Report 2019

IUIS Immunoglobulins (IG), T cell Receptors (TR) and Major Histocompatibility (MH) Nomenclature Sub-Committee (IMGT-NC)

68th IUIS Council Meeting 2019, Beijing, China, on occasion of the 17th International Congress of Immunology (October 19-23, 2019).

IMGT-NC Chair
Marie-Paule Lefranc (Marie-Paule.Lefranc@igh.cnrs.fr)
Professor Emeritus University of Montpellier (France)
IMGT® Founder and Executive Director Emeritus
Institut de Génétique Humaine IGH, UMR9002 CNRS, University of Montpellier
Laboratoire d'ImmunoGénétique Moléculaire LIGM
Web page: www.imgt.org

I. The IUIS IG, TR and MH Nomenclature Sub-Committee (IMGT-NC)

1. Mission of the IUIS IMGT-NC

The IUIS 'Immunoglobulins (IG), T cell receptors (TR) and Major Histocompatibility (MH) Nomenclature Sub-Committee' (IMGT-NC) is part of the IUIS Nomenclature Committee (NOM), sanctioned by WHO since 1992 (http://www.iuisonline.org/).

The IUIS IMGT-NC reports to IUIS NOM on the standardized classification and nomenclature of the immunoglobulins (IG), T cell receptors (TR) and major histocompatibility (MH) genes and proteins of humans and other vertebrate species which are managed by IMGT®, the international ImMunoGeneTics information system® http://www.imgt.org, created in 1989 by Marie-Paule Lefranc, and the global reference in immunogenetics and immunoinformatics.

The IUIS IMGT-NC is the interface of the IMGT Nomenclature Committee (IMGT-NC) with the other IUIS Nomenclature Sub-Committees.

2. Members of the IUIS IMGT-NC

Founding Members of the WHO-IUIS Nomenclature Subcommittee for immunoglobulins (IG), T cell receptors (TR) and major histocompatibility (MH) (IMGT-NC) in 1989 are J. (Joseph) Donald Capra (USA) (1937-2015) (www.jimmunol.org/content/194/12/5575.full), Max Cooper (USA), Tasuku Honjo (Japan), Leroy Hood (USA), Gérard Lefranc (France), Marie-Paule Lefranc (France) IMGT-NC Chair founder, Fumihiko Matsuda (Japan) and Hans Georg Zachau (Germany) (1930-2017).

IMGT Experts are scientists in the field of immunogenetics who in their published work have promoted standardization of the IMGT IG, TR and/or MH genes and alleles and who contribute, on a case by case basis, to IMGT-NC for IG, TR and/or MH loci of given species.
(http://www.imgt.org/IMGTindex/IMGTexperts.php).

3. IUIS IMGT-NC events, publications and reports

Summary reports written by the IUIS IMGT-NC have been sent on an annual basis to the chair of the WHO-IUIS Nomenclature since 1992 (Michel Kazatchkine (Sept 1992-2004), Laurence Boumsell (Sept 2004-2010), Pablo Engel (Sept 2010-2016), Menno van Zelm (Sept 2016-)), for presentation at the annual IUIS Council Meetings (coincident every three years with the International Congress of Immunology (ICI). The links to the IUIS IMGT-NC events, publications and/or reports since its creation are publicly available at http://www.imgt.org/IMGTindex/IUIS-NC.php.

Highlight: 2019 marks the 30 years of IMGT-NC.

The publication in Frontiers in Immunology, invited by the WHO IUIS Nomenclature Committee (Proceedings of ICI Milan 2013)
Lefranc M-P. Immunoglobulin (IG) and T cell receptor genes (TR): IMGT® and the birth and rise of immunoinformatics. Front Immunol. 2014 Feb 05;5:22.
https://www.frontiersin.org/articles/10.3389/fimmu.2014.00022/full
has reached a total of 15,035 views on August 28, 2019.

