to underlying illness or due to administration of immunosuppressive therapeutics, a patient who has some underlying medical condition that may pre-dispose them to acquiring an RSV infection, for example, chronic obstructive pulmonary disease (COPD), congestive heart failure, cystic fibrosis, bronchopulmonary dysplasia, airway malfunction, chronic lung disease, a cancer patient, or a transplant patient who is on immunosuppressive therapy.

In one embodiment, a patient who is a candidate for therapy with an antibody of the invention may suffer from a condition resulting from a compromised pulmonary, cardiovascular, neuromuscular, or immune system. The condition may be selected from the group consisting of an abnormality of the airway, a chronic lung disease, a chronic heart disease, a neuromuscular disease that compromises the handling of respiratory secretions and immunosuppression. The chronic lung disease may be chronic obstructive pulmonary disease (COPD), cystic fibrosis, or bronchopulmonary dysplasia. The chronic heart disease may be congestive heart failure (CHF), or congenital heart disease. The neuromuscular disease or condition may be a neurodegenerative disease, or an inability to handle and/or eliminate respiratory secretions due to an injury or accident to the nervous system, e.g. a stroke, or a spinal cord injury. The immunosuppression may be the result of severe combined immunodeficiency or severe acquired immunodeficiency, or may be a result of any other infectious disease or cancerous condition that leads to immunosuppression, or is a result of treatment with immunosuppressant drug therapy or radiation therapy.

In one embodiment, the antibody is administered prophylactically (administered prior to development of the infection) to a patient at risk for developing an RSV infection, or at risk for developing at least one symptom or complication associated with the RSV infection. The patients who are candidates for treatment with the antibodies of the invention may be administered the compositions comprising one or more antibodies by any route of delivery suitable for administration, including but not limited to intravenous injection, intramuscular injection, or subcutaneous injection.

In one embodiment, the antibody is administered therapeutically (administered after the development of the infection) to a patient to ameliorate or reduce the severity and/or duration of at least one symptom or complication associated with the RSV infection.

In one embodiment, the antibodies of the invention may be administered to the patient in combination with one or more therapeutic agents useful for treating a RSV infection. The one or more therapeutic agents may be selected from the group consisting of an antiviral agent; a vaccine specific for RSV, a vaccine specific for influenza virus, or a vaccine specific for metapneumovirus (MPV); an siRNA specific for an RSV antigen or a metapneumovirus (MPV) antigen; a second antibody specific for an RSV antigen or a metapneumovirus (MPV) antigen; an anti-IL4R antibody, an antibody specific for an influenza virus antigen, an anti-RSV-G antibody and a NSAID.

A sixth aspect of the invention provides an immunogenic composition, or a vaccine, that when administered to an individual, preferably a human, induces an immune response in such individual to a Respiratory Syncytial Virus (RSV) antigen.

In one embodiment, the immunogenic composition, or vaccine, comprises an RSV antigen, for example, an RSV-F protein, polypeptide, or an immunogenic fragment thereof, or an epitope contained within and/or obtained from an antigen of the RSV-F polypeptide or a fragment thereof, and/or comprises DNA and/or RNA which encodes and expresses an epitope from an antigen of the RSV-F polypeptide, or other polypeptides of the invention.

In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise the RSV-F protein as shown in SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise a RSV-F polypeptide fragment comprising residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise SEQ ID NO: 355 and/or SEQ ID NO: 356.

In a related aspect, the invention provides a method for inducing an immune response in an individual, particularly a mammal, preferably humans, by administering to an individual an immunogenic composition, or a vaccine, comprising a RSV-F protein, or an immunogenic fragment thereof, or a RSV-F antigen or an immunogenic fragment thereof comprising one or more epitopes contained within the RSV-F antigen or fragment thereof, adequate to produce an antibody and/or a T cell immune response to protect the individual from infection, particularly infection with Respiratory Syncytial Virus (RSV).

In one embodiment, methods are provided for using the immunogenic compositions, or vaccines of the invention for inducing an immune response that results in inhibiting, or slowing the progression of cell to cell viral spread. Methods are also provided for ameliorating at least one symptom associated with RSV infection by administering an immunogenic composition, or a vaccine, comprising at least one RSV-F antigen, or one or more epitopes contained within the RSV-F antigen, which when administered will induce an immune response in the individual.

For example, in one embodiment the invention provides a method of inducing an immune response in an individual comprising delivering to the individual an immunogenic composition, or vaccine comprising, an RSV-F antigen (e.g. the amino acid sequence shown in SEQ ID NO: 354), or an antigenic fragment thereof, (e.g. a polypeptide comprising residues 161 through 188 of SEQ ID NO: 354), or a nucleic acid vector comprising a nucleotide sequence to direct expression of such viral polypeptide, or a fragment or a variant thereof, in vivo in order to induce an immune response.

In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises SEQ ID NO: 355 and/or SEQ ID

NO: 356. In one embodiment of the invention, the immunogenic composition, or vaccine, may elicit an antibody response or a T cell response specific for the RSV-F antigen of RSV, wherein the antibodies generated interact with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In certain embodiments of the invention, the immunogenic composition, or vaccine may comprise an immunogenic polypeptide and/or polynucleotide of the invention, or a combination thereof, together with a suitable carrier/excipient, such as a pharmaceutically acceptable carrier/excipient. The immunogenic composition, or vaccine of the invention may also include adjuvants for enhancing the immunogenicity of the formulation.

In certain embodiments, it is advantageous for the RSV-F antigens or fragments thereof to be formulated into immunogenic compositions, or vaccines that comprise immunogenic, preferably immunologically effective, amounts of additional antigens to elicit immunity to other pathogens, preferably viruses and/or bacteria. Such additional antigens may include an influenza virus antigen, an antigen from metapneumovirus or from a coronavirus, an antigen from *Haemophilus influenzae, Streptococcus pneumonia*, or *Bordetella pertussis*. Other RSV antigens may be included in the immunogenic compositions, or vaccines, such as the RSV-G glycoprotein, or immunogenic fragments thereof, the HN protein, or derivatives thereof.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1**. A schematic diagram of the RSV-F protein.

FIGS. **2**A and **2**B. Demonstrates that H1H3592P3 blocks viral entry by inhibiting fusion of virus and cell membranes.

DETAILED DESCRIPTION

Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (e.g., 99.1, 99.2, 99.3, 99.4, etc.).

Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

DEFINITIONS

"Respiratory Syncytial Virus-F protein", also referred to as "RSV-F" is a type I transmembrane surface protein, which has an N terminal cleaved signal peptide and a membrane anchor near the C terminus (Collins, P. L. et al., (1984), PNAS (USA) 81:7683-7687). The RSV-F protein is synthesized as an inactive 67 KDa precursor denoted as F0 (Calder, L. J.; et al., *Virology* (2000), 271, 122-131. The F0 protein is activated proteolytically in the Golgi complex by a furin-like protease at two sites, yielding two disulfide linked polypeptides, F2 and F1, from the N and C terminal, respectively. There is a 27 amino acid peptide released called "pep27". There are furin cleavage sites (FCS) on either side of the pep27 (Collins, P. L.; Mottet, G. (1991), *J. Gen. Virol.*, 72: 3095-3101; Sugrue, R. J, et al. (2001), *J. Gen. Virol.*, 82, 1375-1386). The F2 subunit consists of the Heptad repeat C(HRC), while the F1 contains the fusion polypeptide (FP), heptad repeat A (HRA), domain I, domain II, heptad repeat B (HRB), transmembrane (TM) and cytoplasmic domain (CP) (See Sun, Z. et al. Viruses (2013), 5:211-225). The RSV-F protein plays a role in fusion of the virus particle to the cell membrane, and is expressed on the surface of infected cells, thus playing a role in cell to cell transmission of the virus and syncytia formation. The amino acid sequence of the RSV-F protein is provided in GenBank as accession number AAX23994 and is also referred to herein as SEQ ID NO: 354.

A genetically engineered construct of the RSV-F protein is shown herein as having the amino acid sequence of SEQ ID NO: 353.

The term "laboratory strain" as used herein refers to a strain of RSV (subtype A or B) that has been passaged extensively in in vitro cell culture. A "laboratory strain" can acquire adaptive mutations that may affect their biological properties. A "clinical strain" as used herein refers to an RSV isolate (subtype A or B), which is obtained from an infected individual and which has been isolated and grown in tissue culture at low passage.

The term "effective dose 99" or "ED_{99}" refers to the dosage of an agent that produces a desired effect of 99% reduction of viral forming plaques relative to the isotype (negative) control. In the present invention, the ED_{99} refers to the dosage of the anti-RSV-F antibodies that will neutralize the virus infection (ie.g. reduce 99% of viral load) in vivo, as described in Example 5.

The term "IC50" refers to the "half maximal inhibitory concentration", which value measures the effectiveness of compound (e.g. anti-RSV-F antibody) inhibition towards a biological or biochemical utility. This quantitative measure indicates the quantity required for a particular inhibitor to inhibit a given biological process by half.

"Palivizumab", also referred to as "SYNAGIS®", is a humanized anti-RSV-F antibody with heavy and light chain variable domains having the amino acid sequences as set forth in U.S. Pat. No. 7,635,568 and U.S. Pat. No. 5,824,307 (also shown herein as SEQ ID NO: 361 for the heavy chain of the antibody and SEQ ID NO: 362 for the light chain of the antibody). This antibody, which immunospecifically binds to the RSV-F protein, is currently FDA-approved for the passive immunoprophylaxis of serious RSV disease in high-risk children and is administered intramuscularly at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is composed of 95% human and 5% murine antibody sequences. See also Johnson et al., (1997), J. Infect. Diseases 176:1215-1224.

"Motavizumab", also referred to as "NUMAX™", is an enhanced potency RSV-F-specific humanized monoclonal antibody derived by in vitro affinity maturation of the complementarity-determining regions of the heavy and light chains of palivizumab. For reference purposes, the amino acid sequence of the NUMAX™ antibody is disclosed in

U.S. Patent Publication 2003/0091584 and in U.S. Pat. No. 6,818,216 and in Wu et al., (2005) J. Mol. Bio. 350(1):126-144 and in Wu, et al. (2007) J. Mol. Biol. 368:652-665. It is also shown herein as SEQ ID NO: 359 for the heavy chain and as SEQ ID NO: 360 for the light chain of the antibody.

As used herein, the terms "treat," "treatment" and "treating" refer to the reduction or amelioration of the progression, severity, and/or duration of an upper and/or lower respiratory tract RSV infection, otitis media, or a symptom or respiratory condition related thereto (such as asthma, wheezing, or a combination thereof) resulting from the administration of one or more therapies (including, but not limited to, the administration of one or more prophylactic or therapeutic agents). In specific embodiments, such terms refer to the reduction or inhibition of the replication of RSV, the inhibition or reduction in the spread of RSV to other tissues or subjects (e.g., the spread to the lower respiratory tract), the inhibition or reduction of infection of a cell with a RSV, or the amelioration of one or more symptoms associated with an upper and/or lower respiratory tract RSV infection or otitis media.

As used herein, the terms "prevent," "preventing," and "prevention" refer to the prevention or inhibition of the development or onset of an upper and/or lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto in a subject, the prevention or inhibition of the progression of an upper respiratory tract RSV infection to a lower respiratory tract RSV infection, otitis media or a respiratory condition related thereto resulting from the administration of a therapy (e.g., a prophylactic or therapeutic agent), the prevention of a symptom of an upper and/or lower tract RSV infection, otitis media or a respiratory condition related thereto, or the administration of a combination of therapies (e.g., a combination of prophylactic or therapeutic agents).

The term "antibody", as used herein, is intended to refer to immunoglobulin molecules comprised of four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds (i.e., "full antibody molecules"), as well as multimers thereof (e.g. IgM) or antigen-binding fragments thereof. Each heavy chain is comprised of a heavy chain variable region ("HCVR" or "V_H") and a heavy chain constant region (comprised of domains C_H1, C_H2 and C_H3). Each light chain is comprised of a light chain variable region ("LCVR or "V_L") and a light chain constant region (C_L). The V_H and V_L regions can be further subdivided into regions of hypervariability, termed complementarity determining regions (CDR), interspersed with regions that are more conserved, termed framework regions (FR). Each V_H and V_L is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4. In certain embodiments of the invention, the FRs of the antibody (or antigen binding fragment thereof) may be identical to the human germline sequences, or may be naturally or artificially modified. An amino acid consensus sequence may be defined based on a side-by-side analysis of two or more CDRs.

Substitution of one or more CDR residues or omission of one or more CDRs is also possible. Antibodies have been described in the scientific literature in which one or two CDRs can be dispensed with for binding. Padlan et al. (1995 FASEB J. 9:133-139) analyzed the contact regions between antibodies and their antigens, based on published crystal structures, and concluded that only about one fifth to one third of CDR residues actually contact the antigen. Padlan also found many antibodies in which one or two CDRs had no amino acids in contact with an antigen (see also, Vajdos et al. 2002 J Mol Biol 320:415-428).

CDR residues not contacting antigen can be identified based on previous studies (for example residues H60-H65 in CDRH2 are often not required), from regions of Kabat CDRs lying outside Chothia CDRs, by molecular modeling and/or empirically. If a CDR or residue(s) thereof is omitted, it is usually substituted with an amino acid occupying the corresponding position in another human antibody sequence or a consensus of such sequences. Positions for substitution within CDRs and amino acids to substitute can also be selected empirically. Empirical substitutions can be conservative or non-conservative substitutions.

The fully human monoclonal antibodies disclosed herein may comprise one or more amino acid substitutions, insertions and/or deletions in the framework and/or CDR regions of the heavy and light chain variable domains as compared to the corresponding germline sequences. Such mutations can be readily ascertained by comparing the amino acid sequences disclosed herein to germline sequences available from, for example, public antibody sequence databases. The present invention includes antibodies, and antigen-binding fragments thereof, which are derived from any of the amino acid sequences disclosed herein, wherein one or more amino acids within one or more framework and/or CDR regions are mutated to the corresponding residue(s) of the germline sequence from which the antibody was derived, or to the corresponding residue(s) of another human germline sequence, or to a conservative amino acid substitution of the corresponding germline residue(s) (such sequence changes are referred to herein collectively as "germline mutations"). A person of ordinary skill in the art, starting with the heavy and light chain variable region sequences disclosed herein, can easily produce numerous antibodies and antigen-binding fragments which comprise one or more individual germline mutations or combinations thereof. In certain embodiments, all of the framework and/or CDR residues within the V_H and/or V_L domains are mutated back to the residues found in the original germline sequence from which the antibody was derived. In other embodiments, only certain residues are mutated back to the original germline sequence, e.g., only the mutated residues found within the first 8 amino acids of FR1 or within the last 8 amino acids of FR4, or only the mutated residues found within CDR1, CDR2 or CDR3. In other embodiments, one or more of the framework and/or CDR residue(s) are mutated to the corresponding residue(s) of a different germline sequence (i.e., a germline sequence that is different from the germline sequence from which the antibody was originally derived). Furthermore, the antibodies of the present invention may contain any combination of two or more germline mutations within the framework and/or CDR regions, e.g., wherein certain individual residues are mutated to the corresponding residue of a particular germline sequence while certain other residues that differ from the original germline sequence are maintained or are mutated to the corresponding residue of a different germline sequence. Once obtained, antibodies and antigen-binding fragments that contain one or more germline mutations can be easily tested for one or more desired property such as, improved binding specificity, increased binding affinity, improved or enhanced antagonistic or agonistic biological properties (as the case may be), reduced immunogenicity, etc. Antibodies and antigen-binding fragments obtained in this general manner are encompassed within the present invention.

The present invention also includes fully monoclonal antibodies comprising variants of any of the HCVR, LCVR,

and/or CDR amino acid sequences disclosed herein having one or more conservative substitutions. For example, the present invention includes antibodies having HCVR, LCVR, and/or CDR amino acid sequences with, e.g., 10 or fewer, 8 or fewer, 6 or fewer, 4 or fewer, etc. conservative amino acid substitutions relative to any of the HCVR, LCVR, and/or CDR amino acid sequences disclosed herein.

The term "human antibody", as used herein, is intended to include antibodies having variable and constant regions derived from human germline immunoglobulin sequences. The human mAbs of the invention may include amino acid residues not encoded by human germline immunoglobulin sequences (e.g., mutations introduced by random or site-specific mutagenesis in vitro or by somatic mutation in vivo), for example in the CDRs and in particular CDR3. However, the term "human antibody", as used herein, is not intended to include mAbs in which CDR sequences derived from the germline of another mammalian species (e.g., mouse), have been grafted onto human FR sequences.

The term "recombinant" generally refers to any protein, polypeptide, or cell expressing a gene of interest that is produced by genetic engineering methods. The term "recombinant" as used with respect to a protein or polypeptide, means a polypeptide produced by expression of a recombinant polynucleotide. The proteins used in the immunogenic compositions of the invention may be isolated from a natural source or produced by genetic engineering methods.

The antibodies of the invention may, in some embodiments, be recombinant human antibodies. The term "recombinant human antibody", as used herein, is intended to include all human antibodies that are prepared, expressed, created or isolated by recombinant means, such as antibodies expressed using a recombinant expression vector transfected into a host cell (described further below), antibodies isolated from a recombinant, combinatorial human antibody library (described further below), antibodies isolated from an animal (e.g., a mouse) that is transgenic for human immunoglobulin genes (see e.g., Taylor et al. (1992) Nucl. Acids Res. 20:6287-6295) or antibodies prepared, expressed, created or isolated by any other means that involves splicing of human immunoglobulin gene sequences to other DNA sequences. Such recombinant human antibodies have variable and constant regions derived from human germline immunoglobulin sequences. In certain embodiments, however, such recombinant human antibodies are subjected to in vitro mutagenesis (or, when an animal transgenic for human Ig sequences is used, in vivo somatic mutagenesis) and thus the amino acid sequences of the V_H and V_L regions of the recombinant antibodies are sequences that, while derived from and related to human germline V_H and V_L sequences, may not naturally exist within the human antibody germline repertoire in vivo.

The term "specifically binds," or "binds specifically to", or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by an equilibrium dissociation constant of at least about 1×10^{-6} M or less (e.g., a smaller K_D denotes a tighter binding). Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. As described herein, antibodies have been identified by surface plasmon resonance, e.g., BIACORE™, which bind specifically to RSV-F. Moreover, multi-specific antibodies that bind to RSV-F protein and one or more additional antigens or a bi-specific that binds to two different regions of RSV-F are nonetheless considered antibodies that "specifically bind", as used herein.

The term "high affinity" antibody refers to those mAbs having a binding affinity to RSV-F, expressed as K_D, of at least 10^{-6} M; more preferably 10^{-10}M, more preferably 10^{-11}M, more preferably 10^{-12}M as measured by surface plasmon resonance, e.g., BIACORE™ or solution-affinity ELISA.

By the term "slow off rate", "Koff" or "kd" is meant an antibody that dissociates from RSV-F, with a rate constant of 1×10^{-3} s^{-1} or less, preferably $1\times10^{-4}s^{-1}$ or less, as determined by surface plasmon resonance, e.g., BIACORE™.

The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retains the ability to bind to RSV-F.

The specific embodiments, antibody or antibody fragments of the invention may be conjugated to a therapeutic moiety ("immunoconjugate"), such as an antibiotic, a second anti-RSV-7 antibody, a vaccine, or a toxoid, or any other therapeutic moiety useful for treating a RSV infection.

An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies (Abs) having different antigenic specificities (e.g., an isolated antibody that specifically binds RSV-F, or a fragment thereof, is substantially free of Abs that specifically bind antigens other than RSV-F.

A "blocking antibody" or a "neutralizing antibody", as used herein (or an "antibody that neutralizes RSV-F activity"), is intended to refer to an antibody whose binding to RSV-F results in inhibition of at least one biological activity of RSV-F. For example, an antibody of the invention may aid in blocking the fusion of RSV to a host cell, or prevent syncytia formation, or prevent the primary disease caused by RSV. Alternatively, an antibody of the invention may demonstrate the ability to ameliorate at least one symptom of the RSV infection. This inhibition of the biological activity of RSV-F can be assessed by measuring one or more indicators of RSV-F biological activity by one or more of several standard in vitro assays (such as a neutralization assay, as described herein) or in vivo assays known in the art (for example, animal models to look at protection from challenge with RSV following administration of one or more of the antibodies described herein).

The term "surface plasmon resonance", as used herein, refers to an optical phenomenon that allows for the analysis of real-time biomolecular interactions by detection of alterations in protein concentrations within a biosensor matrix, for example using the BIACORE™ system (Pharmacia Biosensor AB, Uppsala, Sweden and Piscataway, N.J.).

The term "K_D", as used herein, is intended to refer to the equilibrium dissociation constant of a particular antibody-antigen interaction.

The term "epitope" refers to an antigenic determinant that interacts with a specific antigen binding site in the variable region of an antibody molecule known as a paratope. A single antigen may have more than one epitope. Thus, different antibodies may bind to different areas on an antigen and may have different biological effects. The term "epitope" also refers to a site on an antigen to which B and/or T cells respond. It also refers to a region of an antigen

that is bound by an antibody. Epitopes may be defined as structural or functional. Functional epitopes are generally a subset of the structural epitopes and have those residues that directly contribute to the affinity of the interaction. Epitopes may also be conformational, that is, composed of non-linear amino acids. In certain embodiments, epitopes may include determinants that are chemically active surface groupings of molecules such as amino acids, sugar side chains, phosphoryl groups, or sulfonyl groups, and, in certain embodiments, may have specific three-dimensional structural characteristics, and/or specific charge characteristics.

The term "substantial identity" or "substantially identical," when referring to a nucleic acid or fragment thereof, indicates that, when optimally aligned with appropriate nucleotide insertions or deletions with another nucleic acid (or its complementary strand), there is nucleotide sequence identity in at least about 90%, and more preferably at least about 95%, 96%, 97%, 98% or 99% of the nucleotide bases, as measured by any well-known algorithm of sequence identity, such as FASTA, BLAST or GAP, as discussed below. A nucleic acid molecule having substantial identity to a reference nucleic acid molecule may, in certain instances, encode a polypeptide having the same or substantially similar amino acid sequence as the polypeptide encoded by the reference nucleic acid molecule.

As applied to polypeptides, the term "substantial similarity" or "substantially similar" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 90% sequence identity, even more preferably at least 95%, 98% or 99% sequence identity. Preferably, residue positions, which are not identical, differ by conservative amino acid substitutions. A "conservative amino acid substitution" is one in which an amino acid residue is substituted by another amino acid residue having a side chain (R group) with similar chemical properties (e.g., charge or hydrophobicity). In general, a conservative amino acid substitution will not substantially change the functional properties of a protein. In cases where two or more amino acid sequences differ from each other by conservative substitutions, the percent or degree of similarity may be adjusted upwards to correct for the conservative nature of the substitution. Means for making this adjustment are well known to those of skill in the art. See, e.g., Pearson (1994) Methods Mol. Biol. 24: 307-331, which is herein incorporated by reference. Examples of groups of amino acids that have side chains with similar chemical properties include 1) aliphatic side chains: glycine, alanine, valine, leucine and isoleucine; 2) aliphatic-hydroxyl side chains: serine and threonine; 3) amide-containing side chains: asparagine and glutamine; 4) aromatic side chains: phenylalanine, tyrosine, and tryptophan; 5) basic side chains: lysine, arginine, and histidine; 6) acidic side chains: aspartate and glutamate, and 7) sulfur-containing side chains: cysteine and methionine. Preferred conservative amino acids substitution groups are: valine-leucine-isoleucine, phenylalanine-tyrosine, lysine-arginine, alanine-valine, glutamate-aspartate, and asparagine-glutamine. Alternatively, a conservative replacement is any change having a positive value in the PAM250 log-likelihood matrix disclosed in Gonnet et al. (1992) Science 256: 1443 45, herein incorporated by reference. A "moderately conservative" replacement is any change having a nonnegative value in the PAM250 log-likelihood matrix.

Sequence similarity for polypeptides is typically measured using sequence analysis software. Protein analysis software matches similar sequences using measures of similarity assigned to various substitutions, deletions and other modifications, including conservative amino acid substitutions. For instance, GCG software contains programs such as GAP and BESTFIT which can be used with default parameters to determine sequence homology or sequence identity between closely related polypeptides, such as homologous polypeptides from different species of organisms or between a wild type protein and a mutein thereof. See, e.g., GCG Version 6.1. Polypeptide sequences also can be compared using FASTA with default or recommended parameters; a program in GCG Version 6.1. FASTA (e.g., FASTA2 and FASTA3) provides alignments and percent sequence identity of the regions of the best overlap between the query and search sequences (Pearson (2000) supra). Another preferred algorithm when comparing a sequence of the invention to a database containing a large number of sequences from different organisms is the computer program BLAST, especially BLASTP or TBLASTN, using default parameters. See, e.g., Altschul et al. (1990) J. Mol. Biol. 215: 403 410 and (1997) Nucleic Acids Res. 25:3389 402, each of which is herein incorporated by reference.

In specific embodiments, the antibody or antibody fragment for use in the method of the invention may be monospecific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for epitopes of more than one target polypeptide. An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_H3 domain and a second Ig C_H3 domain, wherein the first and second Ig C_H3 domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_H3 domain binds Protein A and the second Ig C_H3 domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_H3 may further comprise an Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_H3 include: D16E, L18M, N44S, K52N, V57M, and V821 (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 mAbs; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 mAbs; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 mAbs. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

By the phrase "therapeutically effective amount" is meant an amount that produces the desired effect for which it is administered. The exact amount will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (see, for example, Lloyd (1999) The Art, Science and Technology of Pharmaceutical Compounding).

An "immunogenic composition" relates to a composition containing an antigen/immunogen, e.g. a microorganism, such as a virus or a bacterium, or a component thereof, a protein, a polypeptide, a fragment of a protein or polypeptide, a whole cell inactivated, subunit or attenuated virus, or a polysaccharide, or combination thereof, administered to stimulate the recipient's humoral and/or cellular immune systems to one or more of the antigens/immunogens present in the immunogenic composition. The immunogenic compositions of the present invention can be used to treat a

human susceptible to RSV infection, by means of administering the immunogenic compositions via a systemic route. These administrations can include injection via the intramuscular (i.m.), intradermal (i.d.), intranasal or inhalation route, or subcutaneous (s.c.) routes; application by a patch or other transdermal delivery device. In one embodiment, the immunogenic composition may be used in the manufacture of a vaccine or in the elicitation of polyclonal or monoclonal antibodies that could be used to passively protect or treat a mammal.

The terms "vaccine" or "vaccine composition", which are used interchangeably, refer to a composition comprising at least one immunogenic composition that induces an immune response in an animal.

In one embodiment of the invention, the protein of interest comprises an antigen. The terms "antigen," "immunogen," "antigenic," "immunogenic," "antigenically active," and "immunologically active" when made in reference to a molecule, refer to any substance that is capable of inducing a specific humoral and/or cell-mediated immune response. In one embodiment, the antigen comprises an epitope, as defined above.

"Immunologically protective amount", as used herein, is an amount of an antigen effective to induce an immunogenic response in the recipient that is adequate to prevent or ameliorate signs or symptoms of disease, including adverse health effects or complications thereof. Either humoral immunity or cell-mediated immunity or both can be induced. The immunogenic response of an animal to a composition can be evaluated, e.g. indirectly through measurement of antibody titers, lymphocyte proliferation assays, or directly through monitoring signs and symptoms after challenge with the microorganism. The protective immunity conferred by an immunogenic composition or vaccine can be evaluated by measuring, e.g. reduction of shed of challenge organisms, reduction in clinical signs such as mortality, morbidity, temperature, and overall physical condition, health and performance of the subject. The immune response can comprise, without limitation, induction of cellular and/or humoral immunity. The amount of a composition or vaccine that is therapeutically effective can vary, depending on the particular organism used, or the condition of the animal being treated or vaccinated.

"Immune response", or "immunological response" as used herein, in a subject refers to the development of a humoral immune response, a cellular-immune response, or a humoral and a cellular immune response to an antigen/immunogen. A "humoral immune response" refers to one that is at least in part mediated by antibodies. A "cellular immune response" is one mediated by T-lymphocytes or other white blood cells or both, and includes the production of cytokines, chemokines and similar molecules produced by activated T-cells, white blood cells, or both. Immune responses can be determined using standard immunoassays and neutralization assays, which are known in the art. "Immunogenicity", as used herein, refers to the capability of a protein or polypeptide to elicit an immune response directed specifically against a bacteria or virus that causes the identified disease.

