Antibody Drug Nomenclature:

What is INN a Name?

WHO Has Been Changing Them?

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-umab
-zumab
-ximab
-omab

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Antibody Drug Nomenclature – Presentation Overview

- Introduction to International Nonproprietary Names (INNs) for antibodies including common origin substems: -ximab, -zumab and –umab
- Changes to INN definitions made by WHO: why, what and consequences?
- New INN antibody naming system was well intentioned but has major limitations
- Why is developing a new naming system so difficult?
- Some options to consider in revising the naming system

Selected Limitations of 2014 INN Antibody Naming System
Definitions do not allow researchers to determine reliably how an antibody would be classified
Arbitrary 85% sequence identity cut-off in definitions with no clear functional significance, e.g., immunogenicity
Not consistent with scientific literature or many previous INN antibody names

The INNs and Outs of Antibody Nonproprietary Names*

Tim D. Jones[1], Paul J. Carter[2], Andreas Plückthun[3], Max Vásquez[4], Robert G.E. Holgate[1], Isidro Hötzel[2], Andrew G. Popplewell[5], Paul W. Parren[6], Markus Enzelberger[7], Rik Rademaker[6], Michael R. Clark[8], David C. Lowe[9], Bassil I. Dahiyat[10], Victoria Smith[11],John M. Lambert[12], Herren Wu[13], Mary Reilly[14], John S. Haurum[15], Stefan Dübel[16], James S. Huston[17], Thomas Schirrmann[18], Richard A. J. Janssen[19], Martin Steegmaier[20], Jane A. Gross[21], Andrew Bradbury[22], Dennis R. Burton[23], Dimiter S. Dimitrov[24], Kerry A. Chester[25], Martin J. Glennie[26], Julian Davies[27], Adam Walker[28], Steve Martin[29], John McCafferty[30] and Matthew P. Baker[1]

Panelists for IBC discussion on antibody INNs following this talk

*Jones *et al.* (2015) mAbs (in press)

International Nonproprietary Names (INNs)

- INN system begun in 1950 by the World Health Organization (WHO) to provide a unique (generic) name to identify each pharmaceutical substance

- INN system has important goals and benefits
  - Clear identification, safe prescription and dispensing of medicines to patients
  - Communication and exchange of information among health professionals and scientists worldwide

- INNs are selected by WHO on advice of an expert advisory panel
  - Application from manufacturer
  - Proposed INN selected and published for comments
  - Name designated as a recommended INN

Source: www.who.int

INNs for Monoclonal Antibodies

- "-mab" introduced as the stem for monoclonal antibodies in 1990
- Substems developed in 1997 to describe antibody origin

Common Antibody Origin	INN Substem	Representative Examples
Chimeric	-xi-	Abcixi**mab**, Rituxi**mab**, Infliximab, Cetuximab
Humanized	-zu-	Palivizu**mab**, Trastuzu**mab**, Bevacizu**mab**, Natalizu**mab**
Human	-u-	Adalimu**mab**, Panitumu**mab** Golimu**mab**, Ipilimu**mab**

- Origin substems were developed to classify antibodies based upon their "humanness" and with the assumption that this would correlate with immunogenicity in patients
- Now appreciated that immunogenicity is multi-factorial with no clear sequence threshold
- Does the antibody origin substem still serve a useful purpose?

Origin Substems for Monoclonal Antibodies – Some Key Questions

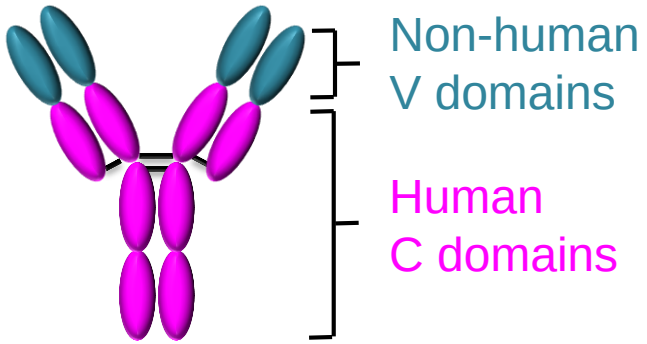
- Why revise the INN stem definitions?
- How have the stem definitions been revised?
- What are the consequences of the revised definitions?
- Why is developing a new naming system so difficult?
- What to consider in revising the naming system?