II. Recent accomplishments for new genes and alleles

1.New IG and TR genes and alleles

The biocuration of new IG and TR genes and alleles approved by IMGT-NC is done by the IMGT® team. This includes genes and alleles of newly sequenced genomes of humans and of any other species of vertebrates with jaws (*gnasthomata*) (IUIS IMGT-NC 2018)**.**
Approved and annotated IG and TR genes and alleles of *Homo sapiens* and other species of vertebrates with jaws are managed in IMGT®. Updates of the IMGT reference directories are reported in the Documentation of the corresponding IMGT® tools. Total number of genes and alleles in IMGT/GENE-DB are annually reported by IUIS IMGT-NC to the IUIS Nomenclature Committee.

On August 28, 2019, IMGT/GENE-DB, the IMGT® gene database, contained 7,007 IMGT genes and 9,145 alleles from 30 species.
• 717 IG and TR genes and 1,585 alleles for *Homo sapiens* (462 IG genes and 1,018 alleles; 249 TR genes and 448 alleles) as well as 11 RPI and 135 alleles
• 826 IG and TR genes and 909 alleles for *Macaca* (618 genes and 692 alleles for *Macaca mulatta*),
• 942 IG and TR genes and 1,395 alleles for *Mus* (871 genes and 1321 alleles for *Mus musculus*),
• 638 IG and TR genes and 644 alleles for *Rattus norvegicus*.
More statistics are available at http://www.imgt.org/genedb/stats.
Detailed IMGT/GENE-DB data updates are available at
http://www.imgt.org/IMGTgenedbdoc/dataupdates.html

2. Nomenclature for genome assemblies

A landmark was the approved IMGT-NC nomenclature of the genes of the seven IG and TR loci of *Canis lupus familiaris* (Martin et al. 2018) (IUIS IMGT-NC 2018). The biocuration of the IG and TR genes and alleles was performed by the IMGT® team. Following the classical IMGT procedure, these genes and alleles led to the entry of the sequences in IMGT/LIGM-DB and IMGT annotation, creation of Gene tables, Alignments of alleles, IMGT reference directories (nucleotide and amino acid sequences). The *Canis lupus familiaris* reference sequences were entered in IMGT/HighV-QUEST reference directories allowing NGS repertoire analysis. This approach was used as a benchmark for other species, and demonstrated that the *Homo sapiens* IGH, IGK, IGL, TRA, TRB, TRG and TRD loci were a paradigm for IG and TR gene and allele nomenclature of other species (The Immunoglobulin FactsBook 2001, The T cell receptor FactsBook 2001, http://www.imgt.org/IMGTindex/factsbook.php).

3. External submissions and IMGT-NC reports

The individual external submissions to IMGT-NC have been upgraded with the publication on-line of the IMGT-NC reports. The first IMGT-NC report (2017-1-1226) was created following the submission by Cathrine Scheepers (South Africa) of 36 genomic sequences with INSDC accession numbers on 15/12/17. Her contribution was detailed and acknowledged in IUIS IMGT-NC 2018.

Since this first IMGT-NC report, sixteen new ones corresponding to external submissions have been edited.and published on-line. They are available at the IMGT Nomenclature Committee (IMGT-NC) page http://www.imgt.org/IMGTindex/IMGT-NC.php
They include submissions on *Homo sapiens* (human, Homap) variable and constant genes and alleles, but also on IG and/or TR genes and alleles of novel genome assemblies such as *Felis catus* (domestic cat, Felcat), *Mustela putorius furo* (ferret, Musputfur), *Oncorhynchus mykiss* (rainbow trout, Oncmyk), *Oryctolagus cuniculus* (rabbit, Orycun) and *Salmo salar* (Atlantic salmon, Salsal).

4. Nomenclature for inferred alleles

One challenge and opportunity presented last year was the entry of inferred alleles in IMGT®. A working group (WG) inferred allele review committee (IARC), within the adaptive immune receptor repertoire (AIRR) community, analysed the criteria for defining inferred alleles from NGS (the procedure includes a submission of inferred alleles validated by the WG to a generalist database, before submission to the IMGT-NC). The WG insures that IMGT data quality requirements are met, so inferred alleles can be submitted to IMGT-NC. The procedure is fully operational and had led to a publication by the WG (Ohlin et al. 2019), the submission to IMGT-NC in the name of IARC of nine inferred allele sequences and the publication of the IMGT-NC report (2019-11-0418)..