General Description

Respiratory syncytial virus (RSV) is a negative sense, single stranded RNA virus that is the leading cause of serious respiratory tract infections in infants and children, with the primary infection occurring in children from 6 weeks to 2 years of age and uncommonly in the first 4 weeks of life during nosocomial epidemics (Hall et al., 1979, New Engl. J. Med. 300:393-396). (Feigen et al., eds., 1987, In: Textbook of Pediatric Infectious Diseases, W B Saunders, Philadelphia at pages 1653-1675; New Vaccine Development, Establishing Priorities, Vol. 1, 1985, National Academy Press, Washington D.C. at pages 397-409; Ruuskanen et al., 1993, Curr. Probl. Pediatr. 23:50-79; Hall et al., 1979, New Engl. J. Med. 300:393-396). Certain populations of children are at risk for developing an RSV infection and these include preterm infants (Hall et al., 1979, New Engl. J. Med. 300:393-396), children with congenital malformations of the airway, children with bronchopulmonary dysplasia (Groothuis et al., 1988, Pediatrics 82:199-203), children with congenital heart disease (MacDonald et al., New Engl. J. Med. 307:397-400), and children with congenital or acquired immunodeficiency (Ogra et al., 1988, Pediatr. Infect. Dis. J. 7:246-249; and Pohl et al., 1992, J. Infect. Dis. 165:166-169), and cystic fibrosis (Abman et al., 1988, J. Pediatr. 113:826-830).

RSV can infect the adult population as well. In this population, RSV causes primarily an upper respiratory tract disease, although elderly patients may be at greater risk for a serious infection and pneumonia (Evans, A. S., eds., 1989, Viral Infections of Humans. Epidemiology and Control, 3rd ed., Plenum Medical Book, New York at pages 525-544), as well as adults who are immunosuppressed, particularly bone marrow transplant patients (Hertz et al., 1989, Medicine 68:269-281). Other at risk patients include those suffering from congestive heart failure and those suffering from chronic obstructive pulmonary disease (ie. COPD). There have also been reports of epidemics among nursing home patients and institutionalized young adults (Falsey, A. R., 1991, Infect. Control Hosp. Epidemiol. 12:602-608; and Garvie et al., 1980, Br. Med. J. 281:1253-1254).

While treatment options for established RSV disease are limited, more severe forms of the disease of the lower respiratory tract often require considerable supportive care, including administration of humidified oxygen and respiratory assistance (Fields et al., eds, 1990, Fields Virology, 2nd ed., Vol. 1, Raven Press, New York at pages 1045-1072).

Ribavirin, which is the only drug approved for treatment of infection, has been shown to be effective in the treatment of pneumonia and bronchiolitis associated with RSV infection, and has been shown to modify the course of severe RSV disease in immunocompetent children (Smith et al., 1991, New Engl. J. Med. 325:24-29). However, the use of ribavirin is limited due to concerns surrounding its potential risk to pregnant women who may be exposed to the aerosolized drug while it is being administered in a hospital environment. Its use is also limited due to its relatively high cost.

Other peptide inhibitors of RSV infection have been identified, which inhibit viral growth in vitro, but have failed when tested in vivo, most likely due to lack of oral availability and a relatively low half life in circulation (Lambert, D. M., et al. (1996), PNAS (USA) 93:2186-2191; Magro, M. et al., (2010), J. Virol. 84:7970-7982; Park, M. et al. (2011), Anal. Biochem. 409:195-201).

Other small molecule inhibitors of RSV infection have also been identified, but have been discontinued for various reasons, some of which may be due to toxic side effects (Wyde, P. R. et al. (1998), Antiviral Res. 38:31-42; Nikitenko, A. A. et al. (2001), Bioorg Med Chem Lett 11:1041-1044; Douglas, J. L., et al. (2003), J. Virol 77:5054-5064; Bonfanti, J. F. et al, (2008), J. Med Chem 51:875-896).

Similarly, while a vaccine may be useful, no commercially available vaccine has been developed to date. Several vaccine candidates have been abandoned and others are

under development (Murphy et al., 1994, Virus Res. 32:13-36). The development of a vaccine has proven to be problematic. In particular, immunization would be required in the immediate neonatal period since the peak incidence of lower respiratory tract disease occurs at 2-5 months of age. However, it is known that the neonatal immune response is immature at that time. Plus, the infant at that point in time still has high titers of maternally acquired RSV antibody, which might reduce vaccine immunogenicity (Murphy et al., 1988, J. Virol. 62:3907-3910; and Murphy et al., 1991, Vaccine 9:185-189).

Currently, passive immunization appears to be the only approved approach to prophylaxis of RSV disease. Initial evidence that suggested a protective role for IgG was obtained from studies demonstrating maternal antibody in ferrets (Prince, G. A., Ph.D. diss., University of California, Los Angeles, 1975) and humans (Lambrecht et al, 1976, J. Infect. Dis. 134:211-217; and Glezen et al., 1981, J. Pediatr. 98:708-715).

Hemming et al. (Morel) et al., eds., 1986, Clinical Use of Intravenous Immunoglobulins, Academic Press, London at pages 285-294) recognized the possible utility of RSV antibody in treatment or prevention of RSV infection during studies involving the pharmacokinetics of an intravenous immune globulin (IVIG) in newborns suspected of having neonatal sepsis. This same group of investigators then examined the ability of hyperimmune serum or immune globulin, enriched for RSV neutralizing antibody, to protect cotton rats and primates against RSV infection (Prince et al., 1985, Virus Res. 3:193-206; Prince et al., 1990, J. Virol. 64:3091-3092; Hemming et al., 1985, J. Infect. Dis. 152: 1083-1087; Prince et al., 1983, Infect. Immun. 42:81-87; and Prince et al., 1985, J. Virol. 55:517-520). Results of these studies suggested that RSV neutralizing antibody given prophylactically inhibited respiratory tract replication of RSV in cotton rats. When given therapeutically, RSV antibody reduced pulmonary viral replication both in cotton rats and in a nonhuman primate model.

More recent studies have concentrated on the role of two glycoproteins, designated F and G, which are found on the surface of RSV, as targets of neutralizing antibodies, due to the role of these glycoproteins in viral attachment and fusion with the host cell (Fields et al., 1990, supra; and Murphy et al., 1994, supra). The G protein binds to a specific cellular receptor and the F protein promotes fusion of the virus with the cell. The F protein is also expressed on the surface of infected cells and is responsible for subsequent fusion with other cells leading to syncytia formation. Thus, antibodies to the F protein may directly neutralize virus, or block fusion of the virus with the cell, or prevent cell to cell spread by preventing syncytia formation.

The first humanized antibody approved for use in pediatric patients for prevention of serious lower respiratory tract disease caused by RSV was palivizumab (SYNAGIS®), which immunospecifically binds to the F protein and is administered intramuscularly at recommended monthly doses of 15 mg/kg of body weight throughout the RSV season (November through April in the northern hemisphere). SYNAGIS® is composed of 95% human and 5% murine antibody sequences. See, Johnson et al., 1997, J. Infect. Diseases 176:1215-1224 and U.S. Pat. No. 5,824,307, the entire contents of which are incorporated herein by reference.

While SYNAGIS® has been successfully used for the prevention of RSV infection in pediatric patients, the need for multiple visits to the doctor's office for multiple intramuscular doses of 15 mg/kg of SYNAGIS® was not only inconvenient for the patient but could also result in missed doses. Thus, there was a need for development of antibodies that retained the immunospecificity for the RSV antigen, but which were more potent, with an improved pharmacokinetic profile, and thus have an overall improved therapeutic profile. Such an antibody is described in U.S. Patent Publication 2003/0091584 and is known as motavizumab (NUMAX™). Although NUMAX™ has improved binding characteristics that may overcome the higher dosing requirements described above for SYNAGIS®, it also had a 3 to 5 fold increase in the frequency and severity of hypersensitivity reactions compared to SYNAGIS®. NUMAX™ was then withdrawn from future development.

Accordingly, there is still a need for effective therapies against RSV infections, and in particular, there is a need to identify a more potent antibody for preventing and treating RSV infections, but without the adverse side effects associated with those described above. The antibodies described herein, while exhibiting a lower binding affinity for RSV-F (i.e. the antibodies of the present invention do not bind as tightly to RSV-F as palivizumab) than that described for palivizumab or motavizumab appears to exhibit better neutralization capabilities and addresses those needs.

In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a whole RSV particle, either live, attenuated, or inactivated, or with a recombinant form of the virus, or with a purified F protein (See GenBank accession number AAX23994.1 (SEQ ID NO: 354)), or a recombinantly produced F protein (See SEQ ID NO: 353), followed by immunization with a secondary immunogen (whole virus, or purified F protein), or with an immunogenically active fragment of the F protein.

The immunogen may be DNA encoding the F protein or an active fragment thereof.

The immunogen may be derived from the N-terminal or C-terminal domain of either the 67 KDa precursor (F0), or from either of the two fragments generated from the precursor by a furin-like protease yielding two disulfide linked polypeptides, designated as F2 and F1, from the N and C terminal, respectively. The fragment may be derived from any of the known regions of RSV-F protein (See Sun, Z. et al. (2013), Viruses 5:211-225).

The full-length amino acid sequence of RSV-F is shown as SEQ ID NO: 354 and is also shown in GenBank accession number AAX23994.1.

A genetic construct containing the F protein of RSV is shown as SEQ ID NO: 353.

In certain embodiments, antibodies that bind specifically to RSV-F may be prepared using fragments of the above-noted regions, or peptides that extend beyond the designated regions by about 5 to about 20 amino acid residues from either, or both, the N or C terminal ends of the regions described herein. In certain embodiments, any combination of the above-noted regions or fragments thereof may be used in the preparation of RSV-F specific antibodies. In certain embodiments, any one or more of the above-noted regions of RSV-F, or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

Antigen-Binding Fragments of Antibodies

Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass antibody molecules comprising two immunoglobulin heavy chains and two immunoglobulin light chains (i.e., "full antibody molecules") as well as antigen-binding fragments thereof. The terms "antigen-binding portion" of an antibody, "antigen-binding fragment" of an antibody, and the like, as

used herein, include any naturally occurring, enzymatically obtainable, synthetic, or genetically engineered polypeptide or glycoprotein that specifically binds an antigen to form a complex. The terms "antigen-binding portion" of an antibody, or "antibody fragment", as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to RSV-F. An antibody fragment may include a Fab fragment, a $F(ab')_2$ fragment, a Fv fragment, a dAb fragment, a fragment containing a CDR, or an isolated CDR. Antigen-binding fragments of an antibody may be derived, e.g., from full antibody molecules using any suitable standard techniques such as proteolytic digestion or recombinant genetic engineering techniques involving the manipulation and expression of DNA encoding antibody variable and (optionally) constant domains. Such DNA is known and/or is readily available from, e.g., commercial sources, DNA libraries (including, e.g., phage-antibody libraries), or can be synthesized. The DNA may be sequenced and manipulated chemically or by using molecular biology techniques, for example, to arrange one or more variable and/or constant domains into a suitable configuration, or to introduce codons, create cysteine residues, modify, add or delete amino acids, etc.

Non-limiting examples of antigen-binding fragments include: (i) Fab fragments; (ii) F(ab')2 fragments; (iii) Fd fragments; (iv) Fv fragments; (v) single-chain Fv (scFv) molecules; (vi) dAb fragments; and (vii) minimal recognition units consisting of the amino acid residues that mimic the hypervariable region of an antibody (e.g., an isolated complementarity determining region (CDR) such as a CDR3 peptide), or a constrained FR3-CDR3-FR4 peptide. Other engineered molecules, such as domain-specific antibodies, single domain antibodies, domain-deleted antibodies, chimeric antibodies, CDR-grafted antibodies, diabodies, triabodies, tetrabodies, minibodies, nanobodies (e.g. monovalent nanobodies, bivalent nanobodies, etc.), small modular immunopharmaceuticals (SMIPs), and shark variable IgNAR domains, are also encompassed within the expression "antigen-binding fragment," as used herein.

An antigen-binding fragment of an antibody will typically comprise at least one variable domain. The variable domain may be of any size or amino acid composition and will generally comprise at least one CDR, which is adjacent to or in frame with one or more framework sequences. In antigen-binding fragments having a V_H domain associated with a V_L domain, the V_H and V_L domains may be situated relative to one another in any suitable arrangement. For example, the variable region may be dimeric and contain V_H-V_H, V_H-V_L or V_L-V_L dimers. Alternatively, the antigen-binding fragment of an antibody may contain a monomeric V_H or V_L domain.

In certain embodiments, an antigen-binding fragment of an antibody may contain at least one variable domain covalently linked to at least one constant domain. Non-limiting, exemplary configurations of variable and constant domains that may be found within an antigen-binding fragment of an antibody of the present invention include: (i) V_H-C_H1; (ii) V_H-C_H2; (iii) V_H-C_H3; (iv) V_H-C_H1-C_H2; (V) V_H-C_H1-C_H2-C_H3, (vi) V_H-C_H2-C_H3; (vii) V_H-C_L; (viii) V_L-C_H1; (ix) V_L-C_H2; (x) V_L-C_H3; (xi) V_L-C_H1-C_H2; (xii) V_L-C_H1-C_H2-C_H3; (xiii) V_L-C_H2-C_H3; and (xiv) V_L-C_L. In any configuration of variable and constant domains, including any of the exemplary configurations listed above, the variable and constant domains may be either directly linked to one another or may be linked by a full or partial hinge or linker region. A hinge region may consist of at least 2 (e.g., 5, 10, 15, 20, 40, 60 or more) amino acids, which result in a flexible or semi-flexible linkage between adjacent variable and/or constant domains in a single polypeptide molecule. Moreover, an antigen-binding fragment of an antibody of the present invention may comprise a homo-dimer or hetero-dimer (or other multimer) of any of the variable and constant domain configurations listed above in non-covalent association with one another and/or with one or more monomeric V_H or V_L domain (e.g., by disulfide bond(s)).

As with full antibody molecules, antigen-binding fragments may be mono-specific or multi-specific (e.g., bi-specific). A multi-specific antigen-binding fragment of an antibody will typically comprise at least two different variable domains, wherein each variable domain is capable of specifically binding to a separate antigen or to a different epitope on the same antigen. Any multi-specific antibody format, including the exemplary bi-specific antibody formats disclosed herein, may be adapted for use in the context of an antigen-binding fragment of an antibody of the present invention using routine techniques available in the art.

Preparation of Human Antibodies

Methods for generating human antibodies in transgenic mice are known in the art. Any such known methods can be used in the context of the present invention to make human antibodies that specifically bind to RSV-F.

Using VELOCIMMUNE® technology (see, for example, U.S. Pat. No. 6,596,541, Regeneron Pharmaceuticals, VELOCIMMUNE®) or any other known method for generating monoclonal antibodies, high affinity chimeric antibodies to RSV-F are initially isolated having a human variable region and a mouse constant region. The VELOCIMMUNE® technology involves generation of a transgenic mouse having a genome comprising human heavy and light chain variable regions operably linked to endogenous mouse constant region loci such that the mouse produces an antibody comprising a human variable region and a mouse constant region in response to antigenic stimulation. The DNA encoding the variable regions of the heavy and light chains of the antibody are isolated and operably linked to DNA encoding the human heavy and light chain constant regions. The DNA is then expressed in a cell capable of expressing the fully human antibody.

Generally, a VELOCIMMUNE® mouse is challenged with the antigen of interest, and lymphatic cells (such as B-cells) are recovered from the mice that express antibodies. The lymphatic cells may be fused with a myeloma cell line to prepare immortal hybridoma cell lines, and such hybridoma cell lines are screened and selected to identify hybridoma cell lines that produce antibodies specific to the antigen of interest. DNA encoding the variable regions of the heavy chain and light chain may be isolated and linked to desirable isotypic constant regions of the heavy chain and light chain. Such an antibody protein may be produced in a cell, such as a CHO cell. Alternatively, DNA encoding the antigen-specific chimeric antibodies or the variable domains of the light and heavy chains may be isolated directly from antigen-specific lymphocytes.

Initially, high affinity chimeric antibodies are isolated having a human variable region and a mouse constant region. As in the experimental section below, the antibodies are characterized and selected for desirable characteristics, including affinity, selectivity, epitope, etc. The mouse constant regions are replaced with a desired human constant region to generate the fully human antibody of the invention, for example wild-type or modified IgG1 or IgG4. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region.

In certain embodiments, the antibodies of the instant invention possess affinities (K_D) ranging from about 1.0×10^{-7} M to about 1.0×10^{-12}M, when measured by binding to antigen either immobilized on solid phase or in solution phase. In certain embodiments, the antibodies of the invention possess affinities (K_D) ranging from about 1×10^{-7} M to about 6×10^{-10}M, when measured by binding to antigen either immobilized on solid phase or in solution phase. In certain embodiments, the antibodies of the invention possess affinities (K_D) ranging from about 1×10^{-7} M to about 9×10^{-10}M, when measured by binding to antigen either immobilized on solid phase or in solution phase. The mouse constant regions are replaced with desired human constant regions to generate the fully human antibodies of the invention. While the constant region selected may vary according to specific use, high affinity antigen-binding and target specificity characteristics reside in the variable region. Surprisingly, certain antibodies of the present invention, while demonstrating lower affinities than motavizumab, are more potent in terms of virus neutralization.

Bioequivalents

The anti-RSV-F antibodies and antibody fragments of the present invention encompass proteins having amino acid sequences that vary from those of the described antibodies, but that retain the ability to bind RSV-F. Such variant antibodies and antibody fragments comprise one or more additions, deletions, or substitutions of amino acids when compared to parent sequence, but exhibit biological activity that is essentially equivalent to that of the described antibodies. Likewise, the antibody-encoding DNA sequences of the present invention encompass sequences that comprise one or more additions, deletions, or substitutions of nucleotides when compared to the disclosed sequence, but that encode an antibody or antibody fragment that is essentially bioequivalent to an antibody or antibody fragment of the invention.

Two antigen-binding proteins, or antibodies, are considered bioequivalent if, for example, they are pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose under similar experimental conditions, either single does or multiple dose. Some antibodies will be considered equivalents or pharmaceutical alternatives if they are equivalent in the extent of their absorption but not in their rate of absorption and yet may be considered bioequivalent because such differences in the rate of absorption are intentional and are reflected in the labeling, are not essential to the attainment of effective body drug concentrations on, e.g., chronic use, and are considered medically insignificant for the particular drug product studied.

In one embodiment, two antigen-binding proteins are bioequivalent if there are no clinically meaningful differences in their safety, purity, and potency.

In one embodiment, two antigen-binding proteins are bioequivalent if a patient can be switched one or more times between the reference product and the biological product without an expected increase in the risk of adverse effects, including a clinically significant change in immunogenicity, or diminished effectiveness, as compared to continued therapy without such switching.

In one embodiment, two antigen-binding proteins are bioequivalent if they both act by a common mechanism or mechanisms of action for the condition or conditions of use, to the extent that such mechanisms are known.

Bioequivalence may be demonstrated by in vivo and/or in vitro methods. Bioequivalence measures include, e.g., (a) an in vivo test in humans or other mammals, in which the concentration of the antibody or its metabolites is measured in blood, plasma, serum, or other biological fluid as a function of time; (b) an in vitro test that has been correlated with and is reasonably predictive of human in vivo bioavailability data; (c) an in vivo test in humans or other mammals in which the appropriate acute pharmacological effect of the antibody (or its target) is measured as a function of time; and (d) in a well-controlled clinical trial that establishes safety, efficacy, or bioavailability or bioequivalence of an antibody.

Bioequivalent variants of the antibodies of the invention may be constructed by, for example, making various substitutions of residues or sequences or deleting terminal or internal residues or sequences not needed for biological activity. For example, cysteine residues not essential for biological activity can be deleted or replaced with other amino acids to prevent formation of unnecessary or incorrect intramolecular disulfide bridges upon renaturation. In other contexts, bioequivalent antibodies may include antibody variants comprising amino acid changes, which modify the glycosylation characteristics of the antibodies, e.g., mutations that eliminate or remove glycosylation.

Biological Characteristics of the Antibodies

In general, the antibodies of the present invention may function by binding to RSV-F and in so doing act to block the fusion of the viral membrane with the host cell membrane. The antibodies of the present invention may also function by binding to RSV-F and in so doing block the cell to cell spread of the virus and block syncytia formation associated with RSV infection of cells.

In certain embodiments, the antibodies of the present invention may function by blocking or inhibiting RSV fusion to the cell membrane by binding to any other region or fragment of the full length native F protein, the amino acid sequence of which is shown in SEQ ID NO: 354, also shown as Gen Bank accession number AAX23994.1. The antibodies may also bind to any region which is found in SEQ ID NO: 353, or to a fragment found within SEQ ID NO: 353.

In one embodiment, the invention provides a fully human monoclonal antibody or antigen-binding fragment thereof that binds to the F protein of RSV subtype A or B, wherein the antibody or fragment thereof exhibits one or more of the following characteristics: (a) is a fully human monoclonal antibody; (b) exhibits a K_D ranging from about 1×10^{-7} M to about 6×10^{-10}M; (c) is capable of neutralizing respiratory syncytial virus subtype A and subtype B strains in vitro; (d) demonstrates the ability to significantly reduce the viral load in an animal model of RSV infection (e) demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers when compared to palivizumab; (f) demonstrates an effective dose 99 (ED_{99}) of about 0.15 mg/kg or less when administered subcutaneously in a mouse model of RSV subtype A infection, or an ED_{99} of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection, or an ED_{99} of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection; (g) demonstrates an ED_{99} that is about 2 to 3 fold lower than the ED_{99} for palivizumab or motavizumab; (h) demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about 10 to 22 fold improvement over palivizumab; (i) demonstrates a neutralization potency against a subtype B laboratory strain of RSV that is about a 2 to 5 fold improvement over palivizumab (j) demonstrates a neutralization

potency against a subtype A laboratory strain or clinical strain of RSV that is about a 0.5 to 2 fold improvement over AM-22; (k) demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22; (l) comprises a HCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (m) comprises a LCVR having an amino acid sequence selected from the group consisting of SEQ ID NO: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (n) comprises a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity and a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 16, 32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (o) comprises a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; and a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NO: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350, or a substantially similar sequence thereof having at least 90%, at least 95%, at least 98% or at least 99% sequence identity; (p) interacts with an amino acid sequence comprising residues ranging from about position 161 to about position 188 of SEQ ID NO: 354; (q) interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354; (r) does not cross-compete for binding to RSV-F protein with palivizumab or motavizumab; (s) inhibits fusion of the virus to the cell.

Certain anti-RSV-F antibodies of the present invention are able to bind to the F protein of RSV and neutralize the infectivity of both subtypes A and B of RSV as determined by in vitro assays. The ability of the antibodies of the invention to bind to and neutralize the infectivity of the subtypes of RSV may be measured using any standard method known to those skilled in the art, including binding assays, or neutralization assays, or in vivo protection assays, as described herein.

Non-limiting, exemplary in vitro and in vivo assays for measuring binding activity and in vitro neutralization and in vivo efficacy are illustrated in Examples 3, 4, 5, 7, 8, 9, 10, 11 and 12 herein. In Example 3, the binding affinities and kinetic constants of human anti-RSV-F antibodies were determined by surface plasmon resonance and the measurements were conducted on a Biacore 4000 or T200 instrument. In Example 4, the potency of the antibodies was tested in a RSV micro-neutralization assay. Example 5 demonstrates the ability of the antibodies of the invention to neutralize an RSV infection in vivo in two different animal models. Examples 7 and 8 demonstrate the interaction of the antibodies of the invention with particular binding sites on RSV-F protein. Examples 9 and 10 demonstrate the neutralization capabilities of the antibodies with several laboratory and clinical strains of RSV subtypes A and B. Example 11 demonstrates the ability of the antibodies of the invention to inhibit fusion of the virus to cells. Example 12 demonstrates the cross-competition of various antibodies for binding to RSV-F.

Epitope Mapping and Related Technologies

Various techniques known to persons of ordinary skill in the art can be used to determine whether an antibody "interacts with one or more amino acids" within a polypeptide or protein. Exemplary techniques include, for example, a routine cross-blocking assay such as that described *Antibodies*, Harlow and Lane (Cold Spring Harbor Press, Cold Spring Harb., N.Y.) can be performed. Other methods include alanine scanning mutational analysis, peptide blot analysis (Reineke (2004) Methods Mol Biol 248:443-63), peptide cleavage analysis crystallographic studies and NMR analysis. In addition, methods such as epitope excision, epitope extraction and chemical modification of antigens can be employed (Tomer (2000) Protein Science 9: 487-496). Another method that can be used to identify the amino acids within a polypeptide with which an antibody interacts is hydrogen/deuterium exchange detected by mass spectrometry. In general terms, the hydrogen/deuterium exchange method involves deuterium-labeling the protein of interest, followed by binding the antibody to the deuterium-labeled protein. Next, the protein/antibody complex is transferred to water and exchangeable protons within amino acids that are protected by the antibody complex undergo deuterium-to-hydrogen back-exchange at a slower rate than exchangeable protons within amino acids that are not part of the interface. As a result, amino acids that form part of the protein/antibody interface may retain deuterium and therefore exhibit relatively higher mass compared to amino acids not included in the interface. After dissociation of the antibody, the target protein is subjected to protease cleavage and mass spectrometry analysis, thereby revealing the deuterium-labeled residues that correspond to the specific amino acids with which the antibody interacts. See, e.g., Ehring (1999) *Analytical Biochemistry* 267(2):252-259; Engen and Smith (2001) *Anal. Chem.* 73:256 A-265A.

The term "epitope" refers to a site on an antigen to which B and/or T cells respond. B-cell epitopes can be formed both from contiguous amino acids or noncontiguous amino acids juxtaposed by tertiary folding of a protein. Epitopes formed from contiguous amino acids are typically retained on exposure to denaturing solvents, whereas epitopes formed by tertiary folding are typically lost on treatment with

denaturing solvents. An epitope typically includes at least 3, and more usually, at least 5 or 8-10 amino acids in a unique spatial conformation.

Modification-Assisted Profiling (MAP), also known as Antigen Structure-based Antibody Profiling (ASAP) is a method that categorizes large numbers of monoclonal antibodies (mAbs) directed against the same antigen according to the similarities of the binding profile of each antibody to chemically or enzymatically modified antigen surfaces (US 2004/0101920, herein specifically incorporated by reference in its entirety). Each category may reflect a unique epitope either distinctly different from or partially overlapping with epitope represented by another category. This technology allows rapid filtering of genetically identical antibodies, such that characterization can be focused on genetically distinct antibodies. When applied to hybridoma screening, MAP may facilitate identification of rare hybridoma clones that produce mAbs having the desired characteristics. MAP may be used to sort the antibodies of the invention into groups of antibodies binding different epitopes.

In certain embodiments, the antibodies or antigen-binding fragments of the invention interact with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354. In certain embodiments, the antibodies of the invention may interact with amino acid residues that extend beyond the region identified above by about 5 to 10 amino acid residues, or by about 10 to 15 amino acid residues, or by about 15 to 20 amino acid residues towards either the amino terminal or the carboxy terminal of the RSV-F protein.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid sequence selected from the group consisting of SEQ ID NO: 355 and 356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within residues 161 through 188 of SEQ ID NO: 354.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with at least one amino acid residue within SEQ ID NO: 355 or SEQ ID NO:356.

In one embodiment, the invention provides an isolated human monoclonal antibody that specifically binds RSV-F, or an antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

The present invention includes anti-RSV-F antibodies that bind to the same epitope as any of the specific exemplary antibodies described herein in Table 1. Likewise, the present invention also includes anti-RSV-F antibodies that compete for binding to RSV-F fragment with any of the specific exemplary antibodies described herein in Table 1.

In certain embodiments, the antibodies of the present invention do not cross-compete for binding to RSV-F with palivizumab, motavizumab, or AM-22.

In certain embodiments, the antibodies of the present invention do not bind to the same epitope on RSV-F protein as palivizumab or motavizumab.

In certain embodiments, the antibodies of the present invention do not bind to an epitope on RSV-F ranging from amino acid residue 255 to amino acid residue 276 of SEQ ID NO: 354.

