Rethinking the INN system for therapeutic antibodies

Jérémy Pottier, Romane Chastang, Christophe Dumet, and Hervé Watier

ABSTRACT
In the context of a possible revision of the International Nonproprietary Names (INN) system of recombinant monoclonal antibodies, which is saturated, we propose several avenues of reflection driven by the primary goal of the INN, information of health-care professionals. Clinical considerations argue for an abandon of the substems A (target category) and B (origin category), which lengthen the INN without real added-value. On the contrary, new substems or suffixes are required to alert on the absence/presence of an Fc portion and/or multispecificity, which are essential from a pharmacological point of view. Moreover, we think it necessary to explicitly mention Fc variations since they could influence the pharmacology of these biopharmaceuticals, and hence their efficacy and side-effects. Besides indicating the subclass/isotype in the documents easily accessible to health care professionals, we propose to systematically describe both the natural variations (allotypes) by using the Gm (G marker) system, and the artificial variations by using a Ge (G engineering) system that is discussed here and could apply to all IgG constant domains (tentatively called the Fy portion).

Introduction
As previously described in mAbs, a debate is in progress regarding whether the nomenclature of therapeutic antibodies would be based henceforth – or not – on the percentage of nucleotide sequence identity between the genomic DNA encoding the variable regions of a given antibody and the closest human variable gene sequence in the international ImMunoGeneTics information system® (IMGT®) database. The International Nonproprietary Names (INN) are assigned by the World Health Organization (WHO) and, up to now, for monoclonal antibodies that have been more or less humanized (hereafter called “recombinant antibodies” for simplification), WHO has distinguished chimeric (-xi-), humanized (-zu-) and fully human (-u-) antibodies, based on the genetic origin of the variable domains of the antibody. This nomenclature, currently incorporated in the penultimate syllable of the INN, is therefore very emblematic of the antibody humanization history, which is tightly associated with the extraordinary current clinical success of this class of biopharmaceuticals. Our objective is not to come back to the very relevant arguments that have been developed, nor to discuss them, but to go really further in the debate. Indeed, Jones et al. pointed out that an overhaul of the INN system is required. They notably brought the idea that a single substem could encompass all engineered antibodies ( -sy- for “synthetic” or -e- for “engineered” for example) and that a new INN system should serve the needs of researchers as well as healthcare professionals. This is at the heart of the debate, and our aim here is to offer new and possibly provocative ideas to achieve this goal.

The xi/zu/u categorization in view of the real purpose of the INN system
As recommended by the Third Health Assembly in 1950, the primary purpose of non-proprietary names for drugs should be the information of health care professionals. Physicians and pharmacists have to find in the INN suitable information about the drug in order to “avoid the difficulties arising from a multiplicity of names for the same medicinal substance” and to treat patients with safety and caution.

This is the reason why the INN should not be the indication of a fabrication process. From this point of view, the xi/zu/u categorization could be viewed as an exception, as it refers to a drug design procedure, although it is not strictly a manufacturing process. At that time, a greater degree of antibody humanization was also very strongly associated with the hope of lower immunogenicity and a better clinical tolerance, as compared to murine monoclonal antibodies. In this respect, it could have been viewed as important information for health care professionals, justifying its presence in the INN.

With distance and hindsight, more and more specialists recognize that the degree of humanization of the variable domains (the current basis for xi/zu/u categorization) is not correlated to immunogenicity, and this vision is not really new. Indeed, anti-drug antibodies (ADA) are mostly directed against the idiotype, even for chimeric antibodies. Even in “fully” human antibodies, the idiotype is always antigenic by nature, based on the fact that it is not germline-encoded (especially the CDR3) and that it does not belong to the immunological self. Although humanization of the variable domain could decrease the

CONTACT Hervé Watier herve.watier@univ-tours.fr

*These authors equally contributed to this work.