III. On-going projects using the IMGT nomenclature

1. Nomenclature for NGS and repertoire analysis

IMGT/HighV-QUEST, http://www.imgt.org/HighV-QUEST/login.action, the first web portal created in October 2010, is freely available for academics for the analysis of next generation sequencing (NGS) data, for the study of repertoires of IG and TR in normal and pathological situations. The tool accepts 500.000 sequences per batch and one million sequences for statistical analysis. The functionality 'identification and characterization of IMGT clonotypes (AA)' is based on the IMGT IG and TR gene and allele names.
IMGT/StatClonotype, http://www.imgt.org/StatClonotype/, is an IMGT® tool for statistical analysis of sets from IMGT/HighV-QUEST output, on the Web since June 2016. IMGT/StatClonotype uses a generic statistical procedure for identifying significant changes in IG and TR differences of proportions of IMGT clonotypes (AA) diversity and expression, bringing an additional level of analysis and comparison between repertoires described using the IMGT IG and TR gene and allele names.

The IMGT reference directories of IMGT/V-QUEST and IMGT/HighV-QUEST are regularly updated with the IG and TR variable (V), diversity (D) and joining (J) new genes and alleles (functional, open reading frame (ORF) and pseudogenes with in-frame V-REGION (P in-frame) approved by the IMGT-NC (and corresponding to new entries in IMGT/GENE-DB).
IMGT reference directory in FASTA format (IG and TR):
http://www.imgt.org/vquest/refseqh.html#VQUEST
Clicking on the release number at the page http://www.imgt.org/IMGT_vquest/vquest (for example, release 201931-4 (1st August 2019) at the time of this report) gives access to the content of the IMGT/V-QUEST reference directory releases.

2. Nomenclature and IG and TR amino acid sequences and three-dimensional structures

IMGT/DomainGapAlign analyses the amino acid sequences of IG (or antibodies) and TR using the IMGT IG and TR gene and allele names and bridge the gap between sequences and three-dimensional structures as the same rules (numbering, CDR-IMGT, FR-IMGT) are used and can be visualized as IMGT Collier de Perles graphical representations. These standards have been used for the last ten years for the monoclonal antibodies definitions published in the proposed and recommended lists of the WHO International Nonproprietary Names (INN) programme. They can describe any novel format resulting from antibody engineering.

3. Nomenclature for global standardisation

IMGT nomenclature is an integral part of many on-going global collaborations with:
1) HGNC, Ensembl, NCBI, UniProt.
2) the European Research Initiative on CLL (ERIC).
3) the EuroClonality-NGS consortium.
4) the Adaptive Immune Receptor Repertoire (AAIR) Consortium.
5) Reciprocal links to IUPHAR-DB and to IEDB.
6) Diffusion of the IMGT booklet (11 papers, 144 pages) edited by Cold Spring Harbor Protocols (CSHP). The content of this booklet was detailed in IUIS IMGT-NC 2012.
CSHP specifically edited the IMGT booklet for educational purposes and authorized IMGT® to have it freely available on the IMGT® site http://www.imgt.org (available in 'IMGT References'). CSHP also authorized that the IMGT booklet be printed and distributed freely. IMGT® databases and tools described in these chapters use the IUIS/IMGT nomenclature approved by Human Genome Organization (HUGO) Nomenclature Committee (HGNC).

IV. Perspectives

IG, TR and MH standardized nomenclature based on the IMGT-ONTOLOGY concepts of identification (standardized keywords), description (standardized labels), classification (gene and allele nomenclature) and numerotation (IMGT unique numbering and IMGT Collier de Perles) have been crucial in the development of immunoinformatics since its creation in 1989.

These concepts are necessary more than ever in large scale genome sequencing, immune repertoire NGS studies and antigen receptor biotechnology for immunotherapy. Future directions consist in promoting IUIS/IMGT/HGNC nomenclature for new data originating from genome analysis of animal models, veterinary and wild life species, repertoire next generation sequencing and antibody engineering.

