International Nonproprietary Names (INN) for monoclonal antibodies (mAbs)

INN for mAbs

- INN for mAbs were introduced in 1991 (pINN List 66)
- The process for them needs to accommodate the large number of potential mAb products
- It also needs to provide some information on target, sequence, production method and immunology
- The process needs to be periodically assessed and, if needed, modified to take account of scientific/technical advances

INN for mAbs

- Recently, the process has been criticised, particularly for some modifications made to it:

‘The INN and outs of antibody nonproprietary

Names’, Jones, T.D et. al., mAbs 8:1, 1--9; January 2016;

- The Antibody society have also criticised the same aspects of the modifications

Antibody Society-petition

- The Antibody Society has organised a petition to ‘support The Antibody Society in its efforts to bring the limitations of the new definitions for the assignment of antibody international nonproprietary names (INN) to the attention of the World Health Organization’

Jones et al paper-what it says

- That INN process needs to be adapted with progress
- But the revised system is ‘critically flawed, ambiguous and contradicts scientific literature’
- That classification is inconsistent
- Criticises assumptions made concerning immunogenicity
- Omission of the sequences encoded by the J-region genes is a major flaw

Jones et al paper-what it says

- The 85% sequence threshold is arbitrary, and does not correlate with ‘improved therapeutic outcome (e.g. reduced immunogenicity)’
- There is no specific definition of what constitutes a human antibody and what differentiates it from a humanized antibody
- The (new) definitions are applied retrospectively and without any notice period

Important Point-Threshold Percentages

- Threshold percentages for sequence homologies to define INN infixes have **NOT** been published by the WHO INN Expert Group
- This is contrary to what is claimed in the Jones et. al. article

How to name mAbs in INN

- 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

International Nonproprietary Names (INN) for biological and biotechnological substances (a review) Bioreview 2014

How to name mAbs in INN

- **Substem B indicates the species on which the immunoglobulin sequence of the mAb is based:**

  ex: *-o- mouse,* *-u-* human, *-xi-* chimeric, *-zu-* humanized…

- **Substem A indicates the target (molecule, cell, organ) class:**

  ex: *-c(i)-* cardiovascular, *-k(i)-* interleukin, *-t(u)-* tumour…

International Nonproprietary Names (INN) for biological and biotechnological substances (a review) **Bioreview 2014**

How to name mAbs in INN

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.

International Nonproprietary Names (INN) for biological and biotechnological substances (a review) **Bioreview 2014**

How to name mAbs in INN

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.

International Nonproprietary Names (INN) for biological and biotechnological substances (a review) **Bioreview 2014**

How to name mAbs in INN

- **Chimeric**

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**

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

International Nonproprietary Names (INN) for biological and biotechnological substances (a review) **Bioreview 2014**

Questions raised by Jones at al., Jan 2016 (1/4)

1) "……..(IMGT)alignment score is made only against germline sequence variable region exons, thus omitting **part of CDR3 and the J-region** ……analysis of the variable domain sequence 'as a whole' should therefore include the J-region"

Response:

The INN Bioreview 2014 definition is based on the 'V region amino acid sequence … analysed as a whole' because this is the most relevant part of the molecule in terms of species comparison (alignment on about 100 residues) and the results are standardized, comparable and reproducible, using IMGT/DomainGapAlign, an international reference tool publicly available online.

To include the J-region for an analysis of the variable domain (V-(D)-J region) amino acid sequence 'as a whole' would mean that this also includes the diverse part of CDR3 between the trimmed V-region and the J-region. This is unrealistic and not useful as not only is each CDR3 unique to each B cell clone but its synthesis results from complex molecular mechanisms (combinatorial diversity, trimming, addition of N nucleotides at random and somatic hypermutations). The final outcome junction is a **unique novel** region, not encoded in any germline genome, and key to the extreme diversity of the antibody specificities and affinities.

Questions raised by Jones at al., Jan 2016 (2/4)

2) "……IMGT data base **includes macaque variable region sequences** which can give rise to the situation where alignment gives the closest match to macaque although "rat-human"…

Response:

Inclusion of macaque sequences in IMGT/DomainGapAlign is considered valuable with respect to having the maximum amount of available information.

→ achievement of "top-hit" "macaque" will indeed support the application of a human/humanized antibody provided that "top-hit" also includes Homo sapiens.

Questions raised by Jones at al., Jan 2016 (3/4)

3) Rationale for **threshold percentages**……(e.g. “85% threshold for ‘human’ is arbitrary”)

Response:

INN naming rules for mAbs (Bioreview 2014) do not contain any percentages as thresholds for the distinction between human/humanized/chimeric antibodies.

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.

Questions raised by Jones at al., Jan 2016 (4/4)

4) "…….even **antibodies from patients fail** the 85% criterion due to somatic hypermutations" (anti-HIV…influenza)…"

Response:

Again, there is no % threshold used to determine INN.

Anti-infectious agent antibodies isolated from patients, with a relatively low percentage of human identity due to somatic hypermutations (e.g., anti-HIV), are of course regarded as "human".

Future...

- The availability of extensive biochemical, biophysical and immunological data would not resolve the issue of univocally assigning an antibody to a specific category
- Sequence comparison analysis should remain the major tool used by WHO-INN to assign an antibody to a specific category

Future...

- Sequence AND conformation control antibody-antigen recognition
- Sequence and conformation of both CDRs and frameworks participate in dictating the correct conformation for binding
- Three-dimensional structure comparison could flank sequence comparison

Future...

- Availability of 3D structure of the antibody would allow the interrogation of structural data base
- Analysis of superimposed structures (r.m.s.d overall, segments, e.g. CDRs/frameworks) could complement sequence analysis
- The new recently published Annex document for the INN application indicates for “Proteins and peptides” that a PDB file, if available, should be provided

Conclusion

- **The WHO INN Expert Group is responsible for selecting INN in line with current policies and Executive Board INN Procedure**
  http://apps.who.int/gb/archive/pdf_files/EB115/B115_11-en.pdf

- **The INN Expert Group has noted the issues raised in the Jones et al. paper and by the Antibody Society and provided clarifications**

- **The INN reference for mAb is the Bioreview 2014 and % are not official INN policy** **http://www.who.int/entity/medicines/services/inn/BioRev2014.pdf?ua=1**

- **The INN Expert Group welcomes dialogue with stakeholders on mAb nomenclature and future joint meetings are envisaged**

  (WHO INN mAb "ad Hoc" meeting - September 2016; INN attendance to Antibody Society General meeting?....)