Published with license by Taylor & Francis Group, LLC © Jérémy Pottier, Romane Chastang, Christophe Dumet, and Hervé Watier

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.
number of T-cell epitopes and contribute to a reduction of idio-
type immunogenicity, there is mounting evidence that factors
other than the degree of humanization play a more important
role in the induction of ADA in clinic, such as antibody aggre-
gates7 and immune complexes.8 Nevertheless, the dosing sched-
ule and the exposition to the therapeutic antibody (circulating
concentrations) are probably the most determining factors asso-
ciated with immunogenicity in clinical practice, which is an
adverse effect paradoxically inversely related to the dose.9 The
fact that murine IgG do not bind to the human neonatal recep-
tor (FcRn) was directly responsible for their poor pharmacoki-
netic profile, a factor that has very likely contributed to their
high immunogenicity.10 Although caution is still advised during
clinical trials, immunogenicity has become a very peripheral
problem for most approved antibodies, since all recombinant
IgG antibodies, independently of the xi/zu/u categorization,
have a human Fc optimal for binding to FcRn. The xi/zu/u cat-
ergization has therefore no real clinical interest, and maintain-
ing it only provides an unfounded basis easily diverted for
marketing purposes. It could also incorrectly reassure health
care professionals about the safety of “human” antibodies. We
therefore strongly suggest abandonment of this categorization.

The labyrinth of substem A

Besides the penultimate syllable (substem B, e.g., o/xi/zu/u), the
antepenultimate one (substem A), indicating the target,2 is
another source of confusion for health care professionals.
Essentially, it is a rather good idea. For example, the antibodies
indicated in cancer can be divided into molecules targeting
tumor cells (-tu(m)- substem: rituximab, trastuzumab, panitu-
mab, dinutuximab, daratumumab, etc.), and those targeting
the microenvironment, themselves divided into antibodies tar-
geting angiogenesis and circulation (-ci(r)- substem: bevacizu-
mab, ramucirumab), bone and osteogenesis (-os- substem:
denosumab), and lymphocytes (-li- substem: ipilimumab, nivo-
lumab, pembrolizumab, etc.). In terms of pharmacodynamics
and possible adverse effects, this distinction appears relevant.
This corresponds more or less to (1) passive anti-tumor immu-
notherapy (-tu(m)-) whose adverse effects are due to antigen
expression in non-cancer tissues; (2) active and non-specific
anti-tumor immunotherapy by immune checkpoint inhibitors
(-li-), whose adverse effects are due to awakening of autoim-
mune and inflammatory T cells; and (3) therapeutic modalities
that can be hardly defined as immunotherapy (-ci(r)-, -os-) and
whose adverse effect are systemic or metabolic (hypertension,
hypocalcemia, etc.). However, there are limitations and excep-
tions. Siltuximab, an anti-interleukin-6 antibody indicated in
Castelman’s disease has the -tu- radical although it targets an
autocrine growth factor/cytokine and not the proliferating B
cells, which, moreover, are not considered malignant! More-
over, a single -tu- radical has been attributed to bispecific anti-
bodies (catumaxomab, blinatumomab), although they also
target CD3+ T cells. It will be interesting to see which substem
will be attributed to MAAbp1 (XilonxTM), an anti-IL-1β anti-
body for treating colorectal cancer, already undergoing review
by the European Medicines Agency.

If we now consider one given targeting entity, i.e., antibodies
targeting the immune system, they can be divided into
“lymphocyte” targeting (-li- substem, such as ipilimumab or
natalizumab) and cytokine targeting (-kin-, such as canakinu-
mab). Logically, antibodies that are cytokine receptor antago-
nists are -li- (basiliximab, tocilizumab). However this is in fact
more complex since -li- is employed for antibodies targeting
tumor necrosis factor (TNF-α), which is usually considered a
cytokine, and for soluble proteins that are produced by lym-
phocytes (such as IgE for omalizumab) or not (such as ecullizu-
mab for complement C5). Moreover, when antibodies targeting
lymphocytes are first developed for malignant lymphoprolifer-
ate diseases and secondarily obtain an approval in a non-can-
cer indication, they keep their -tu- substem (rituximab,
alemtuzumab). This is why some anti-CD20 antibodies are
-tu- (rituximab, ofatumumab, obinutuzumab) while others are
-li- (ocrelizumab). For autoimmune patients being treated by
rituximab, receiving such a drug could suggest that he/she suf-
fers from a cancer. Overall, the INN nomenclature for antibod-
ies targeting the immune system is not only complex and of
little use for health care professionals, it could be also mislead-
ing from a pharmacological point of view. Indeed, most of these
antibodies (most of the -li-, all the -kin- and -tu-) are immuno-
suppressive: they are indicated in autoimmune and inflamma-
tory diseases, with an increased risk of infections and possibly
cancers. In contrast, immune checkpoint inhibitors are immu-
nostimulatory and they are indicated in cancer, with an
increased risk of inflammatory and autoimmune manifesta-
tions, yet they are designated -li-!