One can easily determine whether an antibody binds to the same epitope as, or competes for binding with, a reference anti-RSV-F antibody by using routine methods known in the art. For example, to determine if a test antibody binds to the same epitope as a reference RSV-F antibody of the invention, the reference antibody is allowed to bind to a RSV-F protein or peptide under saturating conditions. Next, the ability of a test antibody to bind to the RSV-F molecule is assessed. If the test antibody is able to bind to RSV-F following saturation binding with the reference anti-RSV-F antibody, it can be concluded that the test antibody binds to a different epitope than the reference anti-RSV-F antibody. On the other hand, if the test antibody is not able to bind to the RSV-F molecule following saturation binding with the reference anti-RSV-F antibody, then the test antibody may bind to the same epitope as the epitope bound by the reference anti-RSV-F antibody of the invention.

To determine if an antibody competes for binding with a reference anti-RSV-F antibody, the above-described binding methodology is performed in two orientations: In a first orientation, the reference antibody is allowed to bind to a RSV-F molecule under saturating conditions followed by assessment of binding of the test antibody to the RSV-F molecule. In a second orientation, the test antibody is allowed to bind to a RSV-F molecule under saturating conditions followed by assessment of binding of the reference antibody to the RSV-F molecule. If, in both orientations, only the first (saturating) antibody is capable of binding to the RSV-F molecule, then it is concluded that the test antibody and the reference antibody compete for binding to RSV-F. As will be appreciated by a person of ordinary skill in the art, an antibody that competes for binding with a reference antibody may not necessarily bind to the identical epitope as the reference antibody, but may sterically block binding of the reference antibody by binding an overlapping or adjacent epitope.

Two antibodies bind to the same or overlapping epitope if each competitively inhibits (blocks) binding of the other to the antigen. That is, a 1-, 5-, 10-, 20- or 100-fold excess of one antibody inhibits binding of the other by at least 50% but preferably 75%, 90% or even 99% as measured in a competitive binding assay (see, e.g., Junghans et al., Cancer Res. 1990 50:1495-1502). Alternatively, two antibodies have the same epitope if essentially all amino acid mutations in the antigen that reduce or eliminate binding of one antibody reduce or eliminate binding of the other. Two antibodies have overlapping epitopes if some amino acid mutations that reduce or eliminate binding of one antibody reduce or eliminate binding of the other.

Additional routine experimentation (e.g., peptide mutation and binding analyses) can then be carried out to confirm whether the observed lack of binding of the test antibody is in fact due to binding to the same epitope as the reference antibody or if steric blocking (or another phenomenon) is responsible for the lack of observed binding. Experiments of this sort can be performed using ELISA, RIA, surface plasmon resonance, flow cytometry or any other quantitative or qualitative antibody-binding assay available in the art.

Immunoconjugates

The invention encompasses a human RSV-F monoclonal antibody conjugated to a therapeutic moiety ("immunoconjugate"), such as an agent that is capable of reducing the severity of primary infection with RSV, or to ameliorate at least one symptom associated with RSV infection, including coughing, fever, pneumonia, or the severity thereof. Such an agent may be a second different antibody to RSV-F, or a vaccine. The type of therapeutic moiety that may be conjugated to the anti-RSV-F antibody and will take into account the condition to be treated and the desired therapeutic effect to be achieved. Alternatively, if the desired therapeutic effect is to treat the sequelae or symptoms associated with RSV infection, or any other condition resulting from such infection, such as, but not limited to, pneumonia, it may be advantageous to conjugate an agent appropriate to treat the sequelae or symptoms of the condition, or to alleviate any side effects of the antibodies of the invention. Examples of suitable agents for forming immunoconjugates are known in the art, see for example, WO 05/103081.

Multi-Specific Antibodies

The antibodies of the present invention may be monospecific, bi-specific, or multi-specific. Multi-specific antibodies may be specific for different epitopes of one target polypeptide or may contain antigen-binding domains specific for more than one target polypeptide. See, e.g., Tutt et al., 1991, J. Immunol. 147:60-69; Kufer et al., 2004, Trends Biotechnol. 22:238-244. The antibodies of the present invention can be linked to or co-expressed with another functional molecule, e.g., another peptide or protein. For example, an antibody or fragment thereof can be functionally linked (e.g., by chemical coupling, genetic fusion, noncovalent association or otherwise) to one or more other molecular entities, such as another antibody or antibody fragment to produce a bi-specific or a multi-specific antibody with a second binding specificity.

An exemplary bi-specific antibody format that can be used in the context of the present invention involves the use of a first immunoglobulin (Ig) C_{H3} domain and a second Ig C_{H3} domain, wherein the first and second Ig C_{H3} domains differ from one another by at least one amino acid, and wherein at least one amino acid difference reduces binding of the bi-specific antibody to Protein A as compared to a bi-specific antibody lacking the amino acid difference. In one embodiment, the first Ig C_{H3} domain binds Protein A and the second Ig C_{H3} domain contains a mutation that reduces or abolishes Protein A binding such as an H95R modification (by IMGT exon numbering; H435R by EU numbering). The second C_{H3} may further comprise a Y96F modification (by IMGT; Y436F by EU). Further modifications that may be found within the second C_{H3} include: D16E, L18M, N44S, K52N, V57M, and V82I (by IMGT; D356E, L358M, N384S, K392N, V397M, and V422I by EU) in the case of IgG1 antibodies; N44S, K52N, and V82I (IMGT; N384S, K392N, and V422I by EU) in the case of IgG2 antibodies; and Q15R, N44S, K52N, V57M, R69K, E79Q, and V82I (by IMGT; Q355R, N384S, K392N, V397M, R409K, E419Q, and V422I by EU) in the case of IgG4 antibodies. Variations on the bi-specific antibody format described above are contemplated within the scope of the present invention.

Therapeutic Administration and Formulations

The invention provides therapeutic compositions comprising the anti-RSV-F antibodies or antigen-binding fragments thereof of the present invention. The administration of therapeutic compositions in accordance with the invention will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LIPOFECTIN™), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. See also Powell et al. "Compendium of excipients for parenteral formulations" PDA (1998) J Pharm Sci Technol 52:238-311.

The dose of each of the antibodies of the invention may vary depending upon the age and the size of a subject to be administered, target disease, conditions, route of administration, and the like. When the antibodies of the present invention are used for treating a RSV infection in a patient, or for treating one or more symptoms associated with a RSV infection, such as the cough or pneumonia associated with a RSV infection in a patient, or for lessening the severity of the disease, it is advantageous to administer each of the antibodies of the present invention intravenously or subcutaneously normally at a single dose of about 0.01 to about 30 mg/kg body weight, more preferably about 0.1 to about 20 mg/kg body weight, or about 0.1 to about 15 mg/kg body weight, or about 0.02 to about 7 mg/kg body weight, about 0.03 to about 5 mg/kg body weight, or about 0.05 to about 3 mg/kg body weight, or about 1 mg/kg body weight, or about 3.0 mg/kg body weight, or about 10 mg/kg body weight, or about 20 mg/kg body weight. Multiple doses may be administered as necessary. Depending on the severity of the condition, the frequency and the duration of the treatment can be adjusted. In certain embodiments, the antibodies or antigen-binding fragments thereof of the invention can be administered as an initial dose of at least about 0.1 mg to about 800 mg, about 1 to about 600 mg, about 5 to about 300 mg, or about 10 to about 150 mg, to about 100 mg, or to about 50 mg. In certain embodiments, the initial dose may be followed by administration of a second or a plurality of subsequent doses of the antibodies or antigen-binding fragments thereof in an amount that can be approximately the same or less than that of the initial dose, wherein the subsequent doses are separated by at least 1 day to 3 days; at least one week, at least 2 weeks; at least 3 weeks; at least 4 weeks; at least 5 weeks; at least 6 weeks; at least 7 weeks; at least 8 weeks; at least 9 weeks; at least 10 weeks; at least 12 weeks; or at least 14 weeks.

Various delivery systems are known and can be used to administer the pharmaceutical composition of the invention, e.g., encapsulation in liposomes, microparticles, microcapsules, recombinant cells capable of expressing the mutant viruses, receptor mediated endocytosis (see, e.g., Wu et al. (1987) J. Biol. Chem. 262:4429-4432). Methods of introduction include, but are not limited to, intradermal, transdermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural and oral routes. The composition may be administered by any convenient route, for example by infusion or bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral mucosa, nasal mucosa, rectal and intestinal mucosa, etc.) and may be administered together with other biologically active agents. Administration can be systemic or local. It may be delivered as an aerosolized formulation (See US2011/0311515 and US2012/0128669). The delivery of agents useful for treating respiratory diseases by inhalation

is becoming more widely accepted (See A. J. Bitonti and J. A. Dumont, (2006), Adv. Drug Deliv. Rev, 58:1106-1118). In addition to being effective at treating local pulmonary disease, such a delivery mechanism may also be useful for systemic delivery of antibodies (See Maillet et al. (2008), Pharmaceutical Research, Vol. 25, No. 6, 2008).

The pharmaceutical composition can be also delivered in a vesicle, in particular a liposome (see, for example, Langer (1990) Science 249:1527-1533).

In certain situations, the pharmaceutical composition can be delivered in a controlled release system. In one embodiment, a pump may be used. In another embodiment, polymeric materials can be used. In yet another embodiment, a controlled release system can be placed in proximity of the composition's target, thus requiring only a fraction of the systemic dose.

The injectable preparations may include dosage forms for intravenous, subcutaneous, intracutaneous and intramuscular injections, drip infusions, etc. These injectable preparations may be prepared by methods publicly known. For example, the injectable preparations may be prepared, e.g., by dissolving, suspending or emulsifying the antibody or its salt described above in a sterile aqueous medium or an oily medium conventionally used for injections. As the aqueous medium for injections, there are, for example, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., which may be used in combination with an appropriate solubilizing agent such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), a nonionic surfactant [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc. As the oily medium, there are employed, e.g., sesame oil, soybean oil, etc., which may be used in combination with a solubilizing agent such as benzyl benzoate, benzyl alcohol, etc. The injection thus prepared is preferably filled in an appropriate ampoule.

A pharmaceutical composition of the present invention can be delivered subcutaneously or intravenously with a standard needle and syringe. In addition, with respect to subcutaneous delivery, a pen delivery device readily has applications in delivering a pharmaceutical composition of the present invention. Such a pen delivery device can be reusable or disposable. A reusable pen delivery device generally utilizes a replaceable cartridge that contains a pharmaceutical composition. Once all of the pharmaceutical composition within the cartridge has been administered and the cartridge is empty, the empty cartridge can readily be discarded and replaced with a new cartridge that contains the pharmaceutical composition. The pen delivery device can then be reused. In a disposable pen delivery device, there is no replaceable cartridge. Rather, the disposable pen delivery device comes prefilled with the pharmaceutical composition held in a reservoir within the device. Once the reservoir is emptied of the pharmaceutical composition, the entire device is discarded.

Numerous reusable pen and autoinjector delivery devices have applications in the subcutaneous delivery of a pharmaceutical composition of the present invention. Examples include, but certainly are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Burghdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, Ind.), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, N.J.), OPTIPENT™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present invention include, but certainly are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousands Oaks, Calif.), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L. P.) and the HUMIRA™ Pen (Abbott Labs, Abbott Park, Ill.), to name only a few.

Advantageously, the pharmaceutical compositions for oral or parenteral use described above are prepared into dosage forms in a unit dose suited to fit a dose of the active ingredients. Such dosage forms in a unit dose include, for example, tablets, pills, capsules, injections (ampoules), suppositories, etc. The amount of the aforesaid antibody contained is generally about 5 to about 500 mg per dosage form in a unit dose; especially in the form of injection, it is preferred that the aforesaid antibody is contained in about 5 to about 100 mg and in about 10 to about 250 mg for the other dosage forms.

Administration Regimens

According to certain embodiments of the present invention, multiple doses of an antibody to RSV-F may be administered to a subject over a defined time course. The methods according to this aspect of the invention comprise sequentially administering to a subject multiple doses of an antibody to RSV-F. As used herein, "sequentially administering" means that each dose of antibody to RSV-F is administered to the subject at a different point in time, e.g., on different days separated by a predetermined interval (e.g., hours, days, weeks or months). The present invention includes methods which comprise sequentially administering to the patient a single initial dose of an antibody to RSV-F, followed by one or more secondary doses of the antibody to RSV-F and optionally followed by one or more tertiary doses of the antibody to RSV-F.

The terms "initial dose," "secondary doses," and "tertiary doses," refer to the temporal sequence of administration of the antibody to RSV-F. Thus, the "initial dose" is the dose which is administered at the beginning of the treatment regimen (also referred to as the "baseline dose"); the "secondary doses" are the doses which are administered after the initial dose; and the "tertiary doses" are the doses which are administered after the secondary doses. The initial, secondary, and tertiary doses may all contain the same amount of antibody to RSV-F, but generally may differ from one another in terms of frequency of administration. In certain embodiments, however, the amount of antibody to RSV-F contained in the initial, secondary and/or tertiary doses vary from one another (e.g., adjusted up or down as appropriate) during the course of treatment. In certain embodiments, two or more (e.g., 2, 3, 4, or 5) doses are administered at the beginning of the treatment regimen as "loading doses" followed by subsequent doses that are administered on a less frequent basis (e.g., "maintenance doses").

In one exemplary embodiment of the present invention, each secondary and/or tertiary dose is administered 1 to 26 (e.g., 1, 1½, 2, 2½, 3, 3½, 4, 4½, 5, 5½, 6, 6½, 7, 7½, 8, 8½, 9, 9½, 10, 10½, 11, 11½, 12, 12½, 13, 13½, 14, 14½, 15, 15½, 16, 16½, 17, 17½, 18, 18½, 19, 19½, 20, 20½, 21, 21½, 22, 22½, 23, 23½, 24, 24½, 25, 25½, 26, 26½, or more) weeks after the immediately preceding dose. The phrase "the immediately preceding dose," as used herein, means, in a sequence of multiple administrations, the dose of

antibody to RSV-F which is administered to a patient prior to the administration of the very next dose in the sequence with no intervening doses.

The methods according to this aspect of the invention may comprise administering to a patient any number of secondary and/or tertiary doses of an antibody to RSV-F. For example, in certain embodiments, only a single secondary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) secondary doses are administered to the patient. Likewise, in certain embodiments, only a single tertiary dose is administered to the patient. In other embodiments, two or more (e.g., 2, 3, 4, 5, 6, 7, 8, or more) tertiary doses are administered to the patient.

In embodiments involving multiple secondary doses, each secondary dose may be administered at the same frequency as the other secondary doses. For example, each secondary dose may be administered to the patient 1 to 2 weeks after the immediately preceding dose. Similarly, in embodiments involving multiple tertiary doses, each tertiary dose may be administered at the same frequency as the other tertiary doses. For example, each tertiary dose may be administered to the patient 2 to 4 weeks after the immediately preceding dose. Alternatively, the frequency at which the secondary and/or tertiary doses are administered to a patient can vary over the course of the treatment regimen. The frequency of administration may also be adjusted during the course of treatment by a physician depending on the needs of the individual patient following clinical examination.

Therapeutic Uses of the Antibodies

Due to their binding to/interaction with, the RSV fusion protein (RSV-F), the present antibodies are useful for preventing fusion of the virus with the host cell membrane, for preventing cell to cell virus spread, and for inhibition of syncytia formation. As such, the antibodies of the present invention are useful for preventing an infection of a subject with RSV when administered prophylactically. Alternatively, the antibodies of the present invention may be useful for ameliorating at least one symptom associated with the infection, such as coughing, fever, pneumonia, or for lessening the severity, duration, and/or frequency of the infection. The antibodies of the invention are also contemplated for prophylactic use in patients at risk for developing or acquiring an RSV infection. These patients include pre-term infants, full term infants born during RSV season (late fall to early spring), the elderly (for example, in anyone 65 years of age or older), or patients immunocompromised due to illness or treatment with immunosuppressive therapeutics, or patients who may have an underlying medical condition that predisposes them to an RSV infection (for example, cystic fibrosis patients, patients with congestive heart failure or other cardiac conditions, patients with airway impairment, patients with COPD). It is contemplated that the antibodies of the invention may be used alone, or in conjunction with a second agent, or third agent for treating RSV infection, or for alleviating at least one symptom or complication associated with the RSV infection, such as the fever, coughing, bronchiolitis, or pneumonia associated with, or resulting from such an infection. The second or third agents may be delivered concurrently with the antibodies of the invention, or they may be administered separately, either before or after the antibodies of the invention. The second or third agent may be an anti-viral such as ribavirin, an NSAID or other agents to reduce fever or pain, another second but different antibody that specifically binds RSV-F, an agent (e.g. an antibody) that binds to another RSV antigen, such as RSV-G, a vaccine against RSV, an siRNA specific for an RSV antigen.

In yet a further embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for treating patients suffering from a RSV infection. In yet another embodiment of the invention the present antibodies are used for the preparation of a pharmaceutical composition for reducing the severity of a primary infection with RSV, or for reducing the duration of the infection, or for reducing at least one symptom associated with the RSV infection. In a further embodiment of the invention the present antibodies are used as adjunct therapy with any other agent useful for treating an RSV infection, including an antiviral, a toxoid, a vaccine, a second RSV-F antibody, or any other antibody specific for an RSV antigen, including an RSV-G antibody, or any other palliative therapy known to those skilled in the art.

Combination Therapies

As noted above, the methods of the present invention, according to certain embodiments, comprise administering to the subject one or more additional therapeutic agents in combination with an antibody to RSV-F. As used herein, the expression "in combination with" means that the additional therapeutic agents are administered before, after, or concurrent with the pharmaceutical composition comprising the anti-RSV-F antibody. The term "in combination with" also includes sequential or concomitant administration of the anti-RSV-F antibody and a second therapeutic agent.

For example, when administered "before" the pharmaceutical composition comprising the anti-RSV-F antibody, the additional therapeutic agent may be administered about 72 hours, about 60 hours, about 48 hours, about 36 hours, about 24 hours, about 12 hours, about 10 hours, about 8 hours, about 6 hours, about 4 hours, about 2 hours, about 1 hour, about 30 minutes, about 15 minutes or about 10 minutes prior to the administration of the pharmaceutical composition comprising the anti-RSV-F antibody. When administered "after" the pharmaceutical composition comprising the anti-RSV-F antibody, the additional therapeutic agent may be administered about 10 minutes, about 15 minutes, about 30 minutes, about 1 hour, about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 24 hours, about 36 hours, about 48 hours, about 60 hours or about 72 hours after the administration of the pharmaceutical composition comprising the anti-RSV-F antibodies. Administration "concurrent" or with the pharmaceutical composition comprising the anti-RSV-F antibody means that the additional therapeutic agent is administered to the subject in a separate dosage form within less than 5 minutes (before, after, or at the same time) of administration of the pharmaceutical composition comprising the anti-RSV-F antibody, or administered to the subject as a single combined dosage formulation comprising both the additional therapeutic agent and the anti-RSV-F antibody.

Combination therapies may include an anti-RSV-F antibody of the invention and any additional therapeutic agent that may be advantageously combined with an antibody of the invention, or with a biologically active fragment of an antibody of the invention.

For example, a second or third therapeutic agent may be employed to aid in reducing the viral load in the lungs, such as an antiviral, for example, ribavirin. The antibodies may also be used in conjunction with other therapies, as noted above, including a toxoid, a vaccine specific for RSV, a

second antibody specific for RSV-F, or an antibody specific for another RSV antigen, such as RSV-G.

Diagnostic Uses of the Antibodies

The anti-RSV antibodies of the present invention may also be used to detect and/or measure RSV in a sample, e.g., for diagnostic purposes. It is envisioned that confirmation of an infection thought to be caused by RSV may be made by measuring the presence of the virus through use of any one or more of the antibodies of the invention. Exemplary diagnostic assays for RSV may comprise, e.g., contacting a sample, obtained from a patient, with an anti-RSV-F antibody of the invention, wherein the anti-RSV-F antibody is labeled with a detectable label or reporter molecule or used as a capture ligand to selectively isolate the virus containing the F protein from patient samples. Alternatively, an unlabeled anti-RSV-F antibody can be used in diagnostic applications in combination with a secondary antibody which is itself detectably labeled. The detectable label or reporter molecule can be a radioisotope, such as ^{3}H, ^{14}C, ^{32}P, ^{35}S, or ^{125}I; a fluorescent or chemiluminescent moiety such as fluorescein isothiocyanate, or rhodamine; or an enzyme such as alkaline phosphatase, β-galactosidase, horseradish peroxidase, or luciferase. Specific exemplary assays that can be used to detect or measure RSV containing the F protein in a sample include enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), and fluorescence-activated cell sorting (FACS).

Samples that can be used in RSV diagnostic assays according to the present invention include any tissue or fluid sample obtainable from a patient, which contains detectable quantities of RSV-F protein, or fragments thereof, under normal or pathological conditions. Generally, levels of RSV-F in a particular sample obtained from a healthy patient (e.g., a patient not afflicted with a disease or condition associated with the presence of RSV-F) will be measured to initially establish a baseline, or standard, level of the F protein from RSV. This baseline level of RSV-F can then be compared against the levels of RSV-F measured in samples obtained from individuals suspected of having an RSV infection, or symptoms associated with such infection.

Vaccines and Immunogenic Compositions

One aspect of the invention provides an immunogenic composition, or a vaccine, that when administered to an individual, preferably a human, induces an immune response in such individual to a Respiratory Syncytial Virus (RSV) antigen, for example, a RSV-F polypeptide, wherein the composition may comprise a recombinant RSV-F protein, or a polypeptide fragment of a RSV-F protein, or an epitope contained within and obtained from an antigen of the RSV-F polypeptide or a fragment thereof, and/or comprises DNA and/or RNA which encodes and expresses an epitope from an antigen of the RSV-F polypeptide, or other polypeptides of the invention. The immunogenic composition or vaccine may be used therapeutically or prophylactically and may be used to elicit antibody immunity and/or cellular immunity, such as cellular immunity arising from CTL or CD4+ T cells.

In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise the RSV-F protein as shown in SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise a RSV-F polypeptide fragment comprising residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the immunogenic composition, or vaccine, may comprise SEQ ID NO: 355 and/or SEQ ID NO: 356.

In a related aspect, the invention provides a method for inducing an immune response in an individual, particularly a mammal, preferably humans, by administering to an individual an immunogenic composition, or a vaccine, comprising a RSV-F protein, or an immunogenic fragment thereof, or a RSV-F antigen or an immunogenic fragment thereof comprising one or more epitopes contained within the RSV-F antigen or fragment thereof, adequate to produce an antibody and/or a T cell immune response to protect the individual from infection, particularly infection with Respiratory Syncytial Virus (RSV). Also provided are methods of using the immunogenic compositions, or vaccines of the invention for inducing an immune response that results in inhibiting, or slowing the progression of cell to cell viral spread. Methods are also provided for ameliorating at least one symptom associated with RSV infection by administering an immunogenic composition, or a vaccine, comprising at least one RSV-F antigen, or one or more epitopes contained within the RSV-F antigen, which when administered will induce an immune response in the individual.

For example, in one embodiment the invention provides a method of inducing an immune response in an individual comprising delivering to the individual an immunogenic composition, or vaccine comprising, an RSV-F antigen (e.g. the amino acid sequence shown in SEQ ID NO: 354), or an antigenic fragment thereof, (e.g. a polypeptide comprising residues 161 through 188 of SEQ ID NO: 354), or a nucleic acid vector comprising a nucleotide sequence to direct expression of such viral polypeptide, or a fragment or a variant thereof, in vivo in order to induce an immune response.

In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises residues 161 through 188 of SEQ ID NO: 354. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises one or more amino acid residues contained within SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the polypeptide to be used in an immunogenic composition or in a vaccine for inducing an immune response in an individual comprises SEQ ID NO: 355 and/or SEQ ID NO: 356. In one embodiment of the invention, the immunogenic composition, or vaccine, may elicit an antibody response specific for the RSV-F antigen of RSV, wherein the antibodies generated interact with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

In certain embodiments, it is advantageous for the RSV-F antigens or fragments thereof to be formulated into immunogenic compositions, or vaccines that comprise immunogenic, preferably immunologically effective, amounts of additional antigens to elicit immunity to other pathogens, preferably viruses and/or bacteria. Such additional antigens may include an influenza virus antigen, an antigen from metapneumovirus or from a coronavirus, an antigen from *Haemophilus influenzae, Streptococcus pneumonia*, or *Bordetella pertussis*. Other RSV antigens may be included in the immunogenic compositions, or vaccines, such as the RSV-G glycoprotein, or immunogenic fragments thereof, the HN protein, or derivatives thereof. In certain embodiments, influenza virus antigens to be included in the immunogenic

compositions or vaccines of the invention may include whole, live or inactivated virus, split influenza virus, grown in eggs or MDCK cells, or Vero cells or whole flu virosomes, or purified or recombinant proteins thereof, such as HA, NP, NA, or M proteins, or combinations thereof.

In certain embodiments of the invention, the immunogenic composition, or vaccine formulation may comprise an immunogenic recombinant polypeptide and/or polynucleotide of the invention, or a combination thereof, together with a suitable carrier/excipient, such as a pharmaceutically acceptable carrier/excipient. The immunogenic composition and/or vaccine is preferably administered parenterally, including, for example, administration that is subcutaneous, intramuscular, intravenous, or intradermal. Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostatic compounds and solutes which render the formulation isotonic with the bodily fluid, preferably the blood, of the individual; and aqueous and non-aqueous sterile suspensions which may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use.

The immunogenic composition, or vaccine formulation of the invention may also include adjuvants for enhancing the immunogenicity of the formulation. At this time, the only adjuvant widely used in humans has been alum (aluminum phosphate or aluminum hydroxide) and calcium phosphate gels. Freund's complete adjuvant and other adjuvants used in research and veterinary applications have toxicities, which limit their potential use in human vaccines. However, chemically defined preparations such as oil emulsions and surfactant based formulations, e.g., MF59 (microfluidized detergent stabilized oil-in-water emulsion), QS21 (purified saponin), AS02 [SBAS2] (oil-in-water emulsion+MPL+QS-21), Montanide ISA-51 and ISA-720 (stabilized water-in-oil emulsion), are also in development. Furthermore, microbial derivatives (natural and synthetic), e.g., muramyl dipeptide, monophosphoryl lipid A (e.g. 3 De-O-acylated monophosphoryl lipid A, also known as 3D-MPL, which is manufactured by Ribi Immunochem, Montana), Detox (MPL+M. Phleicell wall skeleton), AGP [RC-529] (synthetic acylated monosaccharide), DCChoI (lipoidal immunostimulators able to self organize into liposomes), OM-174 (lipid A derivative), CpG motifs (synthetic oligonucleotides containing immunostimulatory CpG motifs), modified LT and CT (genetically modified bacterial toxins to provide non-toxic adjuvant effects), and QS21, an Hplc purified non-toxic fraction derived from the bark of Quillaja Saponaria Molina, have all been in development for human use.

A preferred form of 3 De-O-acylated monophosphoryl lipid A is disclosed in European Patent 0 689 454 B1 (SmithKline Beecham Biologicals SA).

Other particulate adjuvants include, e.g., virosomes (unilamellar liposomal vehicles incorporating a viral antigen), AS04 ([SBAS4] Al salt with MPL), ISCOMS (structured complex of saponins and lipids), polylactide co-glycolide (PLG).

Other suitable adjuvants include all acceptable immunostimulatory compounds, such as cytokines, chemokines, or colony stimulating factors. For example, these may include the interleukins IL-1, IL-2, IL-4, IL-7, IL-12, gamma-interferon, and hGM-CSF.

It is to be understood that the adjuvant and/or immunostimulatory compound to be used will depend on the subject to which the vaccine or immunogenic composition will be administered, the route of injection and the number of injections to be given.

While the invention has been described with reference to certain RSV-F polypeptides, it is to be understood that this covers fragments of the naturally occurring polypeptides, and similar polypeptides with additions, deletions or substitutions which do not substantially affect the immunogenic properties of the recombinant polypeptides or polynucleotides.