Why Change the INN Stem Definitions?

- New definitions needed as old definitions outdated by rapid progress in antibody technologies
  - More methods for humanizing antibodies
  - More technologies for discovery of human antibodies
  - Antibodies often engineered to improve their therapeutic potential
- WHO developed new definitions that are dependent on the final sequence and not how the antibody was made
- INN changes for antibodies are well intentioned but have inconsistencies, ambiguities and other unwanted consequences
- Developing new substem definitions is very challenging as antibody technologies continue to evolve

2011 WHO Definition of Chimeric Antibodies (-ximab)

"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"



Source: www.who.int International Nonproprietary Names (INN) for biological and biotechnological substances (a review)" from 2011

2014 WHO Definition of Chimeric Antibodies (-ximab)

"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" *

Comparison to human sequences should be done with IMGT DomainGapAlign tool as clarified during open session of WHO INN Expert Group (April 2015)**

American Medical Association definitions:
CDR-IMGT and sequence analysis of the variable regions showing percentage of human content: <85% -ximab (≥85% -zumab or -umab)***

Sources: * www.who.int "International Nonproprietary Names (INN) for biological and biotechnological substances (a review)" from 2014; ** www.imgt.org IMGT DomainGapAlign tool;
*** www.ama-assn.org "Monoclonal Antibody Rules" (requires free registration)

Snapshot of AMA-ASSN Document (Nov. 2015)

When naming biologics the following items are required to be submitted with your application materials:

USAN/INN Requirements for Biological Substances

All proteins and Peptides
- ✓ 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 positio
- ✓ Positions of all disulfide bridges and post-tr sequence
- ✓ Glycosylation patterns, including site, type
- ✓ For recombinant proteins: expression syste

Monoclonal Antibodies
- ✓ Complete mature amino acid sequence in a
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- ✓ Precursor nucleotide sequence with spaces lines
- ✓ CDR-IMGT and sequence analysis of the v content (if –ximab, -zumab, or -umab is req
- ✓ IG class and subclass, IG format
- ✓ Species or taxonomy related structure (chi
- ✓ Name and/or structure of targeted antigen
- ✓ List of all disulfide bridges and their locatior
- ✓ Expression system
- ✓ Clone name(s) and laboratory code name(s
- ✓ If appropriate, the closest human V, J, and IMGT/DomainGapAlign tool)

Nucleic Acids

Includes DNA vaccines, oligonucleotides, gene th
- ✓ Full nucleotide sequence with pertinent reg delineated
- ✓ For gene therapies, schematic map of the product and an annotated sequence that delineates relevant sections

