Open Session of the 62nd INN Consultation World Health Organization

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ANTIBODY SOCIETY

Request to the INN programme of the WHO

To work with key stakeholders to develop a new and broadly applicable INN system for antibody therapeutics that provides availability of distinguishing names for therapeutic antibodies in current and future development.

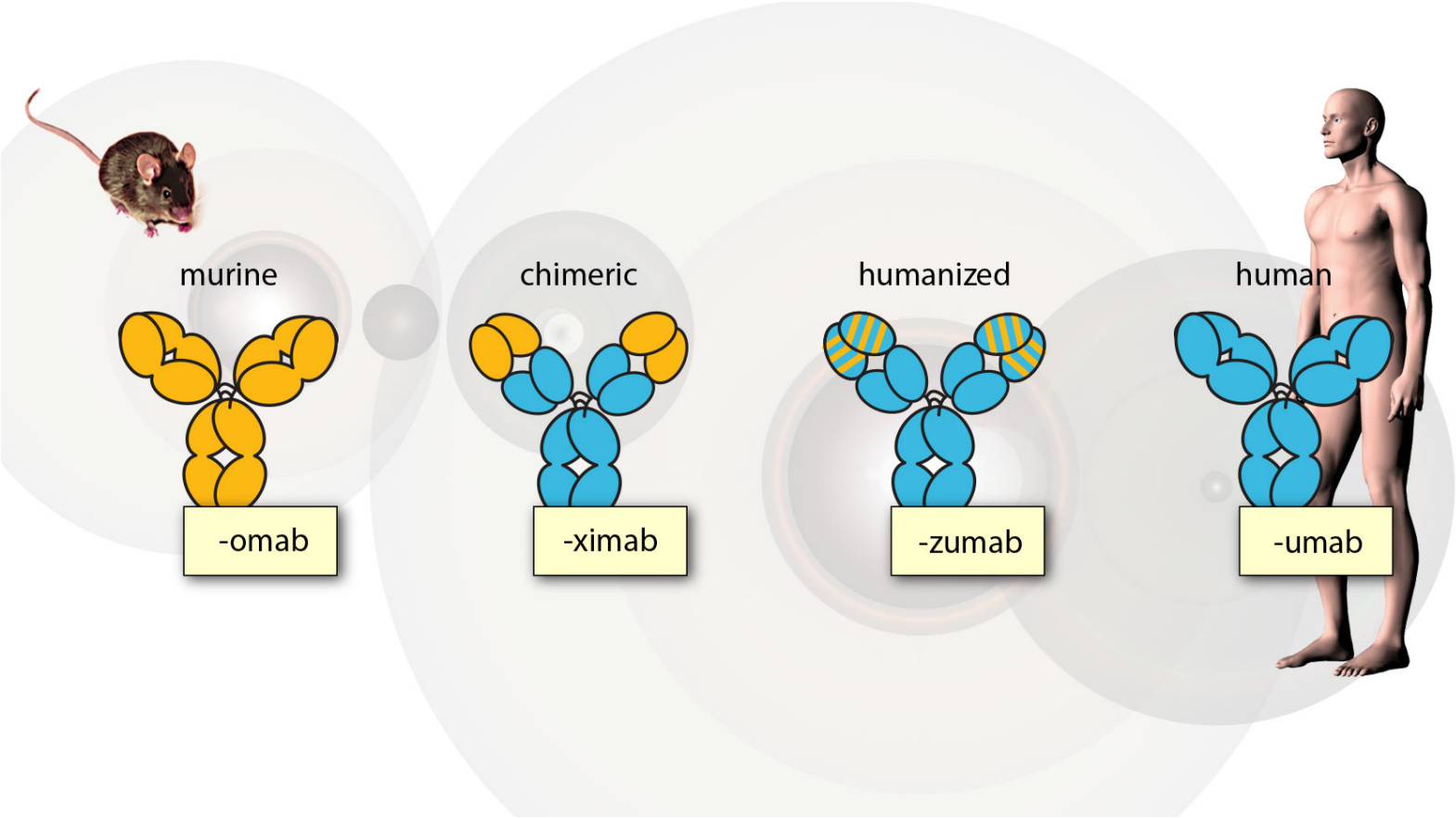
The Antibody Society

Introduction and involvement with INN names

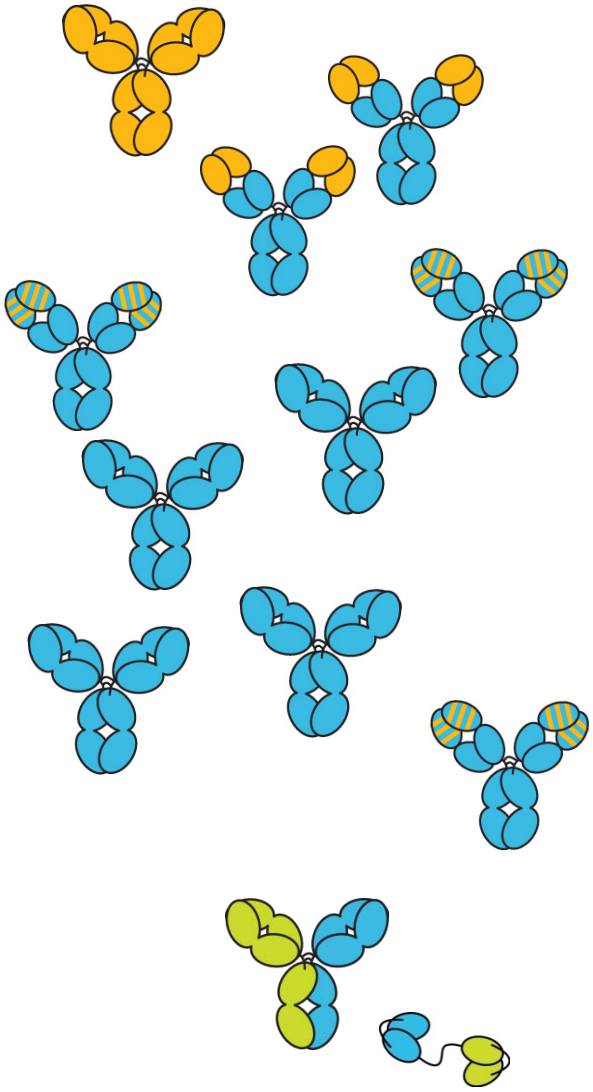
- Non-profit trade association founded in 2007.
- Currently includes 11 companies involved in R&D for antibody therapeutics.
- Corporate sponsors include biotechnology as well as large pharmaceutical firms that have brought numerous antibody-based therapeutics to the market to the benefit of patients world-wide.

- Issues surrounding the 2014 changes in the INN naming system for antibody therapeutics were discussed with our members and with the antibody community.
- Issues are documented by Jones et al. (MAbs *8:*1-9, 2016) with an analysis by 34 authors from 31 organizations.
- Petition to endorse The Antibody Society's involvement in helping to resolve concerns was signed by 290 individuals from 98 commercial and academic institutions from 23 countries.

Designating INN source sub-stems was simple in the early days of antibody engineering



Designating INN source sub-stems in 2016 has become impossible



- Growing number of antibody sources:
  - Human, mouse, rat, rabbit, llama, monkey…
  - Synthetic or semi-synthetic libraries
  - Transgenic animals of distinct genetic backgrounds generating antibodies with human composition
- Expanding repertoire of antibody engineering options:
  - Precise-grafting of CDRs and structural amino acids
  - Affinity optimization
  - Removing manufacturability liabilities
  - Reducing immunogenicity risk
  - Engineered Fc domains or different isotypes
- Increasing number of platforms for antibody-based therapeutics:
  - Monospecific antibodies
  - Antibody-drug conjugates
  - Bispecific and multispecific antibodies
  - Antibody fragments
  - Antibody mixtures and recombinant polyclonals
  - Antibody-fusion proteins

WHO 2014 definitions for INN sub-stems

"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)

Source sub-stems now defined by sequence-alignment of the end-product, not their origin