EXAMPLES

The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1

Generation of Human Antibodies to RSV-F Protein

An immunogen comprising any one of the following can be used to generate antibodies to RSV-F protein. In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a whole respiratory syncytial virus isolate, either live, attenuated or killed/inactivated. The mice may be given one or more booster shots containing either the same virus isolate, or they may be boosted with the RSV-F protein itself. In certain embodiments, the mice are injected with live virus, followed by boosting with the construct shown as SEQ ID NO: 353, or with isolated RSV-F protein, obtained from a virus isolate or prepared recombinantly. (See also GenBank accession number AAX23994.1)

In certain embodiments, the antibodies of the invention are obtained from mice immunized with a primary immunogen, such as a biologically active RSV, subtype A or B, and/or the RSV fusion (F) protein, or an immunogenic fragment of the RSV fusion (RSV-F) protein, or DNA encoding the full length protein or the active fragment thereof. The immunogen may be delivered to the animal via any route including but not limited to intramuscularly, subcutaneously, intravenously or intranasally.

In certain embodiments, whole virus, or the RSV-F protein or fragments thereof may be used for preparing monospecific, bispecific, or multispecific antibodies.

The whole virus, or full length proteins, or fragments thereof, that were used as immunogens, as noted above, were administered directly, with an adjuvant to stimulate the immune response, to a VELOCIMMUNE® mouse comprising DNA encoding human Immunoglobulin heavy and kappa light chain variable regions. The antibody immune response was monitored by a RSV-F immunoassay. When a desired immune response was achieved, splenocytes were harvested and fused with mouse myeloma cells to preserve their viability and form hybridoma cell lines. The hybridoma cell lines were screened and selected to identify cell lines that produce RSV-F-specific antibodies. Using this tech-

nique, and the various immunogens described above, several chimeric antibodies (i.e., antibodies possessing human variable domains and mouse constant domains) were obtained; certain exemplary antibodies generated in this manner were designated as H1M3621N, H1M3622N, H1M2634N and H1M3627N.

Anti-RSV-F antibodies were also isolated directly from antigen-positive B cells without fusion to myeloma cells, as described in U.S. 2007/0280945A1, herein specifically incorporated by reference in its entirety. Using this method, several fully human anti-RSV-F antibodies (i.e., antibodies possessing human variable domains and human constant domains) were obtained; exemplary antibodies generated in this manner were designated as follows: H1H3564P, H1H3565P, H1H3566P, H1H3567P, H1H3581P, H1H3583P, H1H3589P, H1H3591P, H1H3592P, H1H3597P, H1H3598P, H1H3603P, H1H3604P, H1H3605P, H1H3607P, H1H3608P2, H1H3592P2 and H1H3592P3.

The biological properties of the exemplary antibodies generated in accordance with the methods of this Example are described in detail in the Examples set forth below.

Example 2

Heavy and Light Chain Variable Region Amino Acid Sequences

Table 1 sets forth the heavy and light chain variable region amino acid sequence pairs of selected antibodies specific for RSV-F protein and their corresponding antibody identifiers. Antibodies are typically referred to herein according to the following nomenclature: Fc prefix (e.g. "H4H", "H1M, "H2M"), followed by a numerical identifier (e.g. "3117" as shown in Table 1), followed by a "P" or "N" suffix. Thus, according to this nomenclature, an antibody may be referred to as, e.g. "H1H3117". The H4H, H1M, and H2M prefixes on the antibody designations used herein indicate the particular Fc region of the antibody. For example, an "H2M" antibody has a mouse IgG2 Fc, whereas an "H4H" antibody has a human IgG4 Fc. As will be appreciated by a person of ordinary skill in the art, an H1M or H2M antibody can be converted to an H4H antibody, and vice versa, but in any event, the variable domains (including the CDRs), which are indicated by the numerical identifiers shown in Table 1, will remain the same. Antibodies having the same numerical antibody designation, but differing by a letter suffix of N, B or P refer to antibodies having heavy and light chains with identical CDR sequences but with sequence variations in regions that fall outside of the CDR sequences (i.e., in the framework regions). Thus, N, B and P variants of a particular antibody have identical CDR sequences within their heavy and light chain variable regions but differ from one another within their framework regions.

Antibody Comparators

Anti-RSV-F antibody controls were included in the following Examples for comparative purposes. Isotype matched negative controls were also used in the Examples. One anti-RSV-F control antibody is designated herein as Control I and is a humanized anti-RSV-F antibody with heavy and light chain variable domain sequences of the palivizumab (SYNAGIS®) humanized antibody as set forth in U.S. Pat. No. 7,635,568 and U.S. Pat. No. 5,824,307. The variable light and heavy chains were expressed with human kappa and gamma-1 constants, respectively. One anti-RSV-F antibody is designated herein as Control II and is a humanized anti-RSV-F antibody variant of palivizumab, with heavy and light chain variable domain sequences of the motavizumab (NUMAX™) humanized antibody described in US2003/0091584 and by Wu et al, (2007), J. Mol. Biol. 368:652-665. The variable light and heavy chains were expressed with human kappa and gamma-1 constants, respectively. Another anti-RSV-F antibody is designated as Control III (also referred to as AM-22) and is described in U.S. Pat. No. 8,568,726. The amino acid sequence of the heavy and light chain of AM-22 is shown in SEQ ID NO: 357 (for the heavy chain of the antibody) and SEQ ID NO: 358 (for the light chain of the antibody).

TABLE 1

Antibody	SEQ ID NOs:							
Designation	HCVR	HCDR1	HCDR2	HCDR3	LCVR	LCDR1	LCDR2	LCDR3
H1H3564P	2	4	6	8	10	12	14	16
H1H3565P	18	20	22	24	26	28	30	32
H1H3566P	34	36	38	40	42	44	46	48
H1H3567P	50	52	54	56	58	60	62	64
H1H3581P	66	68	70	72	74	76	78	80
H1H3583P	82	84	86	88	90	92	94	96
H1H3589P	98	100	102	104	106	108	110	112
H1H3591P	114	116	118	120	122	124	126	128
H1H3592P	130	132	134	136	138	140	142	144
H1H3597P	146	148	150	152	154	156	158	160
H1H3598P	162	164	166	168	170	172	174	176
H1H3603P	178	180	182	184	186	188	190	192
H1H3604P	194	196	198	200	202	204	206	208
H1H3605P	210	212	214	216	218	220	222	224
H1H3607P	226	228	230	232	234	236	238	240
H1H3608P2	242	244	246	248	250	252	254	256
H1H3592P2	258	260	262	264	266	268	270	272
H1H3592P3	274	276	278	280	282	284	286	288
H1M3621N	290	292	294	296	298	300	302	304
H1M3622N	306	308	310	312	314	316	318	320
H1M2634N	322	324	326	328	330	332	334	336
H1M3627N	338	340	342	344	346	348	350	352

Example 3

Antibody Binding Affinities and Kinetic Constants of Human Monoclonal Anti-RSV-F Antibodies as Determined by Surface Plasmon Resonance

Binding affinities and kinetic constants of human monoclonal anti-RSV-F antibodies were determined by surface plasmon resonance at 25° C. (Tables 2-3). Measurements were conducted on a Biacore 4000 or T-200 instrument. Antibodies, expressed with either mouse Fc (AbPID prefix H1M; H2M) or human IgG1 Fc (AbPID prefix H1H), were captured onto an anti-mouse or anti-human Fc sensor surface (Mab capture format), and soluble monomeric (RSV-F.mmh; SEQ ID NO: 353) protein was injected over the surface. All Biacore binding studies were performed in HBST running buffer (0.01 M HEPES pH 7.4, 0.15 M NaCl, 3 mM EDTA, 0.005% v/v surfactant P20). Different concentrations of RSV-F.mmh prepared in HBST running buffer were injected over the anti-RSV-F monoclonal antibody captured surface at a flow rate of 30 μl/min (Biacore 4000) or at a flow rate of 50 μl/min (Biacore T-200) and the association of RSV-F.mmh to captured monoclonal antibody was monitored for 6 min or 3 min respectively. The dissociation of RSV-F.mmh from the monoclonal antibody in HBST running buffer was monitored for 8-10 min at 25° C. Kinetic association (k_a) and dissociation (k_d) rate constants were determined by processing and fitting the data to a 1:1 binding model using Scrubber 2.0 curve fitting software. Binding dissociation equilibrium constants (K_D) and dissociative half-lives (t½) were calculated from the kinetic rate constants as: K_D (M)=k_d/k_a; and $t_{1/2}$ (min)=(ln 2/(60*k_d).

Anti-RSV-F antibodies of the invention displayed a broad range of affinities for RSV-F.mmh. Control 1, produced based on the public sequence of palivizumab set forth in U.S. Pat. No. 7,635,568, and Control II, produced on the public sequence of motavizumab as described in Wu et al, (2007), (J. Mol. Biol. 368:652-665) displayed the approximately ~70-fold difference (control 1; 38 nM vs control II; 0.43 nM) in affinity that has been previously reported.

TABLE 2

Biacore Binding Affinities of Hybridoma mAbs at 25° C. Binding at 25° C./Mab Capture Format

AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H1M3621N	2.05E+05	2.08E−04	1.01E−09	56
H1M3622N	3.84E+04	9.13E−05	2.38E−09	127
H1M3624N	1.79E+05	1.83E−04	1.02E−09	63
H1M3627N	2.59E+05	5.23E−04	2.02E−09	22

TABLE 3

Biacore binding affinities of human Fc mAbs at 25° C. Binding at 25° C./Mab Capture Format

AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H1H3564P	3.10E+03	7.78E−05	2.50E−08	148
H1H3565P	1.93E+04	5.80E−05	3.01E−09	199
H1H3566P	2.04E+04	4.20E−05	2.06E−09	275
H1H3567P	6.05E+04	2.63E−03	4.34E−08	4
H1H3581P	NB	NB	NB	NB
H1H3583P	8.94E+04	3.08E−03	3.44E−08	4
H1H3589P	3.77E+04	9.14E−03	2.43E−07	1
H1H3591P	4.46E+04	1.53E−03	3.42E−08	8
H1H3592P	1.06E+05	4.66E−04	4.39E−09	25

TABLE 3-continued

Biacore binding affinities of human Fc mAbs at 25° C. Binding at 25° C./Mab Capture Format

AbPID	k_a (1/Ms)	k_d (1/s)	K_D (M)	t½ (min)
H1H3592P2	9.93E+04	1.46E−03	1.47E−08	8
H1H3592P3	8.86E+04	7.47E−04	8.43E−09	15
H1H3597P	NB	NB	NB	NB
H1H3598P	NB	NB	NB	NB
H1H3603P	3.00E+03	1.23E−04	4.10E−08	94
H1H3604P	3.10E+03	9.27E−05	3.00E−08	125
H1H3605P	2.80E+03	1.68E−04	5.90E−08	69
H1H3607P	4.20E+03	1.48E−04	3.50E−08	78
H1H3608P2	4.85E+03	2.60E−05	5.35E−09	445
H1H3627N	2.56E+05	1.49E−04	5.81E−10	78
Control I	6.75E+04	2.57E−03	3.81E−08	4
Control II	1.89E+05	8.13E−05	4.29E−10	142

NB: No binding observed under the conditions of the experiment

Example 4

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtype a and Subtype B Strains

Purified antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10^4 HEp-2 cells cultured in MEM high glucose medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37° C., 5% CO_2). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with the RSV 1540 (A2) strain at an MOI of 0.04 for 2 hours (37 C, 5% CO_2). Virus-free and irrelevant isotype controls were included.

Post incubation, the antibody:virus mixture was added to the HEp-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV A2 (1540) strain (Table 4-5). Several antibodies displayed lower IC_{50} values then control I while only a few exemplary antibodies H1H3627N, H1H3591P, H1H3592P and H1H3592P3 showed better neutralization then control II. Select antibodies (H1H3627N, H1H3592P3) were also tested for their ability to neutralization RSV subtype B strains (Table 6).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several strains of RSV-F, across two subtypes, in vitro, with greater potency than previously demonstrated for established controls.

TABLE 4

Neutralization potency for selected mAbs against RSV A2 (1540)

	IC_{50} [pM] for RSV A2 Neutralization:						
AbPID	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	Trial 6	Trial 7
H1M3621N	582	180	—	—	—	—	—
H1M3622N	320	82	—	—	—	—	—
H1M3624N	540	270	92	—	—	—	—
H1M3627N	4	4	5	—	—	10	—
H1H3564P	>10000	—	—	—	—	—	—
H1H3565P	>10000	—	—	—	—	—	—
H1H3566P	>10000	—	—	—	—	—	—
H1H3567P	—	—	—	257	—	390	—
H1H3581P	>10000	—	—	—	—	—	—
H1H3583P	—	—	—	—	50	—	—
H1H3589P	—	—	—	—	300	—	—
H1H3591P	—	—	—	6	—	8	6
H1H3592P	—	—	—	6	—	5	4
H1H3592P3							10
H1H3597P	>10000	—	—	—	—	—	—
H1H3598P	>10000	—	—	—	—	—	—
H1H3603P	>10000	—	—	—	—	—	—
H1H3604P	>10000	—	—	—	—	—	—
H1H3605P	>10000	—	—	—	—	—	—
H1H3607P	>10000	—	—	—	—	—	—
H1H3608P2	>10000	—	—	—	—	—	—
H1H3570P	>10000	—	—	—	—	—	—
H1H3627N	—	—	—	—	—	—	3
Control 1	1820	950	290	530	160	500	250
Control 2	50	30	23	20	12	12	12

TABLE 5

Neutralization potency for selected mAbs against RSV subtype A

	Subtype A Neutralization: IC_{50} & Fold Improvement Relative to Control 1			
AbPID	RSV-A2 (1540) Neutral. IC50 [pM]	Fold	RSV-Long Neutral. IC50 [pM]	Fold
H1H3627N	2.6	138	7.3	73
H1H3592P3	10	36	15	35
Control I	360	—	536	—
Control II	14	25	65	8.2

TABLE 6

Neutralization potency for selected mAbs against RSV subtype B

	Subtype B Neutralization: IC_{50} & Fold Improvement Relative to Control 1			
AbPID	RSV - 1580 Neutral. IC50 [pM]	Fold	RSV-9320 Neutral. IC50 [pM]	Fold
H1H3627N	6.7	55	11	42
H1H3592P3	31	12	100	4.6
Control I	375	—	460	—
Control II	43	8.7	56	8.2

Example 5

Selected Anti-RSV-F Antibodies Display Potent Neutralization of RSV Infection in Vivo

A. Mouse Model

The exemplary antibodies H1H3627N and H1H3592P3 were selected for in vivo RSV neutralization studies using Balb/c mice. Briefly, 7 week old Balb/c mice (n=4-5) were injected SC at two doses (0.15 or 0.05 mg/kg) using either H1H3627N, H1H3592P3, control I, control II or isotype-matched antibody. The use of carrier antibody (1 mg/kg) was utilized in all experiments to minimize the loss of anti-RSV-F antibody.

One day post-injection, mice were challenged intranasally with 50 ul (10^6 pfu) of RSV A2 (1540) strain. Four days post-infection, sera was drawn, mice were sacrificed, and lungs were extracted and homogenized in 1 mL of PBS using an OmniGLH homogenizer. Lung homogenates were centrifuged to remove cellular debris and a portion of supernatant was used to determine anti-RSV-F mAb concentration in the lung. The remaining supernatant was used to make serial dilutions which were incubated with HEp-2 cells for 2 hours, to allow viral entry. Subsequently, supernatant was removed and the cells were overlaid with 1% methylcellulose. Six days later, cells were stained with crystal violet and plaques were counted and the $\log_{10}$ viral reduction was calculated relative to isotype control.

Exemplary antibodies H1H3627N and H1H3592P3 were more efficacious in reducing the viral load in vivo than control I or control II anti-RSV-F antibodies (Tables 7a-7e). Specifically, at the 0.15 mg/kg dose, antibodies H1H3627N, H1H3592P3 and control II all effectively reduced RSV infection in the lung to near undetectable levels compared to control I (viral reduction log(10) fold change ≥2.10). Total human IgG measurements in the lungs and serum confirmed that antibody levels were relatively consistent between groups.

At a lower administrated dose, greater differentiation in neutralization efficacy between the three antibodies compared to control I was evident. At 0.05 mg/kg, H1H3592P3 showed the greatest reduction in viral load, with fold changes ranging from 1.49 to >2.07 logs, compared with viral load reduction fold changes of 1.08 to 1.36 logs for H1H3627N and 0.01 to 0.65 logs for control II. Control I at this lower dose was only moderately effective with viral load reduction changes of 0.03 to 1.03 logs.

The results indicate that both H1H3627N and H1H3592P3 are potent RSV neutralizing antibodies in vivo, with the latter showing a trend of being a more effective neutralizer of RSV infection at lower doses.

A dosing range experiment was performed following the same protocol described above, injecting SC 4 different doses of control I antibody (0.6, 0.3, 0.15 and 0.05 mg/kg), and two doses (0.15 and 0.05 mg/kg) of H1H3592P3 and control II. Viral reduction in the lungs was calculated as a percentage of isotype control (Exp M4, Tables 7d-e).

Exemplary antibody H1H3592P3 was more efficacious in reducing the viral load in vivo (in mouse) than control I or control II anti-RSV-F antibodies. In addition, the dose of control I required to reach a 99% viral reduction in the lungs was 3-4 fold higher than the dose of H1H3592P3. Tables 7(a-e): RSV viral reduction (log(10)) in mice after administration of Anti-RSV-F antibodies

TABLE 7a

Exp M1		Dose: 0.15 mg/kg			Dose: 0.05 mg/kg		
PID	Mice per group	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum
H1H3627N	5	>2.10	35 ± 18	1041 ± 212	1.20	7 ± 4	274 ± 38
H1H3592P3	5	>2.10	44 ± 14	1731 ± 770	>2.07	17 ± 4	438 ± 51
Control I	5	1.02	33 ± 11	895 ± 132	1.03	9 ± 5	365 ± 111
Control II	5	>2.10	82 ± 24	1948 ± 429	0.65	7 ± 4	555 ± 80
Isotype Ctrl	5	NA	76 ± 28	2180 ± 197	NA	25 ± 2	1287 ± 120

TABLE 7b

Exp M2		Dose: 0.15 mg/kg			Dose: 0.05 mg/kg		
PID	Mice per group	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum
H1H3627N	5	>2.51	23 ± 8	724 ± 148	1.08	3 ± 3	300 ± 35
H1H3592P3	5	>2.51	27 ± 5	1261 ± 74	1.49	10 ± 2	333 ± 55
Control I	5	0.79	9 ± 2	611 ± 61	0.15	1 ± 1	221 ± 35
Control II	5	2.31	13 ± 8	587 ± 36	0.01	1 ± 3	237 ± 22
Isotype Ctrl	5	NA	46 ± 12	1389 ± 170	NA	15 ± 4	498 ± 92

TABLE 7c

Exp M3		Dose: 0.15 mg/kg			Dose: 0.05 mg/kg		
PID	Mice per group	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum	Viral Reduction (log10)	mAb [ng/ml] Lungs	mAb [ng/ml] Serum
H1H3627N	4	2.7	26 ± 6	1143 ± 83	1.36	7 ± 1	394 ± 16
H1H3592P3	4	>2.83	31 ± 12	947 ± 105	1.36	13 ± 4	371 ± 21
Control I	4	1.00	58 ± 14	1426 ± 114	0.03	6 ± 5	442 ± 27
Control II	4	2.35	20 ± 6	1152 ± 142	0.54	BDL	373 ± 21
Isotype Ctrl	4	NA	41 ± 3	808 ± 52	NA	37 ± 8	326 ± 26

55

TABLE 7d

Exp M4 (ED_{99})		Dose: 0.6 mg/kg		Dose: 0.3 mg/kg	
PID	Mice per group	Viral Reduction (%)	mAb [ng/ml] Serum	Viral Reduction (%)	mAb [ng/ml] Serum
Control 1	5	>99	8451.9 ± 2562	96.9	3129.7 ± 403

ND: Not determined

TABLE 7e

Exp M4 (ED_{99})		Dose: 0.15 mg/kg		Dose: 0.05 mg/kg	
PID	Mice per group	Viral Reduction (%)	mAb [ng/ml] Serum	Viral Reduction (%)	mAb [ng/ml] Serum
H1H3592P3	5	>99	1578.9 ± 256	90.6	524.0 ± 42
Control I	5	57.9	1561.2 ± 282	24.2	547.5 ± 59
Control II	5	96.7	1566.0 ± 354	48.5	465.7 ± 85
Isotype Ctrl	5	NA	1406.0 ± 196	NA	375.3 ± 86

ND: Not determined

B. Cotton Rat Model

The exemplary antibodies H1H3627N and H1H3592P3 were selected for in vivo RSV neutralization studies using cotton rats. Briefly, 6-8 week old cotton rats (n=5) were injected IM at two doses (5 or 0.6 mg/kg) using either H1H3627N, H1H3592P3, control I, control II or isotype-matched antibody.

One day post-injection, rats were challenged intranasally with 100 ul (10^5 pfu) of RSV A2 strain. Four days post-infection, sera was drawn, rats were sacrificed, and lung and nasal tissues were extracted for viral titration. Lung homogenates were centrifuged to remove cellular debris and a portion of supernatant was used to determine anti-RSV-F mAb concentration in the lung. The remaining supernatant was used to make serial dilutions, which were incubated with HEp-2 cells to allow viral entry. Subsequently, supernatant was removed and the cells were overlaid with 1% methylcellulose. Six days later, cells were stained and plaques were counted and the $\log_{10}$ viral reduction was calculated relative to isotype control.

Exemplary antibody H1H3592P3 was more efficacious in reducing the viral load in the lungs and nose than control I, and as efficacious as control II in lungs and better in the nose. Exemplary antibody H1H3627N was only better than control I and as efficacious as control II in the nose (Table 8). Specifically, at the 5 mg/kg dose, antibodies H1H3627N, H1H3592P3, control I and control II all effectively reduced RSV infection in the lung to near undetectable levels compared to isotype control (viral reduction log(10) fold change ≥2.33). However, in the nose, greater differentiation in neutralization efficacy between H1H3627N, H1H3592P3, control II compared to control I was evident. H1H3592P3 showed the greater reduction in viral load (2.65 logs) compared to H1H3627N (1.46 logs) or control II (1.33 logs).

At a lower administrated dose, greater differentiation in neutralization efficacy between the three antibodies compared to control I was evident in the lungs. At 0.6 mg/kg, H1H3592P3 showed similar reduction in viral load than control II (1.5 logs) and they were both more efficacious than control I (0.624 logs). H1H3627N showed less efficacy than the other three antibodies.

Exemplary anti-RSV-F antibody H1H3592P3 was next selected for testing its ability to neutralize RSV subtype B in vivo using the cotton rat model. As with RSV/A, 6- to 8-week old cotton rats (n=4-6/group/experiment) were intramuscularly administered either 5 or 0.6 mg/kg of H1H3592P3, Control I or Control II. The next day, animals were challenged with 10^5 pfu of RSV/B strain 18537. Four days post-challenge, viral titers in the lungs and nose were determined along with serum antibody titers. The results shown in table 9 were data pooled from two independent experiments.

H1H3592P3 showed efficacy in reducing RSV/B viral load in lungs at both high and low doses (Table 9). At 5.0 mg/kg, RSV/B viral load in the lungs was reduced by 2.21 logs with H1H3592P3, compared with a reduction of 2.11 logs by Control I and 2.18 logs by Control II. At 0.6 mg/kg, RSV/B viral load in the lungs was reduced by 1.29 logs with H1H3592P3, compared with a reduction of 0.75 logs by Control I and 0.83 logs by Control II.

Overall, H1H3592P3 showed superiority in neutralization of RSV Subtype B in the lungs over both Control I and II at 0.6 mg/kg. At 5 mg/kg, H1H3592P3 showed comparable neutralizing ability than Control I and Control II in reducing viral load in the lungs.

The results indicate that H1H3592P3 is a potent neutralizer of RSV subtype strains A and B in vivo in cotton rats, being a more effective neutralizer of RSV infection at high doses in the nose and at lower doses in the lungs. The efficacy at low doses indicates the possibility of a lower dose regimen in the clinic.

TABLE 8

RSV-A viral reduction (log (10)) in cotton rats after administration of Anti-RSV-F antibodies

		Dose: 0.6 mg/kg			Dose: 5.0 mg/kg		
Exp R1		Viral	Viral	mAb	Viral	Viral	mAb
PID	Rats per group	Reduction lung (log10)	Reduction nose (log10)	[ng/ml] Serum Day 4	Reduction lung (log10)	Reduction nose (log10)	[ng/ml] Serum Day 4
H1H3627N	5	0.34	0.22	3.43 ± 0.25	2.33	1.46	21.52 ± 5.47
H1H3592P3	5	1.66	0.19	3.49 ± 0.55	2.56	2.66	46.28 ± 7.69
Control I	5	0.62	0.21	3.04 ± 0.29	2.37	1.07	39.95 ± 5.23
Control II	5	1.50	0.20	4.26 ± 0.66	2.55	1.33	24.06 ± 2.96
Isotype Ctrl	4	NA	NA	3.78 ± 0.99	NA	NA	30.43 ± 6.66

TABLE 9

RSV-B viral reduction (log (10)) in cotton rats after administration of Anti-RSV-F antibodies

		Dose: 0.6 mg/kg			Dose: 5.0 mg/kg		
Exp R2		Viral	Viral	mAb	Viral	Viral	mAb
PID	Rats per group	Reduction lung (log10)	Reduction nose (log10)	[ng/ml] Serum Day 4	Reduction lung (log10)	Reduction nose (log10)	[ng/ml] Serum Day 4
H1H3592P3	10	1.29	0.21	3.89 ± 0.99	2.21	0.86	42.31 ± 13.5
Control I	11	0.75	0.15	3.87 ± 0.73	2.11	0.79	35.28 ± 11.8
Control II	11	0.83	0.10	3.75 ± 0.49	2.18	1.24	27.65 ± 7.49
Isotype Ctrl	10	NA	NA	3.56 ± 1.17	NA	NA	34.28 ± 9.24

C. Cotton Rat Model—Determination of the ED_{99} of an Exemplary Antibody H1H3592P3

Dose-ranging studies using the cotton rat were performed to determine at which dose an exemplary antibody H1H3592P3 would reduce viral load by >99% (i.e. the ED_{99}). Cotton rats were prophylactically administered an IM dose of H1H3592P3 or Control 1 antibody at either 10, 5, 2.5, 1.25 or 0.62 mg/kg. Additionally an isotype control antibody was dosed in at either 10 or 0.62 mg/kg to bracket the active agents in this study. Following antibody treatments an intranasal RSV challenge of either subtype A (RSV A2 strain) or subtype B (RSV B strain 18537) was performed. Four days post-infection, sera was drawn, rats were sacrificed, and lung tissue was extracted for viral titration. H1H3592P3 at a dose of 0.62 mg/kg achieved >99% viral load reduction in the lungs as compared to Control 1 which required a dose of 2.5 mg/kg to reach the same >99% viral reduction (Table 10). The mean terminal Control 1 concentration (27 μg/mL) at the calculated ED_{99} correlated well with previously published work (Scott and Lamb, 1999), which indicated that a serum palivizumab concentration (i.e. Control 1) of 30-40 μg/mL, at the time of RSV infection, was associated with a 99% reduction in lung viral load. The mean terminal H1H3592P3 concentration (4.9 μg/mL) correlated well with the 4-fold lower dose delivered at its ED_{99}. Results against subtype B challenge were similar (Table 11) in that an ED_{99} for H1H3592P3 was achieved at 2.5 mg/kg while Control 1 required roughly a 4× greater dose (10 mg/kg) to obtain that same >99% viral lung reduction.

In summary these studies support that less frequent dosing of H1H3592P3 may confer the same level of protection as the current monthly dosing paradigm used with palivizumab.