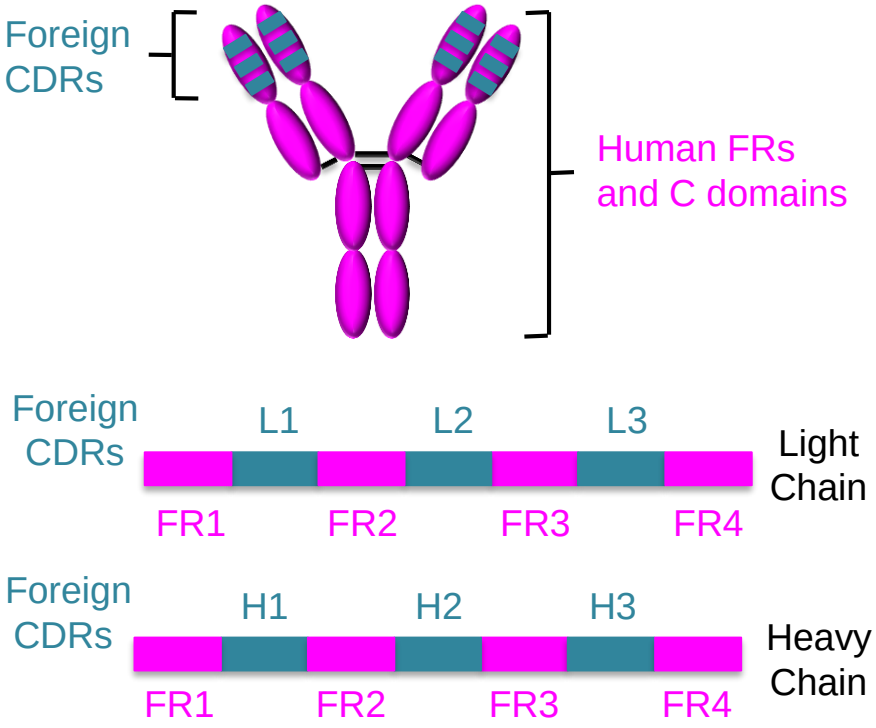
All Pegylated Substances
- ✓ Details of pegylation: end group, polymer chain with average number of repeat units to 2 significant figures, details of the linker, point of attachment of the linker to the active moiety

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)

Source: *** www.ama-assn.org "Monoclonal Antibody Rules" (requires free registration)
https://download.ama-assn.org/resources/doc/usan/x-pub/form-f-monoclonal-antibodies.docx

2011 WHO Definition of Humanized Antibodies

"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 [sic] were used for the humanization."*



Questions

Which definition of CDRs (Kabat, Chothia or IMGT)?
Are foreign FR residues allowed (required for most successful humanizations)?

Source: www.who.int International Nonproprietary Names (INN) for biological and biotechnological substances (a review)" from 2011

2014 WHO Definition of Humanized Antibodies (-zumab)

"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"*

Comparison to human sequences should be done with IMGT DomainGapAlign tool as clarified during open session of WHO INN Expert Group (April 2015)**

American Medical Association definitions:
CDR-IMGT and sequence analysis of the variable regions showing percentage of human content: <85% -ximab (≥85% -zumab or -umab)***

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How are Human Antibodies (-umab) Defined?

- Unclear as current WHO review on INN provides substem for human antibodies (-u-) but without a supporting definition*
- American Medical Association provides definition of human antibodies based on sequence identity**
- Sequence threshold for human designation was apparently reduced from 90% to ≥85% between July and Oct 2015

Sources: * www.who.int "International Nonproprietary Names (INN) for biological and biotechnological substances (a review)" from 2014;

** www.ama-assn.org "Monoclonal Antibody Rules" (requires free registration)

Most Approved Humanized Antibodies Predicted to Be "Chimeric" or "Mixed" Under 2014 INN Rules

Assigning INN names using 2014 definitions is often inconsistent with previous INN names and with decades of scientific literature

*Top "hit" from macaque

Adapted from Jones *et al.* (2015) mAbs (in press)

Approved Humanized Antibody	VH % Human Identity	VL % Human Identity	Predicted Designation Under New Rules
Pembrolizumab	79.6	85.1	Mixed
Vedolizumab	84.7	85.0*	Humanized?
Trastuzumab	81.6	86.3*	Mixed
Obinutuzumab	84.7	87.0	Humanized?
Pertuzumab	78.8	84.2*	Chimeric
Tocilizumab	84.8	89.5*	Humanized?
Certolizumab	77.6	85.3	Mixed
Natalizumab	83.7	80.9	Chimeric
Ranibizumab	75.8	87.4*	Mixed
Bevacizumab	76.8	88.4*	Mixed
Eculizumab	83.7	84.2*	Chimeric
Efalizumab	76.5	89.5*	Mixed
Omalizumab	78.6	86.9*	Mixed
Alemtuzumab	73.7	86.3	Mixed
Palivizumab	87.9	81.9	Mixed
Daclizumab	82.7	84.0	Chimeric
Idarucizumab	82.3	88.0	Mixed
Mepolizumab	73.7	91.1	Mixed
Elotuzumab	83.7	84.2	Chimeric

Approved Human Antibodies Predicted to Still Be Classified as Human Under New INN Rules

But challenges remain….