Other illogicalities and sources of misinterpretations can be
noted. The radical -c(i)- is a common denominator to bevacizu-
mab (anti-VEGF) indicated in cancer and to evolocumab and
alirocumab (anti-PCSK9), which are indicated in familial
hypercholesterolemia. Conversely, a mysterious “-ibi-” radical
had been attributed to ranibizumab because it inhibits angio-
genesis, exactly like bevacizumab, which derives from the same
murine monoclonal antibody as ranibizumab.11 It is therefore
illusory to establish a nomenclature system on such indistinct
categories that evolve over time and could be inaccurate if the
indications evolve. Here again, we thus recommend abandon-
ing the current nomenclature concerning the antepenultimate
syllable (substem A).

At the crossroad!

Abandoning the current xi/zu/u (substem B, penultimate loca-
tion, origin category) and tu/li/ci/kin/etc. (substem A, antepen-
ultimate location, targeting category) syllables is an
opportunity to shorten the current antibodies INN. Indeed, the
names tend to be too long (average 11 letters, extreme 14 letters
for brontictuzumab, and average 4.5 syllables, extreme 6 syllab-
es for dapirolizumab or duligotuzumab), being longer than
those of other biological and chemical products. The growing
number of antibodies is directly responsible for the increase of
their length.12 Besides the difficulties in learning such long
terms, the risk of similarities between different antibody INNs
is a major risk for clinical practice. Look-alike and sound-alike
drug names may be responsible for as many as one in 4 error
reports received by surveillance programs.13 For examples, the
similarities in the INNs incimromab and imicromab, monali-
zumab and motavizumab, sapelizumab and sipilizumab, or
tocilizumab and toralizumab, are apparent. It is thus time to desaturate the INN system. Such a need is also an excellent opportunity to start afresh and to entirely rethink the entire antibody nomenclature, taking into account the clinical experience.

**Antigen binding dominates Fc functions?**

For decades, antibodies have been named after the fact they recognize a specific antigen. As a consequence, antibody fragments (e.g., abciximab, ranibizumab for antigen-binding fragments (Fab’s), pexelizumab for single-chain variable fragments (scFv)) and even camelid VHH (single domain antibodies; e.g. caplacizumab) are considered antibodies, and there is no reason to modify this consensual position. However, in the common sense, an antibody of the IgG class is a Y-shaped molecule, bivalent, monospecific, and has a long half-life, prone to prolonged prophylaxis. Bivalency (most full-length IgG) vs monovalency (fragments) could be important properties to consider from a pharmacological point of view, but are of far lesser importance than the human Fc portion, which is central for prolonging the plasmatic half-life and spacing the infusions/injections. In case of adverse effects, such as risks of bleeding that could be life-threatening, distinguishing an antibody with or without a human Fc is of utmost importance to evaluate the time required to perform surgery securely. When an INN was attributed to a pegylated Fab, it was indeed considered necessary to mention the PEG presence in the INN, notably to alert health care professionals to a different pharmacokinetic profile (the letter L being added for esthetic reasons and in reference to the L letter of pegol). Similarly, in case of fusion with albumin for the same purpose, “albal,” “albol” or “albul” could be added. However, it must be decided whether the use of a second word should be restricted to chemical conjugation, as in the case of chemically conjugated antibodies (certolizumab pegol, ibritumomab tiuxetan, brentuximab vedotin, etc.), and the use of a prefix to genetically-fused proteins. Indeed, instability of the conjugate could be a clinical issue, while considering storage/handling of the product and fate in the organism. In this case, “pegol” should be preferred to the “peg.” prefix whereas “ef-” and “alb-” should then be used for fusion proteins.

Coming back to an antibody, it seems ridiculous to add the “ef-” prefix to all full-length IgG, even if it can be viewed as an antigen-binding protein fused with an Fc. Full-length IgG being the standard for therapeutic applications and our own antibodies having an Fc, we are of the opinion that the presence of an Fc does not need to be mentioned in the INN (Fc would be present by default), but this means that the absence of an Fc should be clearly mentioned!