TABLE 10

Determination of the ED_{99} for Anti RSV-F Antibodies After RSV Subtype A Challenge
ED_{99} Determination with RSV Subtype A

PID	10 mg/kg	5 mg/kg	2.5 mg/kg	1.25 mg/kg	0.62 mg/kg
	% Viral Lung Reduction				
H1H3592P3	>99	>99	>99	>99	>99
Control I	>99	>99	>99	98.9	95.9
Isotype Ctrl	NA	NA	NA	NA	NA
	Antibody Serum Concentration (ug/ml)				
H1H3592P3	107.2 ± 3.4	48.44 ± 6.1	20.15 ± 1.8	10.55 ± 1.5	4.91 ± 0.7
Control I	89.16 ± 6.5	58.07 ± 6.3	26.93 ± 3.3	12.72 ± 2.2	6.65 ± 0.5
Isotype Ctrl	90.57 ± 12.6	—	—	—	5.39 ± 0.5

TABLE 11

Determination of the ED_{99} for Anti RSV-F Antibodies After RSV Subtype B Challenge
ED_{99} Determination with RSV Subtype B

PID	10 mg/kg	5 mg/kg	2.5 mg/kg	1.25 mg/kg	0.62 mg/kg
	% Viral Lung Reduction				
H1H3592P3	>99	>99	>99	98.4	96.7
Control I	>99	97.7	98.4	96.3	88.2
Isotype Ctrl	NA	NA	NA	NA	NA
	Antibody Serum Concentration (ug/ml)				
H1H3592P3	98.04 ± 18.4	50.99 ± 7.8	27.82 ± 4.9	10.49 ± 1.7	7 ± 0.3
Control I	98.89 ± 10.9	42.74 ± 8.9	26.46 ± 3.3	16.06 ± 2.2	7.58 ± 1.1
Isotype Ctrl	99.72 ± 17.4	NA	NA	NA	5.38 ± 0.5

Example 6

Generation of a Bi-Specific Antibody

Various bi-specific antibodies are generated for use in practicing the methods of the invention. For example, RSV-F specific antibodies are generated in a bi-specific format (a "bi-specific") in which variable regions binding to distinct domains of the RSV-F protein are linked together to confer dual-domain specificity within a single binding molecule. Appropriately designed bi-specifics may enhance overall virus neutralization efficacy through increasing both specificity and binding avidity. Variable regions with specificity for individual domains are paired on a structural scaffold that allows each region to bind simultaneously to separate epitopes, or to different regions within one domain. In one example for a bi-specific, heavy chain variable regions (V_H) from a binder with specificity for one domain are recombined with light chain variable regions (V_L) from a series of binders with specificity for a second domain to identify non-cognate V_L partners that can be paired with an original V_H without disrupting the original specificity for that V_H. In this way, a single V_L segment (e.g., V_L1) can be combined with two different V_H domains (e.g., V_H1 and V_H2) to generate a bi-specific comprised of two binding "arms" (V_H1-V_L1 and V_H2-V_L1). Use of a single V_L segment reduces the complexity of the system and thereby simplifies and increases efficiency in cloning, expression, and purification processes used to generate the bi-specific (See, for example, U.S. Ser. No. 13/022,759 and US201010331527).

Alternatively, antibodies that bind RSV-F and a second target, such as, but not limited to, for example, a second different anti-RSV-F antibody, or a toxoid, or a vaccine, may be prepared in a bi-specific format using techniques described herein, or other techniques known to those skilled in the art. Antibody variable regions binding to distinct regions may be linked together with variable regions that bind to relevant sites on, for example, a different viral antigen to confer dual-antigen specificity within a single binding molecule. Appropriately designed bi-specifics of this nature serve a dual function. For example, in the case of a bi-specific antibody that binds ie. RSV-F and RSV-G one may be able to better neutralize the virus, without the need for administration of a composition containing two separate antibodies. Variable regions with specificity for RSV-F, are combined with a variable region with specificity for RSV-G and are paired on a structural scaffold that allows each variable region to bind to the separate antigens.

The bi-specific binders are tested for binding and functional blocking of the target antigens, for example, RSV-F and RSV-G, in any of the assays described above for antibodies. For example, standard methods to measure soluble protein binding are used to assess the bispecific interaction, such as Biacore, ELISA, size exclusion chromatography, multi-angle laser light scattering, direct scanning calorimetry, and other methods. Binding of bi-specific antibodies to both RSV-F and RSV-G is determined through use of an ELISA binding assay in which synthetic peptides representing the different antigens are coated onto the wells of microtiter plates, and binding of a bi-specific is determined through use of a secondary detection antibody. Binding experiments can also be conducted using surface plasmon resonance experiments, in which real-time binding interaction of peptide to antibody is measured by flowing a peptide or bi-specific across a sensor surface on which bi-specific or peptide, respectively, is captured. Functional in vitro blocking of both RSV-F and RSV-G by a bi-specific is determined using any bioassay such as the neutralization assay described herein, or by in vivo protection studies in appropriate animal models, such as those described herein, or in an in vivo model of lung inflammation.

Example 7

In Vitro Generation of RSV Escape Mutants to Determine the Binding Epitope of H1H3592P3

Generation of Escape Mutants to H1H3592P3

3×10^5 Hep-2 cells/well were plated in a 6-well plate for 24 h. Concentrations of H1H3592P3, ranging from 50 ug/mL to 0.016 ug/mL were mixed with RSV subtype A strain 1540 or RSV subtype B strain 1580 for 1 h at 37° C. After coincubation, the RSV/antibody mixture was added to the previously seeded HEp-2 cells at a multiplicity of infection (MOI) of 10 plaque-forming units (pfu)/cell. Cells were incubated for 6 days, and cytopathic effects were monitored daily using light microscopy. At day 6, contents of each well were harvested, adjusted to initial concentration of antibody and used to infect freshly seeded HEp-2 cells. This serial passage was repeated until obvious cytopathic effects were observed at high concentrations of H1H3592P3 (50 ug/mL), which is approximately 2 logs greater than the IC_{50} of the antibody, suggesting the presence of viral mutants. Supernatants from these wells were confirmed from the presence of resistant virus via a micro-neutralization assay (described below) and plaque isolation was performed in 10 cm tissue culture dishes. 10 individual plaques were expanded in 6-well plates and virus were re-tested for resistance via microneutralization. Sequencing was then performed on these viral mutants.

Microneutralization Assay

To confirm whether escape mutants generated under the pressure of H1H3592P3 were resistant to neutralization, a microneutralization assay in Hep-2 cells was performed. Briefly, 10^5 Hep2 cells cultured in DMEM 1× medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37 C, 5% CO_2).

Next, various concentrations of antibodies, starting at 666 nM and diluted 1:5 in media, were incubated for 2 hours (37 C, 5% CO_2) with RSV wild-type (subtype A or B) or escape mutants from both subtype A and B, at an MOI from 0.04 to 0.4. Controls not containing virus or controls containing virus but no antibodies were included. All dilutions of antibody were conducted in duplicates. After incubation, the antibody/virus mixture was added to cells and infection was allowed for 3 days. Infection was determined by fixing the cells in 2% PFA and an ELISA with Goat anti-RSV/anti-Goat HRP antibodies was performed. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

Results

Respiratory syncytial virus escape mutants were generated to map the specific binding region of H1H3592P3 to RSV-F. Briefly, HEp-2 cells, infected with RSV strains 1540 (subtype A) or 1580 (subtype B) were subjected to H1H3592P3 treatment ranging from 50 ug/mL to 0.016 ug/mL. After 6 days, contents from each well were used to infect freshly seeded HEp-2 cells. This serial passage continued until cytopathic effects were observed in HEp-2 cells even in the presence of the highest antibody dose, indicating

the presence of RSV viral mutants generated under selection pressure. Overall, viral mutants were isolated from ten distinct plaques, confirmed for neutralization resistance in the presence of H1H3592P3 and subsequently sequenced.

Sequence analysis confirmed that escape mutations for H1H3592P3 were found at amino acid positions 173 and 174 (S173Y and T174K) of RSV-F (SEQ ID NO: 354), indicating that these amino acids play an important role in antibody binding and viral neutralization. Prior reports have determined that the binding epitopes for anti-RSV Control I and Control II antibodies are located between S255-N276. The data from these studies suggest a binding site for H1H3592P3 on RSV-F that plays a major role in viral neutralization (see table 12) and is distinct from that required for previously established Control antibodies.

TABLE 12

Neutralization Efficacy of H1H3592P3 and anti-RSV Control Antibodies on RSV subtype A and B Strains and Associated Escape Mutants

Virus	H1H3592P3 (IC50, pM)	Control I (IC50, pM)	Control II (IC50, pM)
wt subtype A (RSV/A)	177	1140	108
RSV/A S173Y	Resistant	1710	170
Wt subtype B (RSV/B)	290	1900	260
RSV/B S173T	Resistant	1900	177
RSV/B T174K	Resistant	640	108
RSV/B S173T/T174K	Resistant	980	218

Example 8

Determination of the Binding Epitope of H1H3592P3 to RSV-F Using Hydrogen-Deuterium Exchange & Mass Spectrometry

Hydrogen/Deuterium Exchange (H/D exchange) in combination with peptic digests and mass spectrometry was conducted to determine the binding epitope of the anti-RSV-F antibody H1H3592P3 to recombinant RSV-F. Two H/D exchange formats (described in detail below) were employed: An 'on-solution/off-beads' method in which RSV-F peptide fragments that are protected by H1H3592P3 from back-exchange retain D_20 and yield higher molecule weights (m/z values) by mass spectrometry and an 'on-beads/off-beads' control method which establishes the baseline m/z values for all RSV-F peptides. Subtraction of the control m/z values from the m/z values obtained using the 'on-solution/off beads' method yields certain amino acids regions that show non-zero delta m/z values i.e residual D_20 that correspond to the binding epitope between H1H3592P3 and RSV-F.

Methods

On Solution/Off Beads Format

In the 'on-solution/off-beads' (on-exchange in solution followed by off-exchange on beads) format, RSV-F.mmh protein (SEQ ID NO: 353) was deuterated for 5 min or 10 min in PBS buffer prepared with D_2O, and then bound to H1H3592P3 covalently attached to N-hydroxysuccinimide (NHS) agarose beads (GE Lifescience) via a 2 min incubation. The RSV-F/H1H3592P3 bead complex was washed with PBS buffer (prepared with non-deuterated H_2O) and incubated in PBS buffer for half of the on-exchange time. After the off-exchange, the bound RSV-F was eluted from beads with an ice-cold low pH TFA solution. The eluted RSV-F was then digested with immobilized pepsin (Thermo Scientific) for 5 min. The resulting peptides were desalted using ZipTip chromatographic pipette tips and immediately analyzed by UltrafleXtreme matrix assisted laser desorption ionization time of flight (MALDI-TOF)-TOF mass spectrometry (MS).

On-Beads/Off Beads Format

In the 'on-beads/off-beads' (on-exchange on beads followed by off-exchange on beads) format, RSV-F.mmh (SEQ ID NO: 353) was first bound to H1H3592P3 agarose beads and then incubated for 5 min or 10 min in D_2O for on-exchange. The RSV-F/H1H3592P3 bead complex was washed with PBS buffer (prepared with non-deuterated H_2O) and incubated in PBS buffer for half of the on-exchange time. After the off-exchange, the bound RSV-F was eluted from beads with an ice-cold low pH TFA solution. The eluted RSV-F was then digested with immobilized pepsin (Thermo Scientific) for 5 min. The resulting peptides were desalted using ZipTip chromatographic pipette tips and immediately analyzed by MALDI-TOF-TOF mass spectrometry. The centroid values or average mass-to-charge ratios (m/z) of all the detected peptides were calculated and compared between this and the 'on-solution/off-beads' experiment.

Peptide Identification

The identification of the peptides was carried out using liquid chromatography-Orbitrap Elite (Thermo Scientific).

Results

Table 13 is a detailed comparison of the delta centroid m/z values for all the RSV-F peptides detected by MALDI-TOF mass spectrometry following H/D exchange and peptic digest. Two segments corresponding to amino acids 161-171 (EGEVNKIKSAL, (SEQ ID NO: 355)) and 172-188 (LSTNKAVVSLSNGVSVL, (SEQ ID NO: 356)) of SEQ ID NO: 354 had delta centroid values higher than 0.20, a threshold observed in-house to be considered indicative of antibody-protein contact and thus an epitope region. It should also be noted that the peptide signal corresponding to amino acids 161-171 was not quantified in the 10 min on-exchange experiment due to low signal to noise. However, the delta value of 0.88, detected at the 5 min on-exchange experiment, is far above the 0.2 threshold and can be attributed to the significant alteration in H/D exchange rate upon RSV-F binding to H1H3592P3.

Furthermore the peptide segment corresponding to amino acids 172-188 contains the amino acids of the two RSV escape mutants (S173Y and T174K; see example 7), which were resistant to H1H3592P3 treatment, indicating that these two amino acids play a role in antibody binding and viral neutralization. Thus the combination of sequencing escape RSV mutants along with H/D exchange support amino acids 161-188 of SEQ ID NO: 354 defining at least in part the binding region in RSV-F for antibody H1H3592P3.

TABLE 13

Centroid (m/z) Values of RSV-F Peptic Peptides After Back-exchange following deuteration in the Absence (on-solution/off-beads) and Presence (on-beads/off-beads) of H1H3592P3

	Experiment I 5 min on-/2.5 min off-exchange			Experiment II 10 min on-/5 min off-exchange		
Residues	on-beads/ off beads (m/z)	on-solution/ off-beads (m/z)	delta	on-beads/ off beads (m/z)	on-solution/ off-beads (m/z)	delta
46-52	791.06	791.10	0.04	791.06	791.15	0.09
48-56	1083.32	1083.37	0.05	1083.32	1083.35	0.03
48-58	1297.42	1297.44	0.02	1297.40	1297.44	0.04
79-92	1665.81	1665.96	0.15	1665.86	1665.89	0.03
94-107	1519.93	1520.00	0.06	1520.01	1520.09	0.07
96-107	1278.64	1278.61	−0.03	1278.61	1278.73	0.12
96-108	1434.61	1434.60	−0.01	1434.50	1434.63	0.13
148-160	1308.97	1309.12	0.16	N.A.	N.A.	N.A.
161-171	1188.72	1189.60	0.88	N.A.	N.A.	N.A.
172-188	1689.44	1691.68	2.24	1689.60	1691.07	1.47
220-230	1390.02	1390.06	0.04	1389.98	1389.93	−0.05
220-232	1632.30	1632.34	0.04	1632.29	1632.37	0.08
223-230	1048.49	1048.54	0.05	1048.44	1048.55	0.11
223-232	1291.16	1291.21	0.05	1291.12	1291.18	0.07
231-236	760.95	760.95	0.00	761.02	760.95	−0.06
233-240	966.29	966.33	0.04	966.20	966.30	0.09
233-249	1780.20	1780.39	0.19	1780.38	1780.38	0.00
261-277	1977.81	1977.91	0.10	1977.92	1977.80	−0.13
261-279	2205.05	2205.12	0.07	2205.10	2205.20	0.10
278-285	958.20	958.34	0.14	958.15	958.29	0.14
278-286	1121.50	1121.57	0.07	1121.54	1121.59	0.05
278-289	1453.19	1453.16	−0.03	1453.14	1453.08	−0.06
280-286	894.20	894.22	0.02	894.29	894.28	−0.02
280-289	1225.75	1225.80	0.05	1225.79	1225.81	0.02
280-290	1312.70	1312.70	−0.01	1312.86	1312.74	−0.13
457-467	1329.73	1329.82	0.09	1329.73	1329.76	0.03
468-477	1180.57	1180.67	0.10	1180.60	1180.42	−0.18
527-545	2132.30	2132.32	0.02	2132.39	2132.38	−0.01
534-545	1318.54	1318.54	0.00	1318.64	1318.50	−0.13
537-545	988.92	988.87	−0.05	988.93	988.84	−0.08
546-557	1528.62	1528.68	0.07	1528.64	1528.64	0.00
No ID	743.16	743.06	−0.10	743.10	742.99	−0.11
No ID	844.01	843.98	−0.03	844.03	843.96	−0.07
No ID	901.26	901.40	0.13	901.36	901.40	0.04
No ID	943.15	943.19	0.04	943.24	943.20	−0.04
No ID	1090.41	1090.45	0.04	1090.48	1090.51	0.03
No ID	1143.51	1143.61	0.10	1143.53	1143.57	0.04
No ID	1325.52	1325.56	0.04	1325.54	1325.66	0.12
No ID	1353.69	1353.64	−0.06	1353.77	1353.61	−0.16
No ID	1550.39	1550.44	0.05	1550.45	1550.40	−0.05
No ID	2074.49	2074.41	−0.08	2074.52	2074.36	−0.15
No ID	2257.71	2257.70	−0.01	2257.89	2257.85	−0.04
No ID	2365.83	2365.72	−0.12	2365.94	2365.87	−0.07
No ID	2385.18	2385.17	−0.01	2385.23	2385.25	0.02
No ID	2405.22	2405.09	−0.12	2405.17	2405.15	−0.02
No ID	2456.18	2456.24	0.07	2456.14	2456.09	−0.05
No ID	2513.28	2513.26	−0.01	2513.32	2513.19	−0.14

Example 9

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtype A and B Laboratory Strains

H1H3592P3 and controls I and II antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10^4 HEp-2 cells cultured in DMEM 1× medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37° C., 5% CO_2). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with various RSV subtype A lab strains provided by ATCC at an MOI of 0.042 for 2 hours (37 C, 5% CO_2). Virus-free and irrelevant isotype controls were included.

Post incubation, the antibody:virus mixture was added to the HEp-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV lab strains (Table 14). Antibodies H1H3592P3 and AM22 showed similar potency than control II for RSV subtype A lab strains. Compared to control I, H1H3592P3 showed 15-17 fold

more potency (IC50 44-140 pM), while AM22 showed 9-23 fold more potency (IC50 86-91 pM) (Table 14). For subtype B, antibody H1H3592P3 showed similar potency than control II, but superior than AM22 and control I. Compared to control I, H1H3592P3 showed 2-5 fold more potency (IC50 33-230 pM), while AM22 showed 0.13-2 fold more potency (IC50 190-2508 pM).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several lab strains of RSV from both subtype A and B, in vitro, with greater potency than previously demonstrated for established controls.

TABLE 14

Subtype/strain	H1H3592P3 IC50 (pM)	Control I IC50 (pM)	Control II IC50 (pM)	Control III IC50 (pM)
A/A2	140	2080	202	91
A/Long	44	752	83	86
B/18537	230	1190	187	660
B/1400	33	113	38	190
B/1A2	48	223	40	580
B/9320	151	338	76	2508

Example 10

Respiratory Syncytial Virus Fusion (RSV-F) Protein Antibodies Display Potent Neutralization Capabilities Across RSV Subtype A Clinical Isolates

H1H3592P3 and controls I, II and III antibodies were tested in a RSV micro-neutralization assay to determine potency. Briefly, 10^4 HEp-2 cells cultured in DMEM 1× medium, supplemented with 5% Hyclone FBS, L-glutamine and antibiotics, were seeded into 96-well clear bottom-black microplates and incubated for 16-18 hours (37° C., 5% CO_2). Next, various concentrations of antibodies, starting at 666 nM with subsequent 1:5 dilutions in media, were incubated with various RSV subtype A clinical isolates provided by Dr. Moore (Emory University) at a range of MOIs from 0.015 to 0.128 for 2 hours (37 C, 5% CO_2). Virus-free and irrelevant isotype controls were included.

Post incubation, the antibody:virus mixture was added to the HEp-2 cells and infection was maintained for 3 days. The degree of infection was determined by fixing cells in 2% PFA and performing an ELISA with Goat anti-RSV/anti-Goat HRP antibodies. Luminescence reagents were added to the wells and signal was detected using a plate reader (Victor X3, Perkin Elmer). Luminescence values were analyzed by a three-parameter logistic equation over an 11-point response curve (GraphPad Prism).

The antibodies of the invention displayed a broad range of neutralization activities against the RSV clinical isolates (Table 15). Antibody H1H3592P3 showed similar potency to controls II and III for most clinical isolates. Compared to control I, H1H3592P3 showed 10-22 fold more potency (IC50 34-66 pM) (Table 15).

This example demonstrates the efficacy of the antibodies of this invention to neutralize several clinical isolates of RSV, in vitro, with greater potency than previously demonstrated for established controls.

TABLE 15

RSV-F Antibodies Display Potent Neutralization Capabilities Across RSV Subtype A clinical isolates

	MOI	H1H3592P3 IC50 (pM)	Control I IC50 (pM)	Control II IC50 (pM)	Control III IC50 (pM)	Genbank
A2001/2-20	0.016	43	935	74	72	JX069798.1
A2001/3-12	0.018	66	1259	129	60	JX069799.1
A1997/12-35	0.015	40	478	41	20	JX069800.1
A1998/3-2	0.128	35	344	36	31	JX069801.1
A1998/12-21	0.026	34	580	68	43	JX069802.1
A2000/3-4	0.040	50	899	88	55	JX069803.1

Example 11

H1H3592P3 Blocks Viral Entry by Inhibiting Fusion of Virus and Cell Membranes

A study was done to determine the mechanism by which the antibodies of the invention block respiratory syncytial virus (RSV) infection. One exemplary antibody of the invention, H1H3592P3, was tested to determine whether it acted to prevent/inhibit RSV fusion with host cells (FIGS. **2**A and **2**B). The mechanism of action for control I (the positive control mAb which is based on the sequence of palivizumab) was previously described as inhibition of viral fusion to the host cell (Huang et al., J. of Virol., (2010), August 84(16):8132-40). Because RSV-F is involved in both attachment to the cell via the interaction of the host receptor nucleolin, and fusion of the viral and plasma membranes, assays were performed to determine the mechanism of H1H3592P3.

The attachment assay (FIG. **2**A) was performed by incubating RSV (subtype A, strain A2) in the presence of either H1H3592P3 or the positive control antibody (control I), then incubating the mixture with HEp-2 cells at 4° C. for one hour to allow binding of the virus to the cells. Unbound virus was washed out, cells were fixed and the percentage of attached virus was measured by ELISA. Heparin, which blocks RSV attachment, was used as a control.

Viral fusion was detected by allowing viral attachment at 4° C., washing out unbound virus, then incubating with H1H3592P3, positive Control I, or an isotype negative control antibody at 4° C. and moving cells to 37° C. to promote viral fusion and entry. Viral infection was measured 3 days later by ELISA (FIG. **2**B). RLU: Relative Luminescence Units.

H1H3592P3, like control I, blocks RSV fusion and not the attachment of RSV to the cell surface, while the isotype (negative) control mAb had no effect on viral fusion (FIG. **2**B). Heparin effectively blocked RSV attachment to cells (Hallack et al., Virology (2000), 271(2):264-75), whereas neither antibody inhibited RSV attachment (FIG. **2**A). H1H3592P3 blocked viral fusion in this assay format with an IC_{50} of 230 pM, while the positive control mAb (control

I) blocked viral fusion with an IC_{50} 1 nM (FIG. 2B). Similar results were observed with an RSV subtype B strain (data not shown).

Example 12

Octet Cross Competition of Anti-RSV-F Antibodies for Binding to RSV-F

Binding competition between a panel of anti-RSV-F mAbs was determined using a real time, label-free bio-layer interferometry assay on an Octet® HTX biosensor (Pall ForteBio Corp.). The entire experiment was performed at 25° C. in HBST kinetics buffer (0.01 M HEPES pH7.4, 0.15M NaCl, 3 mM EDTA, 0.05% v/v Surfactant Tween-20, 0.1 mg/mL BSA) with the plate shaking at the speed of 1000 rpm. To assess whether two antibodies are able to compete with one another for binding to their respective epitopes on the recombinant RSV-F protein expressed with a C-terminal myc-myc-hexahistidine tag (RSV-F-mmH), around 0.36 nm of RSV-F-mmH was first captured onto anti-Penta-His antibody coated Octet biosensor (Fortebio Inc, Cat#18-5079) by submerging the biosensors for 3 minutes into wells containing 10 μg/mL solution of recombinant RSV-F-mmH. The antigen captured biosensors were then saturated with the first anti-RSV-F monoclonal antibody (subsequently referred to as mAb-1) by dipping into wells containing 100-200 μg/mL solution of mAb-1 for 10 minutes. The biosensors were then subsequently dipped into wells containing 100-200 μg/mL solution of second anti-RSV-F monoclonal antibody (subsequently referred to as mAb-2) for 5 minutes to check for mAb-2 binding to RSV-F-mmH, which is pre-bound to mAb-1. The biosensors were washed in HBST kinetics buffer in between every step of the experiment. The real-time binding response was monitored throughout the course of the experiment and the maximum binding response for all the steps was recorded. The response of mAb-2 binding to RSV-F-mmH pre-bound with mAb-1 was measured and competitive/non-competitive behavior of different anti-RSV-F monoclonal antibodies was determined.

Results

Sequential binding studies performed on Octet® HTX demonstrate that none of the anti-RSV-F monoclonal antibodies compete with each other and are able to bind non-competitively to RSV-F-mmH. As shown in Table 16, dark grey boxes with black font indicate the binding response for self-competition. No competition between antibodies that suggest a distinct binding epitope is represented as a white box with black font. Binding of the first anti-RSV-F monoclonal antibody (mAb-1) to the anti-His-captured RSV-F-mmH protein does not prevent the binding of the second anti-RSV-F monoclonal antibody (mAb-2). For all the anti-RSV-F monoclonal antibodies in this study, the observed mAb-2 binding signal was found to be comparable to that observed in the absence of mAb-1 (No mAb). Moreover, the observed binding of mAb-2 for all the anti-RSV-F monoclonal antibodies was found to be independent of the order of binding of anti-RSV-F antibody; suggesting that all the anti-RSV-F antibodies under investigation have distinct binding epitopes.