- Some antibodies from human subjects with many somatic hypermutations (e.g., anti-HIV) have <85% sequence identity and would be classified as “chimeric”
- How to classify antibodies as human or humanized as ≥85% sequence identity threshold used for both?

Approved Human Antibody	VH % Human Identity	VL % Human Identify	Current WHO INN Designation
Panitumumab*	89.9	95.8	Human
Adalimumab**	93.9	95.8	Human
Canakinumab*	93.9	98.9	Human
Raxibacumab**	99.0	100.0	Human
Ipilimumab*	94.9	97.9	Human
Belimumab**	86.7	97.9	Human
Denosumab*	98.0	95.8	Human
Nivolumab*	91.8	98.9	Human
Secukinumab*	92.9	100.0	Human
Ramucirumab**	99.0	85.3	Human
Ustekinumab*	87.8	98.9	Human
Ofatumumab*	97.0	100.0	Human
Golimumab*	94.9	98.9	Human
Alirocumab*	89.8	94.1	Human
Evolocumab*	93.9	95.9	Human
Daratumumab*	94.9	100.0	Human

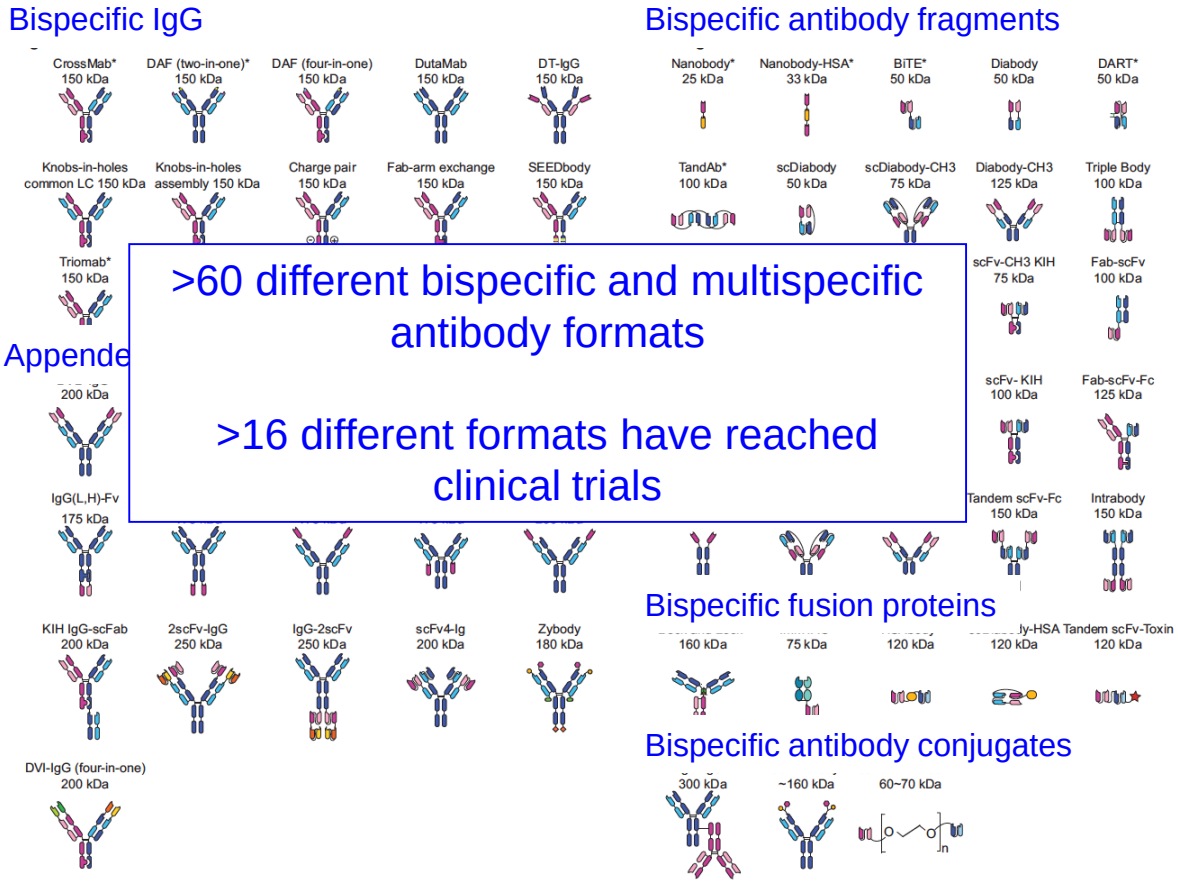
Adapted from Jones *et al.* mAbs (in press)