Limitations of the 2014 sub-stem definitions include inconsistency with existing antibodies

With the 2014 definitions:

- All of 19 marketed humanized antibodies get a mixed (-xizumab) or chimeric (-ximab) designation
- Antibodies directly isolated from human beings may be designated as humanized or even chimeric

Red indicates the closest sequence relative is non-human

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	Mixed
Trastuzumab	81.6	86.3	Mixed
Obinutuzumab	84.7	87.0	Mixed
Pertuzumab	78.8	84.2	Chimeric
Tocilizumab	84.8	89.5	Mixed
Certolizumab	77.6	85.3	Mixed
Natalizumab	83.7	80.9	Chimeric
Ranibizumab	75.8	87.4	Chimeric
Bevacizumab	76.8	88.4	Chimeric
Eculizumab	83.7	84.2	Chimeric
Efalizumab	76.5	89.5	Chimeric
Omalizumab	78.6	86.9	Chimeric
Alemtuzumab	73.7	86.3	Chimeric
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

Multiple limitations of the 2014 origin sub-stem definitions

- Inconsistent with names of many existing antibody therapeutics.
- Scientifically flawed as linear sequence does not define humanness.
- Does not consider advances in antibody technology and antibody development experience.
- Designated IMGT database and search tool are not freely available.
  - Payment required for commercial entities and not licensable to CROs.
- Risk that companies may design future antibody therapeutics to obtain the humanized (-zumab) designation based on this flawed requirement which is undesirable.

Presentation summary

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- Antibody therapeutics are now discovered and engineered in many different ways.
- Capturing an antibody's origin in its name no longer seems useful.
- Sequence alignment methods to determine humanness will easily lead to inconsistencies and should be avoided.
- INN naming definitions need to support the emergence of many new antibody technologies.
    - Including Fc-engineered antibodies, multispecific antibodies, designer polyclonal antibodies and antibody-drug conjugates.

- It is time to let go of the source sub-stem system for antibodies, but also refrain from introducing a sequence comparison sub-stem.
- Instead, we should develop a methodology that takes current and near-future developments into account and consider focusing the INN on functional properties.

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