**To tackle an emblem!**

To resolve the problem that some -mab have an Fc while others do not, the solution we propose is nothing less than abandoning the -mab suffix for recombinant antibodies! We are perfectly aware that we tackle an emblem, which is also the title of this journal, and which has led to a certain Mab-mania that we have also exploited. There is no reason to be worried about such a radical step, because a sufficient number of “-mab” are already attributed to allow keeping “mab” as a flagship for the antibody community, even if future INNs attributed to monoclonal antibodies are not stamped “-mab.” As Mab starts with a consonant, it necessarily forms a syllable, automatically lengthening the INN name and preventing the use of other consonants in association with the suffix -ab (referring both to “Ab,” the historical antibody abbreviation, and also to “antigen binding” like in Fab), which must be absolutely preserved. Moreover, future antibody products will be perfectly well-defined (glyco)-proteins, produced by a clone of genetically-modified factory cells, far from the historical hybridoma! All of them will be monoclonal by essence, rendering its mention in the INN unnecessary.

**New suffixes**

Knowing that health care professionals must know whether an Fc is present or not, or whether the antibody targets one, two or more antigens, the suffixes we propose to use would be:

- rab for recombinant full-length monospecific IgGs;
- frab for fragments of recombinant IgG, without an Fc;
- birab or -bifrab (“-bi-” substem) in case of bispecificity;
- tirab or -tifrab (“-ti-” substem) in case of multispecificity (more than 2);

Substems -axo, -a, -o and -e could be kept in case of variable and constant regions of animal origin, with the -mab suffix. Bispecificity of antibodies derived from heterohybridomas,
such as catumaxomab, is already suggested by the x within -axo-, rendering the use of the “-bi-” substem unnecessary. In the case of recombinant antibody fragments of animal origin without any human constant region, we propose to use the animal subunits with the new suffixes. With this new nomenclature, blinatumomab (CD19 scFv x CD3 scFv) would have been blinatobifrab. A more radical alternative could be to simplify the system, by using a single substem such as “-(a)ni(m)-” indicating the complete animal origin of antibodies.

In the case of antibody cocktails, the problem is more complex, even if we restrict it to cocktails of monospecific antibodies. Indeed, it could be a combination of antibodies targeting different epitopes of the same antigen (monospecificity), or antibodies targeting different antigens (multispecificity). The suffix could be simply -cab or -kab (cocktail of antibodies), but it then becomes difficult to note whether they are fragments or not. The suffixes -corab and -cofrab would be better, and more appropriate when antibodies are targeting the same antigen. In case of multiple specificity, we fear it is necessary to add a syllable, giving -bicorab, -bicofrab, -ticorab, -ticofrab. Of course, bispecificity in the case of a cocktail is different from bispecificity of a single molecule, but we think we can use the same substem.

**Going deeper in Fc engineering and pharmacology?**

Besides binding FcRn, another important Fc-associated function is the ability to recruit immune effector mechanisms, to activate immune functions and to kill target cells. This is highly dependent on the human IgG subclass, since IgG1 are or could be cytotoxic and depleting, and proinflammatory, whereas IgG2 and IgG4 usually are not. It is important for health care professionals to know whether an antibody therapeutic might activate immune functions and to kill target cells. Particularly to interpret adverse events (cytopenias, etc.). The subclass, which depends on the heavy chain isotype, is indicated in the Lists of Recommended and Proposed INNs and is usually reported in documents easily accessible to health care professionals as the Physicians’ Desk Reference or the Summary of Product Characteristics. Therefore, we do not think it is necessary to add this component to the INN.

Mentioning the IgG subclass is not sufficient, however, because IgG constant domains are subjected to natural variations (genetic polymorphisms) called allotypes, which could modify their functions.19-22 Because of their potential clinical impact, it would therefore be important to have a clear and easily description of the allotype used. The Gm (for IgG genetic marker) international nomenclature (with Arabic numbers) appear to be the more consensual, although it is based on allotypes antigenicity, and does not integrate iso-allotypes (unless they are opposite to a Gm marker and could be called Gm- (minus)).23 This nomenclature should be updated to integrate all the polymorphic variants, whatever their supposed antigenicity, and the Gm markers (as well as the Km markers for the light chain) should be systematically mentioned in the INN bulletin, as well as in documents accessible to health care professionals.