TABLE 16

Cross-competition between anti-RSV-F monoclonal antibodies.

mAb-1	Amount of 10 μg/mL of RSV_F.mmh Captured ± Std Dev (nm)	Amount of 100-200 μg/mL of mAb-1 Binding Level (nm)	mAb#	Binding of mAb-2 to the Pre-complex of Captured RSV-F-mmH & mAb-1 1	2	3	4
Comparator III (AM-22)	0.36 ± 0.01	0.33 ± 0.01	1	0.01	0.34	0.44	0.00
H1H3592P3	0.36 ± 0.01	0.35 ± 0.01	2	0.26	0.00	0.30	0.00
Comparator I (Palivizumab)	0.39 ± 0.01	0.45 ± 0.02	3	0.29	0.23	0.01	-0.01
No mAb	0.36 ± 0.01	-0.01 ± 0.01	4	0.20	0.17	0.36	0.00

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35 40 45

Gly Gly Phe Asn Pro Ile Phe Asp Thr Ala Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Ile Thr Ile Thr Leu Asp Ala Ser Thr Gly Thr Val Tyr
65 70 75 80

Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Gly Val Tyr Tyr Cys
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50 55 60

Ser Gly Ser Arg Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
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tcctca 366

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<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 18

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asn Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Thr Phe Ile Trp Ser Asp Gly Ser Asn Lys Tyr Tyr Leu Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 19
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 19

ggattcacct tcaatagtta tggc 24

<210> SEQ ID NO 20
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 20

Gly Phe Thr Phe Asn Ser Tyr Gly
1 5

<210> SEQ ID NO 21
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 21

atatggtctg atggaagtaa taaa 24

<210> SEQ ID NO 22
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 22

Ile Trp Ser Asp Gly Ser Asn Lys
1 5

<210> SEQ ID NO 23
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 23

gcgagaagtg gactagcctc ctattattat tacggtatgg acgtc 45

<210> SEQ ID NO 24
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 24

Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 25
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 25

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatggt gcatccagtt tgcaaagtgg ggtcccgtca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg ccacttattc ctgtctacag cataatagtt acccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 26
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 26

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 27
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 27

cagggcatta gaaatgat 18

<210> SEQ ID NO 28
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 28

Gln Gly Ile Arg Asn Asp
1 5

<210> SEQ ID NO 29
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 29

ggtgcatcc 9

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<210> SEQ ID NO 30
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 30

Gly Ala Ser
1

<210> SEQ ID NO 31
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 31

ctacagcata atagttaccc gtggacg 27

<210> SEQ ID NO 32
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 32

Leu Gln His Asn Ser Tyr Pro Trp Thr
1 5

<210> SEQ ID NO 33
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 33

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtcgggatt caccttcagt agttatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggtattt ctatggtatg atggaagtaa taaacactat 180

gcagactccg tgaagggccg attcaccatc tccagagaca attccaagaa cacattgtat 240

ttgcaaatga atagtctgag agccgaggac acggctgtat attactgtgc gagaagtgga 300

ctagcctcct attattatta cagtatggac gtctggggcc aagggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 34
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 34

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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        35                  40                  45

Val Phe Leu Trp Tyr Asp Gly Ser Asn Lys His Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Tyr Tyr Ser Met Asp Val Trp
            100                 105                 110

Gly Gln Gly Thr Thr Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 35
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 35

ggattcacct tcagtagtta tggc                                          24


<210> SEQ ID NO 36
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 36

Gly Phe Thr Phe Ser Ser Tyr Gly
 1               5


<210> SEQ ID NO 37
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 37

ctatggtatg atggaagtaa taaa                                          24


<210> SEQ ID NO 38
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 38

Leu Trp Tyr Asp Gly Ser Asn Lys
 1               5


<210> SEQ ID NO 39
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 39

gcgagaagtg gactagcctc ctattattat tacagtatgg acgtc                    45
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<210> SEQ ID NO 40
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 40

Ala Arg Ser Gly Leu Ala Ser Tyr Tyr Tyr Tyr Ser Met Asp Val
1 5 10 15

<210> SEQ ID NO 41
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 41

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca gggcattaga aatgatttag cctggtatca gcagaaacca 120

gggaaagccc ctaagcgcct gatctatggt gcatccagtt tacacagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttattc ctgtctacag cataatagtt acccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 42
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 42

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Arg Asn Asp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Arg Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Ser Cys Leu Gln His Asn Ser Tyr Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 43
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 43

cagggcatta gaaatgat 18

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<210> SEQ ID NO 44
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 44

Gln Gly Ile Arg Asn Asp
1 5

<210> SEQ ID NO 45
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 45

ggtgcatcc 9

<210> SEQ ID NO 46
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 46

Gly Ala Ser
1

<210> SEQ ID NO 47
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 47

ctacagcata atagttaccc gtggacg 27

<210> SEQ ID NO 48
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 48

Leu Gln His Asn Ser Tyr Pro Trp Thr
1 5

<210> SEQ ID NO 49
<211> LENGTH: 354
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 49

caggtgcagc tggtgcagtc tggggctgag gtgaagaagc ctggggcctc agtgaaggtc 60

tcctgcaagg cttctggata caccctcacc ggctattatc tacactgggt gcgacaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaacccta ccagtggtgg cacaaactat 180

gcacagaagt ttcagggcag ggtcaccatg accagggaca cgtccatcag tgcagccttc 240

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atggagctga gtaggctgag atctgacgac acggccgtgt atcactgtgc gagagaattt 300

tggccccacg gtatggacgt ctggggccaa gggaccacgg tcaccgtctc ctca 354

<210> SEQ ID NO 50
<211> LENGTH: 118
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 50

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Leu Thr Gly Tyr
20 25 30

Tyr Leu His Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Pro Thr Ser Gly Gly Thr Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Met Thr Arg Asp Thr Ser Ile Ser Ala Ala Phe
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr His Cys
85 90 95

Ala Arg Glu Phe Trp Pro His Gly Met Asp Val Trp Gly Gln Gly Thr
100 105 110

Thr Val Thr Val Ser Ser
115

<210> SEQ ID NO 51
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 51

ggatacaccc tcaccggcta ttat 24

<210> SEQ ID NO 52
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 52

Gly Tyr Thr Leu Thr Gly Tyr Tyr
1 5

<210> SEQ ID NO 53
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 53

atcaacccta ccagtggtgg caca 24

<210> SEQ ID NO 54
<211> LENGTH: 8

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 54

Ile Asn Pro Thr Ser Gly Gly Thr
1 5

<210> SEQ ID NO 55
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 55

gcgagagaat tttggcccca cggtatggac gtc 33

<210> SEQ ID NO 56
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 56

Ala Arg Glu Phe Trp Pro His Gly Met Asp Val
1 5 10

<210> SEQ ID NO 57
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 57

gccatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggccattaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct tcatccagtt tacaaagtgg ggtcccttca 180

aggttcagcg gcagtggatc tggcacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtcttgca gattacaaat acacgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 58
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 58

Ala Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ala Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ser Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Ala Asp Tyr Lys Tyr Thr Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 59
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 59

caggccatta gaaatgat 18

<210> SEQ ID NO 60
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 60

Gln Ala Ile Arg Asn Asp
1 5

<210> SEQ ID NO 61
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 61

gcttcatcc 9

<210> SEQ ID NO 62
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 62

Ala Ser Ser
1

<210> SEQ ID NO 63
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 63

cttgcagatt acaaatacac gtggacg 27

<210> SEQ ID NO 64
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 64

Leu Ala Asp Tyr Lys Tyr Thr Trp Thr
1 5

<210> SEQ ID NO 65
<211> LENGTH: 378
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 65

gaggtgcagc tggtggagtc tgggggaggc ttggtacacc cgggggggtc cctgagactc 60

tcctgtgaag cctctggatt cacacttagc agccatgtca tgagctgggt ccgccaggtt 120

ccaggcaagg ggctggagtg ggtctcacgt atcagtggtc ctggtggtag tacaaagtat 180

gcggactccg tgcagggccg gttcaccacc tccagagaca actccaagaa caccctgtat 240

ctacaaatga acagcctgat agccgaggac tcggccgcat attactgtgc gaaaggggggg 300

ggatatagtg gctacgattg ggacttttat tacggtatgg acgtctgggg ccaagggacc 360

acggtcaccg tctcctca 378

<210> SEQ ID NO 66
<211> LENGTH: 126
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 66

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val His Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Leu Ser Ser His
20 25 30

Val Met Ser Trp Val Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Arg Ile Ser Gly Pro Gly Gly Ser Thr Lys Tyr Ala Asp Ser Val
50 55 60

Gln Gly Arg Phe Thr Thr Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Ile Ala Glu Asp Ser Ala Ala Tyr Tyr Cys
85 90 95

Ala Lys Gly Gly Gly Tyr Ser Gly Tyr Asp Trp Asp Phe Tyr Tyr Gly
100 105 110

Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 67
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 67

ggattcacac ttagcagcca tgtc 24

<210> SEQ ID NO 68
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 68

Gly Phe Thr Leu Ser Ser His Val
1 5

<210> SEQ ID NO 69
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 69

atcagtggtc ctggtggtag taca 24

<210> SEQ ID NO 70
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 70

Ile Ser Gly Pro Gly Gly Ser Thr
1 5

<210> SEQ ID NO 71
<211> LENGTH: 57
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 71

gcgaaagggg ggggatatag tggctacgat tgggactttt attacggtat ggacgtc 57

<210> SEQ ID NO 72
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 72

Ala Lys Gly Gly Gly Tyr Ser Gly Tyr Asp Trp Asp Phe Tyr Tyr Gly
1 5 10 15

Met Asp Val

<210> SEQ ID NO 73
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 73

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaagctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

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gaagattttg caacttacta ttgtcaacag actaacagtt tccctctcac tttcggcgga 300

gggaccaaag tggatatcaa a 321

<210> SEQ ID NO 74
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 74

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Asp Ile Lys
100 105

<210> SEQ ID NO 75
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 75

cagggtatta gcagctgg 18

<210> SEQ ID NO 76
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 76

Gln Gly Ile Ser Ser Trp
1 5

<210> SEQ ID NO 77
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 77

gctgcatcc 9

<210> SEQ ID NO 78
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 78

Ala Ala Ser
1

<210> SEQ ID NO 79
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 79

caacagacta acagtttccc tctcact 27

<210> SEQ ID NO 80
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 80

Gln Gln Thr Asn Ser Phe Pro Leu Thr
1 5

<210> SEQ ID NO 81
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 81

caggtgcagc tggtgcagtc tggggctgag gtgaagaagt ctgggtcctc ggtgaaggtc 60

tcctgcaagg cttctggagg caccttcagc agctatgcta tcagctgggt gcgacaggcc 120

ccgggacaag ggcttgagtg gatgggaggg atcatcccta tctttggtac aggaaattac 180

gcacagaagt tccagggcag agtcacgatt accacggacg aatccacgag cacagcctat 240

atggagctga gcagcctgag atctgaggac acggccgtgt attattgtgc gagagatagc 300

agctcgtccc cgaggtacta cggtatggac gtctggggcc acgggaccac ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 82
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 82

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Ser Gly Ser
1 5 10 15

Ser Val Lys Val Ser Cys Lys Ala Ser Gly Gly Thr Phe Ser Ser Tyr
20 25 30

Ala Ile Ser Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Gly Ile Ile Pro Ile Phe Gly Thr Gly Asn Tyr Ala Gln Lys Phe
50 55 60

Gln Gly Arg Val Thr Ile Thr Thr Asp Glu Ser Thr Ser Thr Ala Tyr
65 70 75 80

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Met Glu Leu Ser Ser Leu Arg Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Ser Ser Ser Ser Pro Arg Tyr Tyr Gly Met Asp Val Trp
100 105 110

Gly His Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 83
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 83

ggaggcacct tcagcagcta tgct 24

<210> SEQ ID NO 84
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 84

Gly Gly Thr Phe Ser Ser Tyr Ala
1 5

<210> SEQ ID NO 85
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 85

atcatcccta tctttggtac agga 24

<210> SEQ ID NO 86
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 86

Ile Ile Pro Ile Phe Gly Thr Gly
1 5

<210> SEQ ID NO 87
<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 87

gcgagagata gcagctcgtc cccgaggtac tacggtatgg acgtc 45

<210> SEQ ID NO 88
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 88

Ala Arg Asp Ser Ser Ser Ser Pro Arg Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 89
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 89

gaaattgtgt tgacacagtc tccagccacc ctgtctttgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gagtgttacc agctacttag cctggtacca acagaaacct 120

ggccaggctc ccaggctcct catctatgat gtatccaaga gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag cctagagcct 240

gaagattttg caacttatta ttgtcagcag cgtagcaact ggcctcccac cttcggccaa 300

gggacacgac tggagattaa a 321

<210> SEQ ID NO 90
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 90

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Thr Ser Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Asp Val Ser Lys Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Glu Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Arg Ser Asn Trp Pro Pro
85 90 95

Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105

<210> SEQ ID NO 91
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 91

cagagtgtta ccagctac 18

<210> SEQ ID NO 92
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 92

Gln Ser Val Thr Ser Tyr
1 5

<210> SEQ ID NO 93
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 93

gatgtatcc 9

<210> SEQ ID NO 94
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 94

Asp Val Ser
1

<210> SEQ ID NO 95
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 95

cagcagcgta gcaactggcc tcccacc 27

<210> SEQ ID NO 96
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 96

Gln Gln Arg Ser Asn Trp Pro Pro Thr
1 5

<210> SEQ ID NO 97
<211> LENGTH: 375
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 97

gaggtgcagc tggtggagtc tgggggaggc ttggtccagc ctgggggtc cctgagactc 60

tcctgtgaag cctctggatt cacctttagt acctattgga tgagttgggt ccgccaggct 120

ccagggaagg ggctagagtg ggtggccaac ataaaacaag atggaagtgt gaaatacttt 180

gtggactctg tgaagggccg attcaccgtc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagcctgag agccgaggac acggctctgt atcactgtgc gagagagagg 300

cacagaggga gctactacgg ctactacgac ggtatggacg tctggggcca agggaccacg 360

gtcaccgtct cctca 375

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<210> SEQ ID NO 98
<211> LENGTH: 125
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 98

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Glu Ala Ser Gly Phe Thr Phe Ser Thr Tyr
20 25 30

Trp Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Asn Ile Lys Gln Asp Gly Ser Val Lys Tyr Phe Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Arg Glu Arg His Arg Gly Ser Tyr Tyr Gly Tyr Tyr Asp Gly Met
100 105 110

Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 99
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 99

ggattcacct ttagtaccta ttgg 24

<210> SEQ ID NO 100
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 100

Gly Phe Thr Phe Ser Thr Tyr Trp
1 5

<210> SEQ ID NO 101
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 101

ataaaacaag atggaagtgt gaaa 24

<210> SEQ ID NO 102
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 102

Ile Lys Gln Asp Gly Ser Val Lys
1 5

<210> SEQ ID NO 103
<211> LENGTH: 54
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 103

gcgagagaga ggcacagagg gagctactac ggctactacg acggtatgga cgtc 54

<210> SEQ ID NO 104
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 104

Ala Arg Glu Arg His Arg Gly Ser Tyr Tyr Gly Tyr Tyr Asp Gly Met
1 5 10 15

Asp Val

<210> SEQ ID NO 105
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 105

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca aaacattgac atctatttaa attggtatca ggagaggcca 120

gggaaagccc ctaatctcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagtag tctgcaacct 240

gaagattttg caacttacta ctgtcaacag agttacaata ccccgttcac tttcggcggc 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 106
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 106

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asn Ile Asp Ile Tyr
20 25 30

Leu Asn Trp Tyr Gln Glu Arg Pro Gly Lys Ala Pro Asn Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

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Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Asn Thr Pro Phe
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 107
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 107

caaaacattg acatctat 18

<210> SEQ ID NO 108
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 108

Gln Asn Ile Asp Ile Tyr
1 5

<210> SEQ ID NO 109
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 109

gctgcatcc 9

<210> SEQ ID NO 110
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 110

Ala Ala Ser
1

<210> SEQ ID NO 111
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 111

caacagagtt acaatacccc gttcact 27

<210> SEQ ID NO 112
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 112

Gln Gln Ser Tyr Asn Thr Pro Phe Thr

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1 5

<210> SEQ ID NO 113
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 113

gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgcag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaaact 120

ccagggaagg gcctggagtg gatctcaggt attagttgga gtagtggtac catagtctat 180

gcagactctg tgaagggccg cttcaccatc tccagagaca acgccaagaa ctccctgtat 240

ctgcaaatga acagtctgag aggtgaggac acggccttgt atcactgtgc aaaagatggg 300

tataggtgga agtcctactc gtacggtttg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 114
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 114

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Thr Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Ser Gly Ile Ser Trp Ser Ser Gly Thr Ile Val Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Gly Glu Asp Thr Ala Leu Tyr His Cys
85 90 95

Ala Lys Asp Gly Tyr Arg Trp Lys Ser Tyr Ser Tyr Gly Leu Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 115
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 115

ggattcacct ttgatgatta tgcc 24

<210> SEQ ID NO 116
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 116

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 117
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 117

attagttgga gtagtggtac cata 24

<210> SEQ ID NO 118
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 118

Ile Ser Trp Ser Ser Gly Thr Ile
1 5

<210> SEQ ID NO 119
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 119

gcaaaagatg ggtataggtg gaagtcctac tcgtacggtt tggacgtc 48

<210> SEQ ID NO 120
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 120

Ala Lys Asp Gly Tyr Arg Trp Lys Ser Tyr Ser Tyr Gly Leu Asp Val
1 5 10 15

<210> SEQ ID NO 121
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 121

gaaatagtga tgacgcagtc tccagccacc ctctctttgt ctccagggga aagagccacc 60

ctctcctgca ggcccagtca gagtgttatc aataacttag cctggtacca gcagaaacct 120

ggccaggctc ccagactcct catctttggt gcatcctcca gggccactgg tatcccagcc 180

agattcagtg gcagtgggtc tgggacagag tttactctca ccatcagcag cctgcagtct 240

gaagattttg cactttatta ctgtcagcag tataataact ggccgctcac cttcggcgga 300

gggaccaagg tggagatcaa a 321

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<210> SEQ ID NO 122
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 122

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Pro Ser Gln Ser Val Ile Asn Asn
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Leu Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 123
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 123

cagagtgtta tcaataac 18

<210> SEQ ID NO 124
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 124

Gln Ser Val Ile Asn Asn
1 5

<210> SEQ ID NO 125
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 125

ggtgcatcc 9

<210> SEQ ID NO 126
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 126

Gly Ala Ser
1

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<210> SEQ ID NO 127
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 127

cagcagtata ataactggcc gctcacc 27

<210> SEQ ID NO 128
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 128

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 129
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 129

gaagtgcagc tggtggagtc tgggggagac ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgtag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt gttagttgga gtggtagtac cgtaggctat 180

gcggactctg tgaagggccg attcaccgtc tccagagaca acgcccagaa atccctgtat 240

ctacaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagacgcg 300

tataaatgga actactacta ctacggtttg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 130
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 130

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Ser Trp Ser Gly Ser Thr Val Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Gln Lys Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Ala Tyr Lys Trp Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val

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100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 131
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 131

ggattcacct ttgatgatta tgcc 24

<210> SEQ ID NO 132
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 132

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 133
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 133

gttagttgga gtggtagtac cgta 24

<210> SEQ ID NO 134
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 134

Val Ser Trp Ser Gly Ser Thr Val
1 5

<210> SEQ ID NO 135
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 135

gtaaaagacg cgtataaatg gaactactac tactacggtt tggacgtc 48

<210> SEQ ID NO 136
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 136

Val Lys Asp Ala Tyr Lys Trp Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
1 5 10 15

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<210> SEQ ID NO 137
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 137

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gactattctc agcaacttag cctggtacct acagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tctcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 138
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 138

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Leu Ser Asn
20 25 30

Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 139
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 139

cagactattc tcagcaac 18

<210> SEQ ID NO 140
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 140

Gln Thr Ile Leu Ser Asn
1 5

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<210> SEQ ID NO 141
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 141

ggtgcatcc 9

<210> SEQ ID NO 142
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 142

Gly Ala Ser
1

<210> SEQ ID NO 143
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 143

cagcagtata ataactggcc tctcact 27

<210> SEQ ID NO 144
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 144

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 145
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 145

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctgggggtc cctgagactc 60

tcctgtggag cctctggatt cacctttagg gactttgaca tgaattgggt ccgtcaggct 120

ccagggaggg ggctggagtg ggtctcaggt attggtggta gtggtggtaa cacatattac 180

gcagactccg tgaagggccg gttcaccata tccagggaca attccaaaaa cacgctgttt 240

ctgcaaatga gcagcctgag agccgaggac acggccgttt attactgtgt gaaagatccc 300

tatggtgact ataggaacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 146
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 146

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Gly Ala Ser Gly Phe Thr Phe Arg Asp Phe
20 25 30

Asp Met Asn Trp Val Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
35 40 45

Ser Gly Ile Gly Gly Ser Gly Gly Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Phe
65 70 75 80

Leu Gln Met Ser Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Val Lys Asp Pro Tyr Gly Asp Tyr Arg Asn Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 147
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 147

ggattcacct ttagggactt tgac 24

<210> SEQ ID NO 148
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 148

Gly Phe Thr Phe Arg Asp Phe Asp
1 5

<210> SEQ ID NO 149
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 149

attggtggta gtggtggtaa caca 24

<210> SEQ ID NO 150
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 150

Ile Gly Gly Ser Gly Gly Asn Thr
1 5

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<210> SEQ ID NO 151
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 151

gtgaaagatc cctatggtga ctataggaac tactacggta tggacgtc 48

<210> SEQ ID NO 152
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 152

Val Lys Asp Pro Tyr Gly Asp Tyr Arg Asn Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 153
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 153

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctccta catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccacaa ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt caggggcagt ggatcagaca aggactttac actgaaaatc 240

agcagagtgg gggctgagga tgttggggtt tattactgca tgcaagctct acaaactatc 300

accttcggcc aagggacacg actggagatt aaa 333

<210> SEQ ID NO 154
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 154

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Arg Gly Ser Gly Ser Asp Lys Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Gly Ala Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

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<210> SEQ ID NO 155
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 155

cagagcctcc tacatagtaa tggatacaac tat 33

<210> SEQ ID NO 156
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 156

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
1 5 10

<210> SEQ ID NO 157
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 157

ttgggttct 9

<210> SEQ ID NO 158
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 158

Leu Gly Ser
1

<210> SEQ ID NO 159
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 159

atgcaagctc tacaaactat cacc 24

<210> SEQ ID NO 160
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 160

Met Gln Ala Leu Gln Thr Ile Thr
1 5

<210> SEQ ID NO 161
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 161

gaggtgcagc tggtggagtc tgggggaggc ttgggacagc ctgggggtc cctgagactc 60

tcctgtggag cctctggatt catgtttaga aactatgcca tgagttgggt ccgccaggct 120

ccagggaagg ggctggagtg ggtctcaact attcttgata gtggtgataa cacatattac 180

gcagactccg tgaagggccg gttcaccatc tccagggaca attccaagaa cacactgtat 240

ctgcaaatga acagcctgag agccgaggac acggccgttt attactgtgc gaaagatccc 300

tatggtgact acagggacta ctacggtatg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 162
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 162

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Gly Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Gly Ala Ser Gly Phe Met Phe Arg Asn Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Thr Ile Leu Asp Ser Gly Asp Asn Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Pro Tyr Gly Asp Tyr Arg Asp Tyr Tyr Gly Met Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 163
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 163

ggattcatgt ttagaaacta tgcc 24

<210> SEQ ID NO 164
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 164

Gly Phe Met Phe Arg Asn Tyr Ala
1 5

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<210> SEQ ID NO 165
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 165

attcttgata gtggtgataa caca 24

<210> SEQ ID NO 166
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 166

Ile Leu Asp Ser Gly Asp Asn Thr
1 5

<210> SEQ ID NO 167
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 167

gcgaaagatc cctatggtga ctacagggac tactacggta tggacgtc 48

<210> SEQ ID NO 168
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 168

Ala Lys Asp Pro Tyr Gly Asp Tyr Arg Asp Tyr Tyr Gly Met Asp Val
1 5 10 15

<210> SEQ ID NO 169
<211> LENGTH: 333
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 169

gatattgtga tgactcagtc tccactctcc ctgcccgtca cccctggaga gccggcctcc 60

atctcctgca ggtctagtca gagcctccta catagtaatg gatacaacta tttggattgg 120

tacctgcaga agccagggca gtctccgcaa ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt caggggcagt ggatcaggca aagactttac actgaaaatc 240

agcagagtgg aggctgagga tgttggactt tattactgca tgcaagctct acaaactatc 300

accttcggcc aagggacacg actggagatt aaa 333

<210> SEQ ID NO 170
<211> LENGTH: 111
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 170

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Pro Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Leu His Ser
20 25 30

Asn Gly Tyr Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Arg Gly Ser Gly Ser Gly Lys Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Leu Tyr Tyr Cys Met Gln Ala
85 90 95

Leu Gln Thr Ile Thr Phe Gly Gln Gly Thr Arg Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 171
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 171

cagagcctcc tacatagtaa tggatacaac tat 33

<210> SEQ ID NO 172
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 172

Gln Ser Leu Leu His Ser Asn Gly Tyr Asn Tyr
1 5 10

<210> SEQ ID NO 173
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 173

ttgggttct 9

<210> SEQ ID NO 174
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 174

Leu Gly Ser
1

<210> SEQ ID NO 175
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 175

atgcaagctc tacaaactat cacc 24

<210> SEQ ID NO 176
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 176

Met Gln Ala Leu Gln Thr Ile Thr
1 5

<210> SEQ ID NO 177
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 177

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg ctccatcagt ggttactact ggacctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattaca gtggggccac caactacaac 180

ccctccctca agagtcgagt caccatatca ttagacacgt ccaagaacca gttctccctg 240

aaactgagct ctgtgaccgc tgcggacacg gccgtgtatt attgtgcgag agatgggaat 300

tacgatattt tgactggtta ttataactac cactattacg gcatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 178
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 178

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Ser Ile Ser Gly Tyr
20 25 30

Tyr Trp Thr Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ala Thr Asn Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Leu Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Asp Gly Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Tyr His Tyr
100 105 110

Tyr Gly Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 179

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<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 179

ggtggctcca tcagtggtta ctac 24

<210> SEQ ID NO 180
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 180

Gly Gly Ser Ile Ser Gly Tyr Tyr
1 5

<210> SEQ ID NO 181
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 181

atctattaca gtggggccac c 21

<210> SEQ ID NO 182
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 182

Ile Tyr Tyr Ser Gly Ala Thr
1 5

<210> SEQ ID NO 183
<211> LENGTH: 66
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 183

gcgagagatg ggaattacga tattttgact ggttattata actaccacta ttacggcatg 60

gacgtc 66

<210> SEQ ID NO 184
<211> LENGTH: 22
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 184

Ala Arg Asp Gly Asn Tyr Asp Ile Leu Thr Gly Tyr Tyr Asn Tyr His
1 5 10 15

Tyr Tyr Gly Met Asp Val
20

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<210> SEQ ID NO 185
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 185

gacatccaga tgacccagtc tccatcctca ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca ggacattggt aattatttag cctggtttca gcagaaacca 120

gggaaagccc ctgagtccct gatctatgct gcatccattt tacaaagtgg ggtcccatca 180

aagttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttatta ctgccaacag tataatactt tcccgtggac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 186
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 186

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Gly Asn Tyr
20 25 30

Leu Ala Trp Phe Gln Gln Lys Pro Gly Lys Ala Pro Glu Ser Leu Ile
35 40 45

Tyr Ala Ala Ser Ile Leu Gln Ser Gly Val Pro Ser Lys Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Tyr Asn Thr Phe Pro Trp
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 187
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 187

caggacattg gtaattat 18

<210> SEQ ID NO 188
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 188

Gln Asp Ile Gly Asn Tyr
1 5

<210> SEQ ID NO 189

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<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 189

gctgcatcc 9

<210> SEQ ID NO 190
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 190

Ala Ala Ser
1

<210> SEQ ID NO 191
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 191

caacagtata atactttccc gtggacg 27

<210> SEQ ID NO 192
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 192

Gln Gln Tyr Asn Thr Phe Pro Trp Thr
1 5

<210> SEQ ID NO 193
<211> LENGTH: 366
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 193

caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgaggctc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgacctggat ccgtcaggct 120

ccagggaggg ggctggagtg ggtttcatac attagtgata ctggcagtca cttatactac 180

gcagactctg tgaggggccg attcaccatc tccagggaca acgccaaaaa ctcactgtat 240

ctgcaaatga acaacctgag agccgaggac acggccgtat attactgtgc gcgagatcag 300

gatggggaaa tggaactacg tttctttgac tactggggcc agggaaccct ggtcaccgtc 360

tcctca 366

<210> SEQ ID NO 194
<211> LENGTH: 122
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 194

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Thr Trp Ile Arg Gln Ala Pro Gly Arg Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Asp Thr Gly Ser His Leu Tyr Tyr Ala Asp Ser Val
50 55 60

Arg Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Asn Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Asp Gln Asp Gly Glu Met Glu Leu Arg Phe Phe Asp Tyr Trp
100 105 110

Gly Gln Gly Thr Leu Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 195
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 195

ggattcacct tcagtgacta ctac 24

<210> SEQ ID NO 196
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 196

Gly Phe Thr Phe Ser Asp Tyr Tyr
1 5

<210> SEQ ID NO 197
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 197

attagtgata ctggcagtca ctta 24

<210> SEQ ID NO 198
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 198

Ile Ser Asp Thr Gly Ser His Leu
1 5

<210> SEQ ID NO 199

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<211> LENGTH: 45
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 199

gcgcgagatc aggatgggga aatggaacta cgtttctttg actac 45

<210> SEQ ID NO 200
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 200

Ala Arg Asp Gln Asp Gly Glu Met Glu Leu Arg Phe Phe Asp Tyr
1 5 10 15

<210> SEQ ID NO 201
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 201

gaaatagtgt tgacgcagtc tccagccact ctgtctttgt ctccagggga aagaggcacc 60

ctctcctgca gggccagtca gagtattaac aactacttag cctggtacca gcagaaacct 120

ggccaggctc ccaggctcct catctttgat gcatccaaca gggccactgg catcccagcc 180

aggttcagtg gcagtgggtc tgggacagac ttcactctca ccatcagcag aatagagcct 240

gaagattttg cagtttatta ctgtcagcag cgtaccaact ggccgctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 202
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 202

Glu Ile Val Leu Thr Gln Ser Pro Ala Thr Leu Ser Leu Ser Pro Gly
1 5 10 15

Glu Arg Gly Thr Leu Ser Cys Arg Ala Ser Gln Ser Ile Asn Asn Tyr
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Phe Asp Ala Ser Asn Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Ile Glu Pro
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Arg Thr Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 203
<211> LENGTH: 18

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 203

cagagtatta acaactac 18

<210> SEQ ID NO 204
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 204

Gln Ser Ile Asn Asn Tyr
1 5

<210> SEQ ID NO 205
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 205

gatgcatcc 9

<210> SEQ ID NO 206
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 206

Asp Ala Ser
1

<210> SEQ ID NO 207
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 207

cagcagcgta ccaactggcc gctcact 27

<210> SEQ ID NO 208
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 208

Gln Gln Arg Thr Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 209
<211> LENGTH: 381
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 209

caggtgcagc tgcaggagtc gggcccagga ctggtgaagc cttcggagac cctgtccctc 60

acctgcactg tctctggtgg cttcatcagt aattactact ggagctggat ccggcagccc 120

ccagggaagg gactggagtg gattggatat atctattata gtgggagcac caagtacaac 180

ccctccctca agagtcgagt caccatatca gtagacacgt ccaagaacca gttctccctg 240

aagctgagct ctgtgagcgc tgcggacacg gccgtgtatt actgtgcgag agatggggtt 300

gtagcagcag ctggtccccc ttaccactac cactacggtt tggacgtctg gggccaaggg 360

accacggtca ccgtctcctc a 381

<210> SEQ ID NO 210
<211> LENGTH: 127
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 210