*from transgenic mice; **from phage display libraries

Some of the Major Limitations of the 2014 INN Antibody Naming System

- Definitions do not allow researchers to determine reliably how an antibody would be classified
- Not consistent with several decades of precedence in naming antibodies in scientific literature or many previously assigned INN names
- No definition of what makes an antibody “human” or how this differs from a “humanized” antibody
- Arbitrary 85% sequence identity threshold used that has no functional significance, e.g., immunogenicity
- Antibody J region forms a critical part of the V domain but is not included in the INN process
- Extent to which an antibody falls within the definition of human/humanized significantly impacted by the identity of the CDRs to closest human germline

Developing a New INN Antibody Naming System – Hitting a Target that is Moving and Expanding



Spiess, Zhai & Carter (2015) Molec. Immunol. **67**: 95

INN Names for Selected Bispecific Antibodies

Name	Format	Description	Comment
Blinatumomab	BiTE	2 mouse tandem scFvs	No constant regions
Solitomab	BiTE	2 mouse tandem scFvs	No constant regions
Pasotuxizumab	BiTE	1 mouse, 1 humanized tandem scFvs	No constant regions, but have -xi- for chimeric?
Vanucizumab	CrossMab	One humanized, one fully human set of Fv	Name sounds like “standard” humanized
Emicizumab	Common light chain	Two humanized sets of Fv with a common VL	

-o- substem: mouse

Options for a New INN Antibody Naming System

- Develop new substems:
  e.g., -sy- for synthetic or -e- for engineered
- Drop substems entirely:
  i.e., -mab
- Other?

Antibody INNs – Take Home Messages

- INN definitions for naming antibodies were revised by WHO in 2014 so that they are based upon identity with human V gene germline sequences
- New INN system for antibodies was well intentioned but has several major limitations including:
  - Ambiguous definitions that prevent reliable assignment
  - Arbitrary 85% sequence identify cut-off with no clear functional significance
  - Inconsistent with scientific literature or many previous INN antibody names
- Risk that antibodies with –zumab/–umab designation will be perceived as being better than –ximab based on the faulty assumption that immunogenicity can be defined by “humanness” of the sequence
- Dialog between the WHO INN Expert Group and key stakeholders is urgently needed to develop a more robust INN system for new antibody drugs

WHO Open Session with INN Stakeholders

- **When:** 12 April 2016, 9-10:30 AM at WHO in Geneva
- **Purpose:** Improve communication between INN Expert Group and the INN stakeholders; opportunity for stakeholders to present their arguments on outstanding requests or policies issue
- Deadline for sending an expression of interest (EOI) letter is 7 March 2016
- Applicants allocated time to present dependent on the number of requests
- IFPMA members encouraged to submit their EOI through their Organization

Source: www.who.int

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