Since 1987,24 substantial efforts have been made to modulate IgG properties through Fc engineering (peptide engineering, glycoengineering, etc.). Emphasis had initially been placed on reducing effector functions and prevention of cell depletion and/or adverse effects, but Fc engineering was also developed to increase IgG stability, to potentiate effector mechanisms, to precisely tune the different effector functions, to improve FcRn binding and extend IgG half-life, etc. More generally, exactly what comprises an Fc needs to be better defined for biopharmaceuticals. The historical definition (crystallizable fragment after papain cleavage of IgG) has the disadvantage of giving different N-terminal endings depending on the subclass. It is therefore simpler to include the entire hinge region within the Fc, when considering Fc engineering.25 With this definition, 15 approved antibody-based therapeutics harbor Fc variations (Table 1 and 2). Beyond the Fc, protein engineering in the constant regions of the Fab has already been envisioned to modify interchain disulfide bridges and increase IgG stability,26,27 and even to improve FcRn binding.21,28 In the future, it will probably be necessary to consider all the constant regions of an IgG, which could be named the Fy (in reference to its Y-shape) (Fig. 1).

Fc/Fy variations can have pharmacological consequences and clinical impact. For example, obinutuzumab has been glycoengineered to increase its binding to FcγRIIA (and FcγRIIB), and this modification could explain the higher number of cytokine release syndromes and chronic neutropenias, in comparison to rituximab.29 Furthermore, mydriasis and impaired accommodation has been more frequently observed in patients with neuroblastoma receiving the anti-GD2 hu14.18K322A antibody than in patients receiving dinutuximab, an anti-GD2 IgG1 antibody.30 The fact that these effects could be related to the K322A mutation in IgG1 has not been considered nor discussed, but is possible. We can also imagine that identical adverse effects could be observed for 2 completely different antibodies, directed against very different antigens and administered to patients with completely different diseases.

**Table 1. IgG1 modified Fc-based biopharmaceuticals, classified by year of first approval, with allotypes, Fc variations and correspondence with the proposed G1e numbering.**

| International non-proprietary names | First approval year (US, EU or Japan) | Allotype | Fc variations (Eu) | Numbering |
|-------------------------------------|--------------------------------------|----------|-------------------|-----------|
| abatacept                           | 2005                                 | G1m1     | C2205 C2265 C2295 P2385 substitutions | G1e1      |
| romiplostim                         | 2008                                 | G1m1     | Production in E.coli (aglycosylation) | G1e2      |
| belatacept                          | 2011                                 | G1m1     | C2205 C2265 C2295 P2385 substitutions | G1e1      |
| afilibercept                        | 2011                                 | G1m1     | Deletion of the 5 first amino-acids of hinge region | G1e3      |
| mogamulizumab                       | 2012                                 | G1m17,1  | Afucosylation      | G1e4      |
| obinutuzumab                        | 2013                                 | G1m17,1  | Addition of a bisecting GlcNAc | G1e5      |
| vedolizumab                         | 2014                                 | G1m17,1  | L235A and G237A substitutions | G1e6      |
| efmoroctocog α                      | 2014                                 | G1m1     | Deletion of the 5 first amino-acids of hinge region | G1e3      |
| efrenonacog α                       | 2014                                 | G1m1     | Deletion of the 5 first amino-acids of hinge region | G1e3      |
| atezolizumab                        | 2016                                 | G1m17,-1 | N297A substitution  | G1e7      |
because these events originate from the same Fc variation. If health care professionals do not have direct access to information about the IgG Fc/Fy variants, it is likely that the connection will not be made quickly enough.

Due to the clinical impact of Fc/Fy variations, their presence should be explicitly mentioned under an international nomenclature that does not exist yet. The INN bulletins and the IMGT mAb-DB mention all the peptide variations, as well as the variations of glycosylation, but the format is not convenient. First of all, the variations are listed under the IMGT nomenclature, which is very useful for the variable regions, but is not practical at all for constant domains because it restarts at 1 for each region or domain. Moreover, it is far less used than the old Eu nomenclature.31 Secondly, for complex mutations such as those of emicizumab,32 the description under the IMGT nomenclature is tedious and difficult for health care professionals. Artificial variations can be extremely complex, giving rise to molecules with many modified amino-acids, a modified glycosylation pattern or even entire domains substitutions. A combination of those 3 types of modification is even conceivable; it is therefore very difficult to systematize an appropriate nomenclature.