Gln Val Gln Leu Gln Glu Ser Gly Pro Gly Leu Val Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Thr Val Ser Gly Gly Phe Ile Ser Asn Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Tyr Ile Tyr Tyr Ser Gly Ser Thr Lys Tyr Asn Pro Ser Leu Lys
50 55 60

Ser Arg Val Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Ser Ser Val Ser Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Arg Asp Gly Val Val Ala Ala Ala Gly Pro Pro Tyr His Tyr His Tyr
100 105 110

Gly Leu Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 211
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 211

ggtggcttca tcagtaatta ctac 24

<210> SEQ ID NO 212
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 212

Gly Gly Phe Ile Ser Asn Tyr Tyr
1 5

<210> SEQ ID NO 213
<211> LENGTH: 21

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 213

atctattata gtgggagcac c 21

<210> SEQ ID NO 214
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 214

Ile Tyr Tyr Ser Gly Ser Thr
1 5

<210> SEQ ID NO 215
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 215

gcgagagatg gggttgtagc agcagctggt ccccccttacc actaccacta cggtttggac 60

gtc 63

<210> SEQ ID NO 216
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 216

Ala Arg Asp Gly Val Val Ala Ala Ala Gly Pro Pro Tyr His Tyr His
1 5 10 15

Tyr Gly Leu Asp Val
20

<210> SEQ ID NO 217
<211> LENGTH: 339
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 217

gacatcgtga tgacccagtc tccagactcc ctggctgtgt ctctgggcga gagggccacc 60

atcaactgca agtccagcca gaatctttta tacacctcca gcaataagaa ctccttagct 120

tggtaccagc agaaaccagg acagcctcct gagctgctca tttactgggc atctacccgg 180

gaatccgggg tccctgaccg attcagtggc agcgggtctg ggacagattt cattctcacc 240

atcagcagcc tgcaggctga agatgtggca gtttattact gtcagcaata ttatagtagt 300

ccgtggacgt tcggccaagg gaccaaggtg gaaatcaaa 339

<210> SEQ ID NO 218
<211> LENGTH: 113
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 218

Asp Ile Val Met Thr Gln Ser Pro Asp Ser Leu Ala Val Ser Leu Gly
1 5 10 15

Glu Arg Ala Thr Ile Asn Cys Lys Ser Ser Gln Asn Leu Leu Tyr Thr
20 25 30

Ser Ser Asn Lys Asn Ser Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln
35 40 45

Pro Pro Glu Leu Leu Ile Tyr Trp Ala Ser Thr Arg Glu Ser Gly Val
50 55 60

Pro Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Ile Leu Thr
65 70 75 80

Ile Ser Ser Leu Gln Ala Glu Asp Val Ala Val Tyr Tyr Cys Gln Gln
85 90 95

Tyr Tyr Ser Ser Pro Trp Thr Phe Gly Gln Gly Thr Lys Val Glu Ile
100 105 110

Lys

<210> SEQ ID NO 219
<211> LENGTH: 36
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 219

cagaatcttt tatacacctc cagcaataag aactcc 36

<210> SEQ ID NO 220
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 220

Gln Asn Leu Leu Tyr Thr Ser Ser Asn Lys Asn Ser
1 5 10

<210> SEQ ID NO 221
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 221

tgggcatct 9

<210> SEQ ID NO 222
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 222

Trp Ala Ser
1

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<210> SEQ ID NO 223
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 223

cagcaatatt atagtagtcc gtggacg 27

<210> SEQ ID NO 224
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 224

Gln Gln Tyr Tyr Ser Ser Pro Trp Thr
1 5

<210> SEQ ID NO 225
<211> LENGTH: 372
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 225

caggtgcagc tggtggagtc tgggggaggc ttggtcaagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccttcagt gactactaca tgacctggat ccgccaggtt 120

ccagggaagg gactggagtg ggtttcatat atcagtagta ctgggaataa cagatattac 180

ggagactctg tgaagggccg attcgccatc tcaagggaca acgccaagaa cttactgttt 240

ctgcaaatga acagcctgaa agccgaggac acggccgttt attactgtgc aagagagaat 300

aattggaatc cttacttctt ctactatggt atggacgtct ggggccaagg gaccacggtc 360

accgtctcct ca 372

<210> SEQ ID NO 226
<211> LENGTH: 124
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 226

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Lys Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Asp Tyr
20 25 30

Tyr Met Thr Trp Ile Arg Gln Val Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Tyr Ile Ser Ser Thr Gly Asn Asn Arg Tyr Tyr Gly Asp Ser Val
50 55 60

Lys Gly Arg Phe Ala Ile Ser Arg Asp Asn Ala Lys Asn Leu Leu Phe
65 70 75 80

Leu Gln Met Asn Ser Leu Lys Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Glu Asn Asn Trp Asn Pro Tyr Phe Phe Tyr Tyr Gly Met Asp
100 105 110

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Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 227
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 227

ggattcacct tcagtgacta ctac 24

<210> SEQ ID NO 228
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 228

Gly Phe Thr Phe Ser Asp Tyr Tyr
1 5

<210> SEQ ID NO 229
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 229

atcagtagta ctgggaataa caga 24

<210> SEQ ID NO 230
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 230

Ile Ser Ser Thr Gly Asn Asn Arg
1 5

<210> SEQ ID NO 231
<211> LENGTH: 51
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 231

gcaagagaga ataattggaa tccttacttc ttctactatg gtatggacgt c 51

<210> SEQ ID NO 232
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 232

Ala Arg Glu Asn Asn Trp Asn Pro Tyr Phe Phe Tyr Tyr Gly Met Asp
1 5 10 15

Val

<210> SEQ ID NO 233
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 233

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60

atcacttgtc gggcgagtca gggtattagc atctggttag cctggtatca gcagaaacca 120

gggaaagccc ctaaactcct gatctctgct gcgtccactt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240

gaagattttg caacttacta ttgtcaacag gctaacagtt tcccgttgac gttcggccaa 300

gggaccaagg tggaaatcaa a 321

<210> SEQ ID NO 234
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 234

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ile Trp
20 25 30

Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Ser Ala Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 235
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 235

cagggtatta gcatctgg 18

<210> SEQ ID NO 236
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 236

Gln Gly Ile Ser Ile Trp
1 5

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<210> SEQ ID NO 237
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 237

gctgcgtcc 9

<210> SEQ ID NO 238
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 238

Ala Ala Ser
1

<210> SEQ ID NO 239
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 239

caacaggcta acagtttccc gttgacg 27

<210> SEQ ID NO 240
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 240

Gln Gln Ala Asn Ser Phe Pro Leu Thr
1 5

<210> SEQ ID NO 241
<211> LENGTH: 351
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 241

caggtgcagc tggtggagtc tgggggaggc gtggtccagc ctgggaggtc cctgagactc 60

tcctgtgcag cgtctggatt caccttcagt agctatggca tgcactgggt ccgccaggct 120

ccaggcaagg ggctggagtg ggtggcagtt atatattatg aaggaagtaa tgattactat 180

gtagactccg tgaagggccg attcaccatc tccagagaca attccaaaaa cacgctatat 240

ctgcaaatga acagcctgag agccgaggac acggctgtgt attactgtgc gagaagggac 300

tggaactcct ttgactattg gggccagggc accctggtca ccgtctcctc a 351

<210> SEQ ID NO 242
<211> LENGTH: 117
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 242

Gln Val Gln Leu Val Glu Ser Gly Gly Gly Val Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Gly Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ala Val Ile Tyr Tyr Glu Gly Ser Asn Asp Tyr Tyr Val Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Arg Asp Trp Asn Ser Phe Asp Tyr Trp Gly Gln Gly Thr Leu
100 105 110

Val Thr Val Ser Ser
115

<210> SEQ ID NO 243
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 243

ggattcacct tcagtagcta tggc 24

<210> SEQ ID NO 244
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 244

Gly Phe Thr Phe Ser Ser Tyr Gly
1 5

<210> SEQ ID NO 245
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 245

atatattatg aaggaagtaa tgat 24

<210> SEQ ID NO 246
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 246

Ile Tyr Tyr Glu Gly Ser Asn Asp
1 5

<210> SEQ ID NO 247

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<211> LENGTH: 30
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 247

gcgagaaggg actggaactc ctttgactat 30

<210> SEQ ID NO 248
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 248

Ala Arg Arg Asp Trp Asn Ser Phe Asp Tyr
1 5 10

<210> SEQ ID NO 249
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 249

gatattgtga tgactcagtc tccactctcc ctgtccgtca cccctggaga gccggcctcc 60

atctcctgca ggtccagtca gaacctccta aatagaaatg gattcaacta tttggattgg 120

tatttgcaga agccagggca gtctccacag ctcctgatct atttgggttc taatcgggcc 180

tccggggtcc ctgacaggtt cagtggcagt ggatcaggca cagattttac actgaaaatc 240

agcagagtgg aggttgagga tgttggggtt tattattgca tgcaagctat acaaactccg 300

tacacttttg gccaggggac caagctggag atcaaa 336

<210> SEQ ID NO 250
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 250

Asp Ile Val Met Thr Gln Ser Pro Leu Ser Leu Ser Val Thr Pro Gly
1 5 10 15

Glu Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Asn Leu Leu Asn Arg
20 25 30

Asn Gly Phe Asn Tyr Leu Asp Trp Tyr Leu Gln Lys Pro Gly Gln Ser
35 40 45

Pro Gln Leu Leu Ile Tyr Leu Gly Ser Asn Arg Ala Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Val Glu Asp Val Gly Val Tyr Tyr Cys Met Gln Ala
85 90 95

Ile Gln Thr Pro Tyr Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105 110

<210> SEQ ID NO 251
<211> LENGTH: 33

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 251

cagaacctcc taaatagaaa tggattcaac tat 33

<210> SEQ ID NO 252
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 252

Gln Asn Leu Leu Asn Arg Asn Gly Phe Asn Tyr
1 5 10

<210> SEQ ID NO 253
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 253

ttgggttct 9

<210> SEQ ID NO 254
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 254

Leu Gly Ser
1

<210> SEQ ID NO 255
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 255

atgcaagcta tacaaactcc gtacact 27

<210> SEQ ID NO 256
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 256

Met Gln Ala Ile Gln Thr Pro Tyr Thr
1 5

<210> SEQ ID NO 257
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 257

gaagtgcagc tggtggagtc tgggggagac ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgtag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt gttagttgga gtggtagtac cgtaggctat 180

gcggactctg tgaagggccg attcaccgtc tccagagaca acgcccagaa atccctgtat 240

ctacaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagacgcg 300

tataaataca actactacta ctacggtttg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 258
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 258

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Ser Trp Ser Gly Ser Thr Val Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Gln Lys Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Ala Tyr Lys Tyr Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 259
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 259

ggattcacct ttgatgatta tgcc 24

<210> SEQ ID NO 260
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 260

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 261
<211> LENGTH: 24

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<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 261

gttagttgga gtggtagtac cgta 24

<210> SEQ ID NO 262
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 262

Val Ser Trp Ser Gly Ser Thr Val
1 5

<210> SEQ ID NO 263
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 263

gtaaaagacg cgtataaata caactactac tactacggtt tggacgtc 48

<210> SEQ ID NO 264
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 264

Val Lys Asp Ala Tyr Lys Tyr Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
1 5 10 15

<210> SEQ ID NO 265
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 265

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gactattctc agcaacttag cctggtacct acagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tctcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 266
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 266

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Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Leu Ser Asn
20 25 30

Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 267
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 267

cagactattc tcagcaac 18

<210> SEQ ID NO 268
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 268

Gln Thr Ile Leu Ser Asn
1 5

<210> SEQ ID NO 269
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 269

ggtgcatcc 9

<210> SEQ ID NO 270
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 270

Gly Ala Ser
1

<210> SEQ ID NO 271
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 271

cagcagtata ataactggcc tctcact 27

<210> SEQ ID NO 272
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 272

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 273
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 273

gaagtgcagc tggtggagtc tgggggagac ttggtacagc ctggcaggtc cctgagactc 60

tcctgtgtag cctctggatt cacctttgat gattatgcca tgcactgggt ccggcaagct 120

ccagggaagg gcctggagtg ggtctcaggt gttagttgga gtggtagtac cgtaggctat 180

gcggactctg tgaagggccg attcaccgtc tccagagaca acgcccagaa atccctgtat 240

ctacaaatga acagtctgag agctgaggac acggccttgt attactgtgt aaaagacgcg 300

tataaattca actactacta ctacggtttg gacgtctggg gccaagggac cacggtcacc 360

gtctcctca 369

<210> SEQ ID NO 274
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 274

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
1 5 10 15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
20 25 30

Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Gly Val Ser Trp Ser Gly Ser Thr Val Gly Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Gln Lys Ser Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
85 90 95

Val Lys Asp Ala Tyr Lys Phe Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
100 105 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 275
<211> LENGTH: 24
<212> TYPE: DNA

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 275

ggattcacct ttgatgatta tgcc 24

<210> SEQ ID NO 276
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 276

Gly Phe Thr Phe Asp Asp Tyr Ala
1 5

<210> SEQ ID NO 277
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 277

gttagttgga gtggtagtac cgta 24

<210> SEQ ID NO 278
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 278

Val Ser Trp Ser Gly Ser Thr Val
1 5

<210> SEQ ID NO 279
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 279

gtaaaagacg cgtataaatt caactactac tactacggtt tggacgtc 48

<210> SEQ ID NO 280
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 280

Val Lys Asp Ala Tyr Lys Phe Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
1 5 10 15

<210> SEQ ID NO 281
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

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<400> SEQUENCE: 281

gaaatagtga tgacgcagtc tccagccacc ctgtctgtgt ctccagggga aagagccacc 60

ctctcctgca gggccagtca gactattctc agcaacttag cctggtacct acagaaacct 120

ggccaggctc ccaggctcct catctatggt gcatccacca gggccactgg tctcccagcc 180

aggttcagtg gcagtgggtc tgggacagag ttcactctca ccatcagcag cctgcagtct 240

gaagattttg cagtttatta ctgtcagcag tataataact ggcctctcac tttcggcgga 300

gggaccaagg tggagatcaa a 321

<210> SEQ ID NO 282
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 282

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
1 5 10 15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Leu Ser Asn
20 25 30

Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
35 40 45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65 70 75 80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
85 90 95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> SEQ ID NO 283
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 283

cagactattc tcagcaac 18

<210> SEQ ID NO 284
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 284

Gln Thr Ile Leu Ser Asn
1 5

<210> SEQ ID NO 285
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 285

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ggtgcatcc 9

<210> SEQ ID NO 286
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 286

Gly Ala Ser
1

<210> SEQ ID NO 287
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 287

cagcagtata ataactggcc tctcact 27

<210> SEQ ID NO 288
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 288

Gln Gln Tyr Asn Asn Trp Pro Leu Thr
1 5

<210> SEQ ID NO 289
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 289

caggtgcagc tggagcagtc tggggctgag gtgaagaagc ctggggcctc agtgaggatc 60

tcctgtaagg cttctggcga caccttcacc ggctactata taaactgggt gcgccaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaatacta acagtggtgg cacatacttt 180

tcacagaaat ttcaggtcag ggtcatcctg accagggaca cgtccatcaa cacagcctac 240

atggagttga gcaggctgag atctgacgac acggccgttt attactgtgc gagaatgttt 300

tacgatattt tgactaattc tgatattttt gatatttggg gccaagggac aatggtcacc 360

gtctcttca 369

<210> SEQ ID NO 290
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 290

Gln Val Gln Leu Glu Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Asp Thr Phe Thr Gly Tyr

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            20                  25                  30

Tyr Ile Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
        35                  40                  45

Gly Trp Ile Asn Thr Asn Ser Gly Gly Thr Tyr Phe Ser Gln Lys Phe
    50                  55                  60

Gln Val Arg Val Ile Leu Thr Arg Asp Thr Ser Ile Asn Thr Ala Tyr
65                  70                  75                  80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
                85                  90                  95

Ala Arg Met Phe Tyr Asp Ile Leu Thr Asn Ser Asp Ile Phe Asp Ile
            100                 105                 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
        115                 120


<210> SEQ ID NO 291
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 291

ggcgacacct tcaccggcta ctat                                          24


<210> SEQ ID NO 292
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 292

Gly Asp Thr Phe Thr Gly Tyr Tyr
 1               5


<210> SEQ ID NO 293
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 293

atcaatacta acagtggtgg caca                                          24


<210> SEQ ID NO 294
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 294

Ile Asn Thr Asn Ser Gly Gly Thr
 1               5


<210> SEQ ID NO 295
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 295
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gcgagaatgt tttacgatat tttgactaat tctgatattt ttgatatt 48

<210> SEQ ID NO 296
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 296

Ala Arg Met Phe Tyr Asp Ile Leu Thr Asn Ser Asp Ile Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 297
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 297

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacataaga aatgatttag gctggtatca gcagaaacca 120

gggaaagccc ctaagtgcct gatctatggt gcatccagtt tgcaaagtgg ggtcccatca 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacaa cataaaaatt acatgtacac ttttggccag 300

gggaccaagt tggagatcaa a 321

<210> SEQ ID NO 298
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 298

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Asn Tyr Met Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 299
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 299

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caggacataa gaaatgat 18

<210> SEQ ID NO 300
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 300

Gln Asp Ile Arg Asn Asp
1 5

<210> SEQ ID NO 301
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 301

ggtgcatcc 9

<210> SEQ ID NO 302
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 302

Gly Ala Ser
1

<210> SEQ ID NO 303
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 303

ctacaacata aaaattacat gtacact 27

<210> SEQ ID NO 304
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 304

Leu Gln His Lys Asn Tyr Met Tyr Thr
1 5

<210> SEQ ID NO 305
<211> LENGTH: 345
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 305

caggtgcagc tacagcagtg gggcgcagga ctgttgaagc cttcggagac cctgtccctc 60

acctgcgctg tctatggtgg gtccctcagt gattactact ggagctggat ccgccagccc 120

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ccagggaagg ggctggagtg gattggggaa atcaatcata gtggagacac caactacgac 180

ccgtccctca agagtcgact caccatctca gtagacacgt ccaagaacca gttctccctg 240

aagctgaact ctgtgaccgc cgcggacacg gctgtgtatt actgtgcgag cctgtatttc 300

aatttttgga tgtggggtcg aggagccctg gtcaccgtct cctca 345

<210> SEQ ID NO 306
<211> LENGTH: 115
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 306

Gln Val Gln Leu Gln Gln Trp Gly Ala Gly Leu Leu Lys Pro Ser Glu
1 5 10 15

Thr Leu Ser Leu Thr Cys Ala Val Tyr Gly Gly Ser Leu Ser Asp Tyr
20 25 30

Tyr Trp Ser Trp Ile Arg Gln Pro Pro Gly Lys Gly Leu Glu Trp Ile
35 40 45

Gly Glu Ile Asn His Ser Gly Asp Thr Asn Tyr Asp Pro Ser Leu Lys
50 55 60

Ser Arg Leu Thr Ile Ser Val Asp Thr Ser Lys Asn Gln Phe Ser Leu
65 70 75 80

Lys Leu Asn Ser Val Thr Ala Ala Asp Thr Ala Val Tyr Tyr Cys Ala
85 90 95

Ser Leu Tyr Phe Asn Phe Trp Met Trp Gly Arg Gly Ala Leu Val Thr
100 105 110

Val Ser Ser
115

<210> SEQ ID NO 307
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 307

ggtgggtccc tcagtgatta ctac 24

<210> SEQ ID NO 308
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 308

Gly Gly Ser Leu Ser Asp Tyr Tyr
1 5

<210> SEQ ID NO 309
<211> LENGTH: 21
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 309

atcaatcata gtggagacac c 21

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<210> SEQ ID NO 310
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 310

Ile Asn His Ser Gly Asp Thr
1 5

<210> SEQ ID NO 311
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 311

gcgagcctgt atttcaattt ttggatg 27

<210> SEQ ID NO 312
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 312

Ala Ser Leu Tyr Phe Asn Phe Trp Met
1 5

<210> SEQ ID NO 313
<211> LENGTH: 336
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 313

gatattgtga tgacccagac tccactctcc tcacctgtca ttcttggaca gccggcctcc 60

atctcctgca ggtctagtca aagcctcgta tacagtgatg gaaacaccta cttgagttgg 120

cttcagcaga ggccaggcca gcctccaaga ctcctaattt ataagatttc taaccggttc 180

tctggggtcc cagacagatt cagtggcagt gggacaggga cagatttcac actgaaaatc 240

agcagggtgg aagctgagga tgtcggaatt tattactgca tgcaaactac acaatttccg 300

ctcactttcg gcggagggac caaggtggag atcaaa 336

<210> SEQ ID NO 314
<211> LENGTH: 112
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 314

Asp Ile Val Met Thr Gln Thr Pro Leu Ser Ser Pro Val Ile Leu Gly
1 5 10 15

Gln Pro Ala Ser Ile Ser Cys Arg Ser Ser Gln Ser Leu Val Tyr Ser
20 25 30

Asp Gly Asn Thr Tyr Leu Ser Trp Leu Gln Gln Arg Pro Gly Gln Pro
35 40 45

-continued

Pro Arg Leu Leu Ile Tyr Lys Ile Ser Asn Arg Phe Ser Gly Val Pro
50 55 60

Asp Arg Phe Ser Gly Ser Gly Thr Gly Thr Asp Phe Thr Leu Lys Ile
65 70 75 80

Ser Arg Val Glu Ala Glu Asp Val Gly Ile Tyr Tyr Cys Met Gln Thr
85 90 95

Thr Gln Phe Pro Leu Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105 110

<210> SEQ ID NO 315
<211> LENGTH: 33
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 315

caaagcctcg tatacagtga tggaaacacc tac 33

<210> SEQ ID NO 316
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 316

Gln Ser Leu Val Tyr Ser Asp Gly Asn Thr Tyr
1 5 10

<210> SEQ ID NO 317
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 317

aagatttct 9

<210> SEQ ID NO 318
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 318

Lys Ile Ser
1

<210> SEQ ID NO 319
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 319

atgcaaacta cacaatttcc gctcact 27

<210> SEQ ID NO 320
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 320

Met Gln Thr Thr Gln Phe Pro Leu Thr
1 5

<210> SEQ ID NO 321
<211> LENGTH: 369
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 321

caggtgcagt tggagcaatc tggggctgag gtgaagaagc ctgggacctc agtgaggatc 60

tcctgcaagg cttctggcga catcttcacc ggctactata tgaactgggt gcgccaggcc 120

cctggacaag ggcttgagtg gatgggatgg atcaatacta acagtggtgg cacatacttt 180

tcacagagat ttcagggcag ggtcaccctg accagggaca cgtccatcag aacagcctac 240

atggagttga gcaggctgag atctgacgac acggccgttt attactgtgc gagaatgttt 300

tacgatattt tgactggttc tgatgttttt gatatttggg gccaagggac aatggtcacc 360

gtctcttca 369

<210> SEQ ID NO 322
<211> LENGTH: 123
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 322

Gln Val Gln Leu Glu Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Thr
1 5 10 15

Ser Val Arg Ile Ser Cys Lys Ala Ser Gly Asp Ile Phe Thr Gly Tyr
20 25 30

Tyr Met Asn Trp Val Arg Gln Ala Pro Gly Gln Gly Leu Glu Trp Met
35 40 45

Gly Trp Ile Asn Thr Asn Ser Gly Gly Thr Tyr Phe Ser Gln Arg Phe
50 55 60

Gln Gly Arg Val Thr Leu Thr Arg Asp Thr Ser Ile Arg Thr Ala Tyr
65 70 75 80

Met Glu Leu Ser Arg Leu Arg Ser Asp Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Met Phe Tyr Asp Ile Leu Thr Gly Ser Asp Val Phe Asp Ile
100 105 110

Trp Gly Gln Gly Thr Met Val Thr Val Ser Ser
115 120

<210> SEQ ID NO 323
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 323

ggcgacatct tcaccggcta ctat 24

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<210> SEQ ID NO 324
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 324

Gly Asp Ile Phe Thr Gly Tyr Tyr
1 5

<210> SEQ ID NO 325
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 325

atcaatacta acagtggtgg caca 24

<210> SEQ ID NO 326
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 326

Ile Asn Thr Asn Ser Gly Gly Thr
1 5

<210> SEQ ID NO 327
<211> LENGTH: 48
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 327

gcgagaatgt tttacgatat tttgactggt tctgatgttt ttgatatt 48

<210> SEQ ID NO 328
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 328

Ala Arg Met Phe Tyr Asp Ile Leu Thr Gly Ser Asp Val Phe Asp Ile
1 5 10 15

<210> SEQ ID NO 329
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 329

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgttggaga cagagtcacc 60

atcacttgcc gggcaagtca ggacataaga aatgatttag gctggtatca ccagaaacca 120

gggaaagccc ctaagtgcct gatctatggt gcatccagtt tgcaaagtgg ggtcccatct 180

aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagcag cctgcagcct 240

gaagattttg caacttatta ctgtctacaa cataaaaatt acatgtacac ttttggccag 300

gggaccaagt tggagatcaa a 321

<210> SEQ ID NO 330
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 330

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Arg Asn Asp
20 25 30

Leu Gly Trp Tyr His Gln Lys Pro Gly Lys Ala Pro Lys Cys Leu Ile
35 40 45

Tyr Gly Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Leu Gln His Lys Asn Tyr Met Tyr
85 90 95

Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
100 105

<210> SEQ ID NO 331
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 331

caggacataa gaaatgat 18

<210> SEQ ID NO 332
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 332

Gln Asp Ile Arg Asn Asp
1 5

<210> SEQ ID NO 333
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 333

ggtgcatcc 9

<210> SEQ ID NO 334
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 334

Gly Ala Ser
 1

<210> SEQ ID NO 335
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 335

ctacaacata aaaattacat gtacact 27

<210> SEQ ID NO 336
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 336

Leu Gln His Lys Asn Tyr Met Tyr Thr
 1 5

<210> SEQ ID NO 337
<211> LENGTH: 384
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 337

gaggtgcagc tggtggagtc tgggggaggc ttggtacagc ctggagggtc cctgagactc 60

tcctgtgcag cctctggatt caccatcagt aattatgaaa tgaactgggt ccgtcaggct 120

ccagggaagg ggctggagtg ggtttcatac attagtacta gtggtattac catatactac 180

gcagactctg tgcagggccg attcaccatc tccagagaca atgccaagaa ctcactgtat 240

ctgcaattga acagcctgag agccgaggac acggctgttt attactgtgc gcggggatat 300

tgtacaaatg gtgtatgcta tccccattac tactactccg atatggacgt ctggggccaa 360

gggaccacgg tcaccgtctc ctca 384

<210> SEQ ID NO 338
<211> LENGTH: 128
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 338

Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Ile Ser Asn Tyr
 20 25 30

Glu Met Asn Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Tyr Ile Ser Thr Ser Gly Ile Thr Ile Tyr Tyr Ala Asp Ser Val
 50 55 60

Gln Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Tyr

-continued

65 70 75 80

Leu Gln Leu Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Gly Tyr Cys Thr Asn Gly Val Cys Tyr Pro His Tyr Tyr Tyr
100 105 110

Ser Asp Met Asp Val Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser
115 120 125

<210> SEQ ID NO 339
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 339

ggattcacca tcagtaatta tgaa 24

<210> SEQ ID NO 340
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 340

Gly Phe Thr Ile Ser Asn Tyr Glu
1 5

<210> SEQ ID NO 341
<211> LENGTH: 24
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 341

attagtacta gtggtattac cata 24

<210> SEQ ID NO 342
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 342

Ile Ser Thr Ser Gly Ile Thr Ile
1 5

<210> SEQ ID NO 343
<211> LENGTH: 63
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 343

gcgcggggat attgtacaaa tggtgtatgc tatccccatt actactactc cgatatggac 60

gtc 63

<210> SEQ ID NO 344
<211> LENGTH: 21
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 344

Ala Arg Gly Tyr Cys Thr Asn Gly Val Cys Tyr Pro His Tyr Tyr Tyr
 1   5   10   15

Ser Asp Met Asp Val
            20

<210> SEQ ID NO 345
<211> LENGTH: 321
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 345

gacatccaga tgacccagtc tccatcctcc ctgtctgcat ctgtaggaga cagactcacc   60

atcacttgcc gggcaagtca gaccattagc acctatttaa attggtttca gcagaaagta   120

gggaatgccc ctaaactcct gatctattct acatccagtt tgcaaagtgg ggtcccagca   180

aggttcagtg gcagtggatc tgggacagat ttcactctca ccatcagcag tctgcaacct   240

gaagattttg caacttacta ctgtcaacag agttacagta gtcctccgac gttcggccaa   300

gggaccaagg tggaaatcaa a   321

<210> SEQ ID NO 346
<211> LENGTH: 107
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 346

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1   5   10   15

Asp Arg Leu Thr Ile Thr Cys Arg Ala Ser Gln Thr Ile Ser Thr Tyr
            20   25   30

Leu Asn Trp Phe Gln Gln Lys Val Gly Asn Ala Pro Lys Leu Leu Ile
        35   40   45

Tyr Ser Thr Ser Ser Leu Gln Ser Gly Val Pro Ala Arg Phe Ser Gly
    50   55   60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65   70   75   80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Tyr Ser Ser Pro Pro
                85   90   95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
            100   105

<210> SEQ ID NO 347
<211> LENGTH: 18
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 347

cagaccatta gcacctat   18

<210> SEQ ID NO 348

-continued

<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 348

Gln Thr Ile Ser Thr Tyr
1 5

<210> SEQ ID NO 349
<211> LENGTH: 9
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 349

tctacatcc 9

<210> SEQ ID NO 350
<211> LENGTH: 3
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 350

Ser Thr Ser
1

<210> SEQ ID NO 351
<211> LENGTH: 27
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 351

caacagagtt acagtagtcc tccgacg 27

<210> SEQ ID NO 352
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 352

Gln Gln Ser Tyr Ser Ser Pro Pro Thr
1 5

<210> SEQ ID NO 353
<211> LENGTH: 560
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 353

Met His Arg Pro Arg Arg Arg Gly Thr Arg Pro Pro Pro Leu Ala Leu
1 5 10 15

Leu Ala Ala Leu Leu Leu Ala Ala Arg Gly Ala Asp Ala Asn Ile Thr
20 25 30

Glu Glu Phe Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu
35 40 45

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```
Ser Ala Leu Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu
    50                  55                  60

Ser Asn Ile Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys
65                  70                  75                  80

Leu Ile Asn Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu
                85                  90                  95

Gln Leu Leu Met Gln Ser Thr Thr Ala Ala Asn Asn Arg Ala Arg Arg
            100                 105                 110

Glu Leu Pro Arg Phe Met Asn Tyr Thr Leu Asn Asn Thr Lys Lys Thr
        115                 120                 125

Asn Val Thr Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu
    130                 135                 140

Leu Gly Val Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val
145                 150                 155                 160

Leu His Leu Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser
                165                 170                 175

Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr
            180                 185                 190

Ser Lys Val Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro
        195                 200                 205

Ile Val Asn Lys Gln Ser Cys Arg Ile Ser Asn Ile Glu Thr Val Ile
    210                 215                 220

Glu Phe Gln Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe
225                 230                 235                 240

Ser Val Asn Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr
                245                 250                 255

Asn Ser Glu Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp
            260                 265                 270

Gln Lys Lys Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser
        275                 280                 285

Tyr Ser Ile Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val
    290                 295                 300

Gln Leu Pro Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His
305                 310                 315                 320

Thr Ser Pro Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys
                325                 330                 335

Leu Thr Arg Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val
            340                 345                 350

Ser Phe Phe Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val
        355                 360                 365

Phe Cys Asp Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu
    370                 375                 380

Cys Asn Val Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr
385                 390                 395                 400

Ser Lys Thr Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile
                405                 410                 415

Val Ser Cys Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg
            420                 425                 430

Gly Ile Ile Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys
        435                 440                 445

Gly Val Asp Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys
    450                 455                 460
```

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```
Gln Glu Gly Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe
465                 470                 475                 480

Tyr Asp Pro Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser
                485                 490                 495

Gln Val Asn Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser
            500                 505                 510

Asp Glu Leu Leu His His Val Asn Ala Gly Lys Ser Thr Thr Asn Ile
        515                 520                 525

Met Ile Thr Thr Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu Gly Gly
    530                 535                 540

Glu Gln Lys Leu Ile Ser Glu Glu Asp Leu His His His His His His
545                 550                 555                 560


<210> SEQ ID NO 354
<211> LENGTH: 574
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 354

Met Glu Leu Pro Ile Leu Lys Ala Asn Ala Ile Thr Thr Ile Leu Ala
 1               5                  10                  15

Ala Val Thr Phe Cys Phe Ala Ser Ser Gln Asn Ile Thr Glu Glu Phe
            20                  25                  30

Tyr Gln Ser Thr Cys Ser Ala Val Ser Lys Gly Tyr Leu Ser Ala Leu
        35                  40                  45

Arg Thr Gly Trp Tyr Thr Ser Val Ile Thr Ile Glu Leu Ser Asn Ile
    50                  55                  60

Lys Glu Asn Lys Cys Asn Gly Thr Asp Ala Lys Val Lys Leu Ile Asn
65                  70                  75                  80

Gln Glu Leu Asp Lys Tyr Lys Asn Ala Val Thr Glu Leu Gln Leu Leu
                85                  90                  95

Met Gln Ser Thr Thr Ala Ala Asn Asn Arg Ala Arg Arg Glu Leu Pro
            100                 105                 110

Arg Phe Met Asn Tyr Thr Leu Asn Asn Thr Lys Lys Thr Asn Val Thr
        115                 120                 125

Leu Ser Lys Lys Arg Lys Arg Arg Phe Leu Gly Phe Leu Leu Gly Val
    130                 135                 140

Gly Ser Ala Ile Ala Ser Gly Ile Ala Val Ser Lys Val Leu His Leu
145                 150                 155                 160

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu Leu Ser Thr Asn Lys
                165                 170                 175

Ala Val Val Ser Leu Ser Asn Gly Val Ser Val Leu Thr Ser Lys Val
            180                 185                 190

Leu Asp Leu Lys Asn Tyr Ile Asp Lys Gln Leu Leu Pro Ile Val Asn
        195                 200                 205

Lys Gln Ser Cys Arg Ile Ser Asn Ile Glu Thr Val Ile Glu Phe Gln
    210                 215                 220

Gln Lys Asn Asn Arg Leu Leu Glu Ile Thr Arg Glu Phe Ser Val Asn
225                 230                 235                 240

Ala Gly Val Thr Thr Pro Val Ser Thr Tyr Met Leu Thr Asn Ser Glu
                245                 250                 255

Leu Leu Ser Leu Ile Asn Asp Met Pro Ile Thr Asn Asp Gln Lys Lys
            260                 265                 270
```

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```
Leu Met Ser Asn Asn Val Gln Ile Val Arg Gln Gln Ser Tyr Ser Ile
        275                 280                 285

Met Ser Ile Ile Lys Glu Glu Val Leu Ala Tyr Val Val Gln Leu Pro
    290                 295                 300

Leu Tyr Gly Val Ile Asp Thr Pro Cys Trp Lys Leu His Thr Ser Pro
305                 310                 315                 320

Leu Cys Thr Thr Asn Thr Lys Glu Gly Ser Asn Ile Cys Leu Thr Arg
                325                 330                 335

Thr Asp Arg Gly Trp Tyr Cys Asp Asn Ala Gly Ser Val Ser Phe Phe
            340                 345                 350

Pro Gln Ala Glu Thr Cys Lys Val Gln Ser Asn Arg Val Phe Cys Asp
        355                 360                 365

Thr Met Asn Ser Leu Thr Leu Pro Ser Glu Val Asn Leu Cys Asn Val
    370                 375                 380

Asp Ile Phe Asn Pro Lys Tyr Asp Cys Lys Ile Met Thr Ser Lys Thr
385                 390                 395                 400

Asp Val Ser Ser Ser Val Ile Thr Ser Leu Gly Ala Ile Val Ser Cys
                405                 410                 415

Tyr Gly Lys Thr Lys Cys Thr Ala Ser Asn Lys Asn Arg Gly Ile Ile
            420                 425                 430

Lys Thr Phe Ser Asn Gly Cys Asp Tyr Val Ser Asn Lys Gly Val Asp
        435                 440                 445

Thr Val Ser Val Gly Asn Thr Leu Tyr Tyr Val Asn Lys Gln Glu Gly
    450                 455                 460

Lys Ser Leu Tyr Val Lys Gly Glu Pro Ile Ile Asn Phe Tyr Asp Pro
465                 470                 475                 480

Leu Val Phe Pro Ser Asp Glu Phe Asp Ala Ser Ile Ser Gln Val Asn
                485                 490                 495

Glu Lys Ile Asn Gln Ser Leu Ala Phe Ile Arg Lys Ser Asp Glu Leu
            500                 505                 510

Leu His His Val Asn Ala Gly Lys Ser Thr Thr Asn Ile Met Ile Thr
        515                 520                 525

Thr Ile Ile Ile Val Ile Ile Val Ile Leu Leu Ser Leu Ile Ala Val
    530                 535                 540

Gly Leu Leu Leu Tyr Cys Lys Ala Arg Ser Thr Pro Val Thr Leu Ser
545                 550                 555                 560

Lys Asp Gln Leu Ser Gly Ile Asn Asn Ile Ala Phe Ser Asn
                565                 570


<210> SEQ ID NO 355
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 355

Glu Gly Glu Val Asn Lys Ile Lys Ser Ala Leu
 1               5                  10


<210> SEQ ID NO 356
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 356
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Leu Ser Thr Asn Lys Ala Val Val Ser Leu Ser Asn Gly Val Ser Val
1 5 10 15

Leu

<210> SEQ ID NO 357
<211> LENGTH: 454
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
AM22 HC

<400> SEQUENCE: 357

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Lys Pro Gly Ala
1 5 10 15

Thr Val Lys Val Ser Cys Lys Ile Ser Gly His Thr Leu Ile Lys Leu
20 25 30

Ser Ile His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Met
35 40 45

Gly Gly Tyr Glu Gly Glu Val Asp Glu Ile Phe Tyr Ala Gln Lys Phe
50 55 60

Gln His Arg Leu Thr Val Ile Ala Asp Thr Ala Thr Asp Thr Val Tyr
65 70 75 80

Met Glu Leu Gly Arg Leu Thr Ser Asp Asp Thr Ala Val Tyr Phe Cys
85 90 95

Gly Thr Leu Gly Val Thr Val Thr Glu Ala Gly Leu Gly Ile Asp Asp
100 105 110

Tyr Trp Gly Gln Gly Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys
115 120 125

Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly
130 135 140

Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro
145 150 155 160

Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr
165 170 175

Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val
180 185 190

Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn
195 200 205

Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro
210 215 220

Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu
225 230 235 240

Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp
245 250 255

Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp
260 265 270

Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly
275 280 285

Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn
290 295 300

Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp
305 310 315 320

Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro
325 330 335

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```
Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu
            340                 345                 350

Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn
        355                 360                 365

Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile
    370                 375                 380

Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr
385                 390                 395                 400

Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys
                405                 410                 415

Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys
            420                 425                 430

Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu
        435                 440                 445

Ser Leu Ser Pro Gly Lys
    450


<210> SEQ ID NO 358
<211> LENGTH: 215
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
      AM22 LC

<400> SEQUENCE: 358

Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
 1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ile Val Ser Arg Asn
            20                  25                  30

His Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
        35                  40                  45

Ile Phe Gly Ala Ser Ser Arg Ala Thr Gly Ile Pro Val Arg Phe Ser
    50                  55                  60

Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Asn Gly Leu Ala
65                  70                  75                  80

Pro Glu Asp Phe Ala Val Tyr Tyr Cys Leu Ser Ser Asp Ser Ser Ile
                85                  90                  95

Phe Thr Phe Gly Pro Gly Thr Lys Val Asp Phe Lys Arg Thr Val Ala
            100                 105                 110

Ala Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser
        115                 120                 125

Gly Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu
    130                 135                 140

Ala Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser
145                 150                 155                 160

Gln Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu
                165                 170                 175

Ser Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val
            180                 185                 190

Tyr Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys
        195                 200                 205

Ser Phe Asn Arg Gly Glu Cys
    210                 215
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<210> SEQ ID NO 359
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
Motavizumab HC

<400> SEQUENCE: 359

Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
1 5 10 15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ala
20 25 30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
35 40 45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys His Tyr Asn Pro Ser
50 55 60

Leu Lys Asp Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65 70 75 80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
85 90 95

Cys Ala Arg Asp Met Ile Phe Asn Phe Tyr Phe Asp Val Trp Gly Gln
100 105 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
115 120 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
130 135 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145 150 155 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
165 170 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
180 185 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
195 200 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
210 215 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225 230 235 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
245 250 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
260 265 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
275 280 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
290 295 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305 310 315 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
325 330 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
340 345 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
355 360 365

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Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
                405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 360
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
      Motavizumab LC

<400> SEQUENCE: 360

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Ser Ala Ser Ser Arg Val Gly Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 361
<211> LENGTH: 450
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
      Palivizumab HC
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<400> SEQUENCE: 361

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Gln Val Thr Leu Arg Glu Ser Gly Pro Ala Leu Val Lys Pro Thr Gln
 1               5                  10                  15

Thr Leu Thr Leu Thr Cys Thr Phe Ser Gly Phe Ser Leu Ser Thr Ser
            20                  25                  30

Gly Met Ser Val Gly Trp Ile Arg Gln Pro Pro Gly Lys Ala Leu Glu
        35                  40                  45

Trp Leu Ala Asp Ile Trp Trp Asp Asp Lys Lys Asp Tyr Asn Pro Ser
    50                  55                  60

Leu Lys Ser Arg Leu Thr Ile Ser Lys Asp Thr Ser Lys Asn Gln Val
65                  70                  75                  80

Val Leu Lys Val Thr Asn Met Asp Pro Ala Asp Thr Ala Thr Tyr Tyr
                85                  90                  95

Cys Ala Arg Ser Met Ile Thr Asn Trp Tyr Phe Asp Val Trp Gly Ala
            100                 105                 110

Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val
        115                 120                 125

Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala
    130                 135                 140

Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser
145                 150                 155                 160

Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val
                165                 170                 175

Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro
            180                 185                 190

Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys
        195                 200                 205

Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp
    210                 215                 220

Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly
225                 230                 235                 240

Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile
                245                 250                 255

Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu
            260                 265                 270

Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His
        275                 280                 285

Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg
    290                 295                 300

Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys
305                 310                 315                 320

Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu
                325                 330                 335

Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr
            340                 345                 350

Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu
        355                 360                 365

Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp
    370                 375                 380

Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val
385                 390                 395                 400

Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp
```

-continued

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               405                 410                 415

Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His
            420                 425                 430

Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro
        435                 440                 445

Gly Lys
    450


<210> SEQ ID NO 362
<211> LENGTH: 213
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic
      Palivizumab LC

<400> SEQUENCE: 362

Asp Ile Gln Met Thr Gln Ser Pro Ser Thr Leu Ser Ala Ser Val Gly
 1               5                  10                  15

Asp Arg Val Thr Ile Thr Cys Lys Cys Gln Leu Ser Val Gly Tyr Met
            20                  25                  30

His Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr
        35                  40                  45

Asp Thr Ser Lys Leu Ala Ser Gly Val Pro Ser Arg Phe Ser Gly Ser
    50                  55                  60

Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro Asp
65                  70                  75                  80

Asp Phe Ala Thr Tyr Tyr Cys Phe Gln Gly Ser Gly Tyr Pro Phe Thr
                85                  90                  95

Phe Gly Gly Gly Thr Lys Leu Glu Ile Lys Arg Thr Val Ala Ala Pro
            100                 105                 110

Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr
        115                 120                 125

Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys
    130                 135                 140

Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu
145                 150                 155                 160

Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser
                165                 170                 175

Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala
            180                 185                 190

Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe
        195                 200                 205

Asn Arg Gly Glu Cys
    210


<210> SEQ ID NO 363
<211> LENGTH: 453
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 363

Glu Val Gln Leu Val Glu Ser Gly Gly Asp Leu Val Gln Pro Gly Arg
 1               5                  10                  15

Ser Leu Arg Leu Ser Cys Val Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
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-continued

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Ala Met His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45

Ser Gly Val Ser Trp Ser Gly Ser Thr Val Gly Tyr Ala Asp Ser Val
    50                  55                  60

Lys Gly Arg Phe Thr Val Ser Arg Asp Asn Ala Gln Lys Ser Leu Tyr
65                  70                  75                  80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95

Val Lys Asp Ala Tyr Lys Phe Asn Tyr Tyr Tyr Tyr Gly Leu Asp Val
            100                 105                 110

Trp Gly Gln Gly Thr Thr Val Thr Val Ser Ser Ala Ser Thr Lys Gly
        115                 120                 125

Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly
    130                 135                 140

Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val
145                 150                 155                 160

Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe
                165                 170                 175

Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val
            180                 185                 190

Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val
        195                 200                 205

Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys
    210                 215                 220

Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu
225                 230                 235                 240

Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr
                245                 250                 255

Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val
            260                 265                 270

Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val
        275                 280                 285

Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser
    290                 295                 300

Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu
305                 310                 315                 320

Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala
                325                 330                 335

Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro
            340                 345                 350

Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln
        355                 360                 365

Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala
    370                 375                 380

Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr
385                 390                 395                 400

Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu
                405                 410                 415

Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser
            420                 425                 430

Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser
        435                 440                 445
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Leu Ser Pro Gly Lys
    450


<210> SEQ ID NO 364
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Synthetic

<400> SEQUENCE: 364

Glu Ile Val Met Thr Gln Ser Pro Ala Thr Leu Ser Val Ser Pro Gly
 1               5                  10                  15

Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Thr Ile Leu Ser Asn
            20                  25                  30

Leu Ala Trp Tyr Leu Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu Ile
        35                  40                  45

Tyr Gly Ala Ser Thr Arg Ala Thr Gly Leu Pro Ala Arg Phe Ser Gly
    50                  55                  60

Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
65                  70                  75                  80

Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Tyr Asn Asn Trp Pro Leu
                85                  90                  95

Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
            100                 105                 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
        115                 120                 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
    130                 135                 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145                 150                 155                 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
                165                 170                 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
            180                 185                 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
        195                 200                 205

Phe Asn Arg Gly Glu Cys
    210
```

What is claimed is:

1. An isolated human antibody or antigen-binding fragment thereof that binds specifically to RSV-F, wherein the antibody or antigen-binding fragment comprises three heavy chain complementarity determining regions (CDRs) (HCDR1, HCDR2 and HCDR3) contained within any one of the heavy chain variable region (HCVR) amino acid sequences selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338; and comprises three light chain CDRs (LCDR1, LCDR2 and LCDR3) contained within any one of the light chain variable region (LCVR) amino acid sequences selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

2. The isolated human antibody or antigen-binding fragment of claim **1**, comprising:

(a) a HCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 4, 20, 36, 52, 68, 84, 100, 116, 132, 148, 164, 180, 196, 212, 228, 244, 260, 276, 292, 308, 324 and 340;

(b) a HCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 6, 22, 38, 54, 70, 86, 102, 118, 134, 150, 166, 182, 198, 214, 230, 246, 262, 278, 294, 310, 326 and 342;

(c) a HCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 24, 40, 56, 72, 88, 104, 120, 136, 152, 168, 184, 200, 216, 232, 248, 264, 280, 296, 312, 328, and 344;

(d) a LCDR1 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 12, 28, 44, 60, 76, 92, 108, 124, 140, 156, 172, 188, 204, 220, 236, 252, 268, 284, 300, 316, 332 and 348;

(e) a LCDR2 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 14, 30, 46, 62, 78, 94, 110, 126, 142, 158, 174, 190, 206, 222, 238, 254, 270, 286, 302, 318, 334 and 350; and

(f) a LCDR3 domain having an amino acid sequence selected from the group consisting of SEQ ID NOs: 16,

32, 48, 64, 80, 96, 112, 128, 144, 160, 176, 192, 208, 224, 240, 256, 272, 288, 304, 320, 336 and 352.

3. An isolated antibody or antigen-binding fragment thereof that competes for specific binding to RSV-F with an antibody or antigen-binding fragment comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, wherein the antibody that competes for specific binding to RSV-F interacts with an epitope comprising an amino acid sequence ranging from about position 161 to about position 188 of SEQ ID NO:354, or interacts with the serine at position 173 of SEQ ID NO: 354, and/or the threonine at position 174 of SEQ ID NO: 354.

4. An isolated antibody or antigen-binding fragment thereof that binds the same epitope on RSV-F that is recognized by an antibody comprising heavy and light chain sequence pairs selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346, wherein the epitope comprises an amino acid sequence ranging from about position 161 to about position 188 of SEQ ID NO:354.

5. The isolated antibody of claim **1**, wherein the antibody does not cross-compete for binding to RSV-F with palivizumab, or AM-22.

6. The isolated human antibody of claim **1**, wherein the antibody does not bind to an epitope on RSV-F ranging from amino acid residue 255 to amino acid residue 276 of SEQ ID NO: 354.

7. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody is a human recombinant monoclonal antibody.

8. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding fragment thereof interacts with an amino acid sequence comprising amino acid residues ranging from about position 161 to about position 188 of SEQ ID NO: 354.

9. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding fragment thereof interacts with either the serine at position 173 of SEQ ID NO: 354, or the threonine at position 174 of SEQ ID NO: 354, or both the serine at position 173 of SEQ ID NO: 354 and the threonine at position 174 of SEQ ID NO: 354.

10. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding fragment comprises a heavy chain variable region (HCVR) amino acid sequence selected from the group consisting of SEQ ID NO: 2, 18, 34, 50, 66, 82, 98, 114, 130, 146, 162, 178, 194, 210, 226, 242, 258, 274, 290, 306, 322 and 338.

11. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding fragment comprises a light chain variable region (LCVR) amino acid sequence selected from the group consisting of SEQ ID NOs: 10, 26, 42, 58, 74, 90, 106, 122, 138, 154, 170, 186, 202, 218, 234, 250, 266, 282, 298, 314, 330 and 346.

12. The isolated antibody or antigen-binding fragment of claim **1**, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 2/10, 18/26, 34/42, 50/58, 66/74, 82/90, 98/106, 114/122, 130/138, 146/154, 162/170, 178/186, 194/202, 210/218, 226/234, 242/250, 258/266, 274/282, 290/298, 306/314, 322/330 and 338/346.

13. The isolated antibody or antigen-binding fragment of claim **12**, comprising a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NOs: 274/282 and 338/346.

14. The isolated antibody or antigen-binding fragment of claim **13**, comprising the HCVR/LCVR amino acid sequence pair of SEQ ID NOs: 274/282.

15. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates the ability to significantly reduce the lung viral load in a mouse model of RSV infection when administered at a dose ranging from about 0.05 mg/kg to about 0.15 mg/kg.

16. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates a 1-2 logs greater reduction of nasal and/or lung viral titers as compared to palivizumab in a cotton rat model of RSV infection when administered at a dose ranging from about 0.62 mg/kg to about 5.0 mg/kg.

17. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 0.15 mg/kg or less when administered in a mouse model of RSV subtype A infection.

18. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 0.62 mg/kg or less when administered in a cotton rat model of RSV subtype A infection.

19. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} of about 2.5 mg/kg or less when administered in a cotton rat model of RSV subtype B infection.

20. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates an ED_{99} that is about 2 to 3 fold lower than the ED_{99} for palivizumab or motavizumab.

21. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype A laboratory strains of RSV that is about a 15 to 17 fold improvement over palivizumab, or demonstrates a neutralization potency against one or more subtype A clinical strains of RSV that is about 10 to 22 fold improvement over palivizumab.

22. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2 to 5 fold improvement over palivizumab.

23. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype A laboratory strains or subtype A clinical strains of RSV that is about a 0.5 to 2 fold improvement over AM-22.

24. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or the antigen-binding fragment thereof demonstrates a neutralization potency against one or more subtype B laboratory strains of RSV that is about a 2.5 to 17 fold improvement over AM-22.

25. The isolated antibody or an antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding

fragment thereof binds specifically to RSV-F with a K_D ranging from 1.0×10^{-7}M to 6.0×10^{-10} M, as measured by surface plasmon resonance.

26. The isolated antibody or antigen-binding fragment thereof of claim **1**, wherein the antibody or antigen-binding fragment thereof has one or more of the following characteristics:

(a) is capable of neutralizing respiratory syncytial virus subtype A and subtype B strains in vitro;

(b) demonstrates the ability to significantly reduce the nasal and/or lung viral load in vivo in an animal model of RSV infection;

(c) interacts with at least one amino acid residue within SEQ ID NO: 355 or 356; or

(d) inhibits fusion of the virus to the cell.

27. An isolated nucleic acid molecule encoding an antibody or antigen-binding fragment of claim **1**.

28. An expression vector comprising the nucleic acid molecule of claim **27**.

29. A host cell comprising the expression vector of claim **28**.

30. A method for preventing or treating a respiratory syncytial virus (RSV) infection, or at least one symptom associated with the RSV infection, the method comprising administering an antibody or antigen-binding fragment of claim **1**, or a composition comprising an antibody or antigen-binding fragment of claim **1**, to a patient in need thereof, such that the RSV infection is prevented, or at least one symptom associated with the infection is alleviated or reduced in number or severity.

31. The method of claim **30**, wherein the administering results in prevention of recurrent wheezing in the patient.

32. The method of claim **30**, wherein the administering results in prevention of RSV-associated asthma in a child.

33. The method of claim **30**, wherein the RSV infection is caused by a subtype A or a subtype B respiratory syncytial virus.

34. The method of claim **30**, wherein the patient in need thereof is a patient at high risk of acquiring an RSV infection, or a patient who may experience a more severe form of the RSV infection due to an underlying or pre-existing medical condition.

35. The method of claim **34**, wherein the patient is a pre-term infant, a full term infant, a child greater than or equal to one year of age with or without an underlying medical condition (e.g. congenital heart disease, chronic lung disease, cystic fibrosis, immunodeficiency, a neuromuscular disorder), an institutionalized or hospitalized patient, or an elderly adult (greater than 65 years of age) with or without an underlying medical condition such as congestive heart failure or chronic obstructive pulmonary disease).

36. The method of claim **34**, wherein the patient suffers from a condition resulting from a compromised pulmonary, cardiovascular, neuromuscular, or immune system.

37. The method of claim **36**, wherein the condition is selected from the group consisting of an abnormality of the airway, a chronic lung disease, a chronic heart disease, a neuromuscular disease that compromises the handling of respiratory secretions and immunosuppression.

38. The method of claim **37**, wherein the chronic lung disease is chronic obstructive pulmonary disease (COPD), cystic fibrosis, or bronchopulmonary dysplasia.

39. The method of claim **37**, wherein the chronic heart disease is congestive heart failure (CHF), or congenital heart disease.

40. The method of claim **37**, wherein the immunosuppression is a result of severe combined immunodeficiency or severe acquired immunodeficiency, or is a result of any other infectious disease or cancerous condition that leads to immunosuppression, or is a result of treatment with immunosuppressant drug therapy or radiation therapy.

41. The method of claim **30**, wherein the at least one symptom is selected from the group consisting of fever, nasal congestion, cough, decreased appetite, hypoxia, breathing difficulties (rapid breathing or shortness of breath), wheezing, apnea, dehydration, poor feeding and altered mental status.

42. The method of claim **30**, wherein the patient in need thereof is administered the antibody or antigen-binding fragment thereof prophylactically, or therapeutically.

43. The method of claim **30**, wherein the antibody or antigen-binding fragment thereof is administered via a route selected from the group consisting of intravenously, intramuscularly, and subcutaneously.

44. The method of claim **30**, wherein the antibody or antigen-binding fragment is administered to the patient in combination with a second therapeutic agent.

45. The method of claim **44**, wherein the second therapeutic agent is selected from the group consisting of an antiviral agent; a vaccine specific for RSV, a vaccine specific for influenza virus, or a vaccine specific for metapneumovirus (MPV); an siRNA specific for an RSV antigen or a metapneumovirus (MPV) antigen; a second antibody specific for an RSV antigen or a metapneumovirus (MPV) antigen; an anti-IL4R antibody, an antibody specific for an influenza virus antigen, an anti-RSV-G antibody and a NSAID.

46. A pharmaceutical composition comprising any one or more of the isolated antibodies or antigen binding fragments thereof of claim **1** and a pharmaceutically acceptable carrier.

* * * * *

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