Use a single substem for all engineered antibodies ( -sy- for “synthetic” or -e- for “engineered” for example) was suggested by Jones et al.1 This suggestion probably relates mostly to variable domains and implies an integration in the INN, but it would be too complex and would not indicate which antibody portion is engineered, or the kind of variation. We rather think that the artificial Fc variants, and more generally variants in constant domains (Fy), could be indicated by a nomenclature system similar but different from the natural variant/allotypes system, permitting, for example, easy identification of the cause of some adverse events for molecules that have nothing in common except their constant region mutations. The substem -e- proposed by Jones et al.1 could be integrated in a Ge system, besides the Gm system. For IgG1, there would be the G1m and the G1e systems, for IgG2, G2m and G2e, for IgG4, G4m and G4e. If the constant domain of the κ light chain is subjected to

---

Table 2. IgG4 modified Fc-based biopharmaceuticals, classified by year of first approval, with allotypes, Fc variations and correspondence with the proposed G4e numbering.

| International non-proprietary name | First approval year | Allotypes | Fc variations (Eu) | Numbering |
|-----------------------------------|---------------------|-----------|-------------------|-----------|
| gemtuzumab ozogamicin              | 2000                | —         | S228P substitution | G4e1      |
| eculizumab                        | 2007                | L309 / R409 | Hybrid IgG2 (before T260) / IgG4 (after) | G2e1 and G4e2 |
| dulaglutide                       | 2014                | L309 / R409 | S228P F234A, L235A substitutions and removal of K447 | G4e2 |
| pembrolizumab                     | 2014                | L309 / R409 | S228P substitution | G4e1 |
| ixekizumab                        | 2016                | L309 / R409 | S228P substitution and removal of K447 | G4e3 |

- No sequence available.
- Eculizumab is a hybrid between IgG2 and IgG4. No other IgG2 has been approved with Fc modification.
- Withdrawn or marketing discontinued for the first approved indication.

---

Figure 1. Designation of antibody fragments. (A) Schematic representation of a full-length IgG. (B) Papain digestion of an IgG generates 2 Fab fragments (antigen binding) and one Fc (crystallizable), but the precise cleavage site could vary from one IgG subclass to another. We have therefore to include the entire hinge region in the definition of Fc.25 (C) The fragment containing VH and VL was called Fv in 197233 and was popularized when it was possible to produce it as a single chain (scFv). However, a name has never been attributed to the remaining part of the IgG, containing the whole constant domains (CH1-CL and Hinge-CH2-CH3). This portion of the IgG is subjected to natural variations (allotypes) and is engineered for therapeutic purposes. Because it is encoded by the genes determining the heavy and light chain isotypes, it could be logical to name “Fy” (for isoype), but the “y” letter would be hard to read and poorly understandable. We rather propose to name it “Fy”, in relation to its Y-shaped configuration.
engineering, there would be a Ke system. Our system would be very pragmatic, attributing a new number to each newly approved antibody whose constant regions have been subjected to engineering. In case an antibody is a chimera between 2 subclasses, like IgG2/4 eculizumab, it will have a double nomenclature (G2e and G4e). Because 15 engineered IgG-based therapeutics are already on the market, we propose the following numbering (Table 1 and 2), based on the date of first approval in the world.

**Conclusion**

We are aware that our proposals are radical and that they will unsettle habits and consenses, but they fit better to the fundamental guidelines promulgated by WHO, and will therefore be far more useful for professionals and for the key stakeholders, i.e., patients. Obviously our proposals must be discussed and debated with all the stakeholders in the antibody research and development field, but we hope that our proposals will promptly lead to a broad consensus. With the increasing number of antibodies approved every year, these new standards should be assimilated quickly.

**Acknowledgments and disclosures**

This work was supported by the French Higher Education and Research Ministry under the program "Investissements d’Avenir” grant agreement: LabEx MAbImprove ANR-10-LABX-53-01. We thank Dr. Paul Parren and Dr. Alain Beck for their helpful comments.

The authors declare no competing financial interests that are directly relevant to the content of this article.

**References**

1. Jones TD, Carter PJ, Plückthun A, Vásquez M, Holgate RGE, Hötzel I, Popplewell AG, Parren PWHL, Enzelberger M, Rademaker HJ, et al. The INNs and outs of antibody nonproprietary names. MAbs 2016; 8:1-9; PMID:26716992; http://dx.doi.org/10.1080/19420862.2015.1114320
2. World Health Organization. General policies for monoclonal antibodies. 2009; http://www.who.int/medicines/services/inn/Generalpoliciesformonoclonalantibodies2009.pdf
3. Watier H, Reichert J. Evolution of antibody therapeutics (Chapter 2). In: Jallal B, Vaughan T, Osbourn L, eds Protein Therapeutics. Wiley, 2016 in press
4. World Health Organization. Expert Committee of the Unification of Pharmacopoeias. Report on the Sixth Session, 1950; http://apps.who.int/iris/bitstream/10665/38948/1/WHO_TRS_29.pdf
5. Clark M. Antibody humanization: a case of the "Emperor’s" new clothes? Immunol Today 2000; 21:397–402; PMID:10916143; http://dx.doi.org/10.1016/S0167-6599(00)01680-7
6. Van Schie KA, Hart MH, de Groot ER, Kruithof S, Aarden LA, Wobink GI, Rispens T. The antibody response against human and chimeric anti-TNF therapeutic antibodies primarily targets the TNF binding region. Ann Rheum Dis 2015; 74:311–4; PMID:25342759; http://dx.doi.org/10.1136/annrheumdis-2014-206237
7. Ratani JD, Derrick JP, Dearman RJ, Kimber I. Immunogenicity of therapeutic proteins: influence of aggregation. J Immunotoxicol 2013; 11:99-109; PMID:23919460; http://dx.doi.org/10.3109/1547691X.2013.821564
8. Krishna M, Nadler SG. Immunogenicity to Biotherapeutics - The role of anti-drug immune complexes. Front Immunol 2016; 7:21; PMID:26870037; http://dx.doi.org/10.3389/fimmu.2016.00021
9. Chaigne BG, Watier H. Monoclonal antibodies in excess: A simple way to avoid immunogenicity in patients? J Allergy Clin Immunol 2015; 136:814-6; PMID:25930194; http://dx.doi.org/10.1016/j.jaci.2015.03.013
10. Ober RJ, Radu CG, Ghetie V, Ward ES. Differences in promiscuity for antibody-FcRn interactions across species: implications for therapeutic antibodies. Int Immunol 2001; 13:1551-9; PMID:11717196; http://dx.doi.org/10.1093/immunbol/13.12.1551
11. Magdalene-Beuzelin C, Kaas Q, Welhi V, Ohresser M, Jefferis R, Lefranc M-P, Watier H. Structure-function relationships of the vari- able domains of monoclonal antibodies approved for cancer treatment. Crit Rev Oncol Hematol 2007; 64:210–25; PMID:17624800; http://dx.doi.org/10.1016/j.croh.2007.04.011
12. World Health Organization. WHO Drug Information 2009; 23:195-9; http://www.who.int/medicines/publications/druginformation/issues/Druginfo09vol23-2.pdf
13. Sally Pepper, Malan S, Mignot G, Mattavelli RB. WHO Programme on International Nonproprietary Names (INN). Work Doc 15381 2015:29-34
14. World Health Organization. 62nd Consultation on International Nonproprietary Names for Pharmaceutical Substances. 2016; http://www.who.int/medicines/services/inn/62nd_Executive_Summary.pdf?ua=1
15. World Health Organization. International nonproprietary names (INN) for biological and biotechnological substances (a review). 2016; http://www.who.int/medicines/services/inn/BioReview2016.pdf
16. World Health Organization. 36th Consultation on International Nonproprietary Names for Pharmaceutical Substances. 2013; http://www.who.int/medicines/services/inn/36th_Executive_Summary.pdf
17. Thulliez M, Angoulvant D, Le Lez ML, Jonville-Bera A-P, Pisella P-J, Gueyffier F, Bejan-Angoulvant T. Cardiovascular events and bleeding risk associated with intravenous antiangiogenic endothelial growth factor monoclonal antibodies: systematic review and meta-analysis. JAMA Ophthalmol 2014; 132:1317-26; PMID:25058694; http://dx.doi.org/10.1001/jamaophthalmol.2014.2333
18. Pelegrin A, Daguet A, Watier H. MAbImprove: a French “Laboratoire d’excellence” (LabEx) dedicated to therapeutic antibodies. MAbs 2014; 6:403-4; http://dx.doi.org/10.4161/mabs.29262
19. Pandey JP, Namb底odir AM. Genetic variants of IgG1 antibodies and Fcγ/Rlla receptors influence the magnitude of antibody-dependent cell-mediated cytoxicity against prostate cancer cells. Oncoimmunology 2014; 3:e27317; PMID:24701371; http://dx.doi.org/10.4161/onci.27317
20. Vidarsson G, Dekkers G, Rispens T. IgG Subclasses and Allotypes: From structure to effector functions. Front Immunol 2014; 5:1-17; http://dx.doi.org/10.3389/fimmu.2014.00520
21. Ternant D, Arnoult C, Pugnière M, Dhommée C, Drocourt D, Perozuel EF, Passot C, Baroukh N, Mulleman D, Tiraby G, et al. IgG1 Allotypes Influence the Pharmacokinetics of Therapeutic Monoclonal Antibodies through FcRn Binding. J Immunol 2016; 196:607-13; PMID:26685205; http://dx.doi.org/10.4049/jimmunol.1501780
22. Stapleton NM, Andersson JT, Stemmering AM, Bjarnarson SP, Verheul HRG, Geenen A, van der Valk P, et al. Human IgG3 and offers therapeutic potential. Nat Commun 2011; 2:599; PMID:22186895; http://dx.doi.org/10.1038/ncomms1608
23. Jefferis R, Lefranc M. Human immunoglobulin allotypes: possible implications for immunogenicity. MAbs 2009; 1:332-8; PMID:20017333; http://dx.doi.org/10.4161/mabs.1.4.9122
24. Winter GP, Duncan AR, Burton DR. Altered antibodies. 1987
25. Pottier J, Watier H, Gouilleux-Gruart V. Modifications in the IgG4 Fc portion of therapeutics in patents: opportunities for a twisting IgG subclass. Submitted 2016
26. White AL, Chan HTC, French RR, Willoughby J, Mockridge CI, Rosenthal W, Trigg C, Henkle B, Li Y, Deechongkit S, et al. Structural and functional characterization of disulfide isomers of the human IgG2 subclass. J Biol Chem 2008; 283:16206-15; PMID:18339626; http://dx.doi.org/10.1074/jbc.M709988200
27. Monnet C, Jorjeux S, Urban B, Rournier N, Bouyadi K, De Romeuf C, Behrens CK, Fontayne A, Mondon P. Selection of IgG variants with increased FcRn binding using random and directed mutagenesis.
29. Snowden A, Hayden I, Dixon J, Gregory G. Prevention and management of obinutuzumab-associated toxicities: Australian experience. Int J Nurs Pract 2015; 21 Suppl 3:15-27; PMID:26681665; http://dx.doi.org/10.1111/ijn.12412

30. Tse BC, Navid F, Billups CA, O’Donnell T, Hoehn ME. Ocular abnormalities in patients treated with a novel anti-GD2 monoclonal antibody, hu14.18K322A. J AAPOS 2015; 19:112-5; PMID:25818285; http://dx.doi.org/10.1016/j.jaapos.2014.11.005

31. Edelman GM, Cunningham BA, Gall WE, Gottlieb PD, Rutishauser U, Waxdal MJ. The covalent structure of an entire gamma G immunoglobulin molecule. Proc Natl Acad Sci U S A 1969; 63:78-85; PMID:5257969; http://dx.doi.org/10.1073/pnas.63.1.78

32. World Health Organization. International Nonproprietary Names for Pharmaceutical Substances (INN): Recommended International Nonproprietary Names List 75. WHO Drug Inf 2016; 75:19; http://www.who.int/medicines/publications/druginformation/innlists/RL75.pdf?ua=1

33. Inbar D, Hochman J, Givol D. Localization of antibody-combining sites within the variable portions of heavy and light chains. Proc Natl Acad Sci U S A 1972; 69:2659-62; PMID:4560694; http://dx.doi.org/10.1073/pnas.69.9.2659