V. Award for representing IMGT-NC at the IUIS NOM meeting (ICI, October 2019)

Given the research scope of Cathrine Scheepers and her contribution to the IUIS 'Immunoglobulins (IG), T cell receptors (TR) and Major Histocompatibility (MH) Nomenclature Sub-Committee' (IMGT-NC), which led to the first IMGT-NC report (2017-1-1226), the Sub-Committee Chair would like to propose Cathrine Scheepers for an **Award of the IUIS Nomenclature Committee** to represent IMGT-NC Subcommittee at the ICI in Beijing, China in October 2019.

VI. Selected recent publications derived from the work of the IUIS IMGT-NC committee

Mondot S, Lantz O, Lefranc M-P, Boudinot P.
The T cell receptor (TRA) locus in the rabbit (*Oryctolagus cuniculus*): Genomic features and consequences for invariant T cells.
Eur J Immunol. 2019 Jul 29. doi: 10.1002/eji.201948228. [Epub ahead of print] PMID:,31355919

Lefranc M-P. Lefranc G.
IMGT® and 30 years of immunoinformatics insight in antibody V and C domain structure and function.
In Jefferis R; Strohl W. R., Kato K. Antibodies 2019, 8, 29; doi: 10.3390/antib8020029.

Ohlin M., Scheepers C., Corcoran M., Lees W.D., Busse C.E. , Bagnara D., Thörnqvist L., Bürckert J.-P., Jackson K.J.L., Ralph D., Schramm C.A., Marthandan N., Breden F., Scott J., Matsen IV F.A., Greiff V., Yaari G., Kleinstein S.H., Christley S., Sherkow J.S., Kossida S., Lefranc M.-P., van Zelm M.C., Watson C.T., Collins A.M.
Inferred allelic variants of immunoglobulin receptor genes: a system for their evaluation, documentation, and naming.
Front Immunol. 2019 March 18. doi.org/10.3389/fimmu.2019.00435 Open access.

Xochelli A, Bikos V, Polychronidou E, Galigalidou C, Agathangelidis A, Charlotte F, Moschonas P, Davis Z, Colombo M, Roumelioti M, Sutton L-A, Groenen P, van den Brand M, Boudjoghra M, Algara P, Traverse-Glehen A, Ferrer A, Stalika E, Karypidou M, Kanellis G, Kalpadakis C, Mollejo M, Pangalis G, Vlamos P, Amini R-M, Pospisilova S, Gonzalez D, Ponzoni M, Anagnostopoulos A, Giudicelli V, Lefranc M-P, Espinet B, Panagiotidis P, Piris MA, Du M-Q, Rosenquist R, Papadaki T, Belessi C, Ferrarini M, Oscier D, Tzovaras D, Ghia P, Davi F, Hadzidimitriou A, Stamatopoulos K.
Disease-biased and shared characteristics of the immunoglobulin gene repertoires in marginal zone B cell lymphoproliferations.
J Pathol. 2019 Apr:247(4):416-421. doi: 10.1002/path.5209. Epub 2019 Jan 30.PMID: 30484876

Lefranc M-P, Ehrenmann F., Kossida S., Giudicelli V., Duroux P.
Use of IMGT® databases and tools for antibody engineering and humanization.
In Nevoltris D and Chames P. (Eds) Antibody engineering, Humana Press, Springer, New York, USA. Methods Mol Biol. 2018;1827:35-69. doi: 10.1007/978-1-4939-8648-4_3.PMID: 30196491

Bradbury ARM, Trinklein ND, Thie H, Wilkinson IC, Tandon AK, Anderson S, Bladen CL, Jones B, Aldred SF, Bestagno M, Burrone O, Maynard J, Ferrara F, Trimmer JS, Görnemann J, Glanville J, Wolf P, Frenzel A, Wong J, Koh XY, Eng HY, Lane D, Lefranc M-P, Clark M, Dübel S.
When monoclonal antibodies are not monospecific: hybridomas frequently express additional functional variable regions.
MAbs. 2018 Feb 27:1-8. 10(3). doi: 10.1080/19420862.2018.1445456. [Epub ahead of print] 10(3).

Han SY, Antoine A, Howard D, Chang B, Chang WS, Slein M, Deikus G, Kossida S, Duroux P, Lefranc M-P, Sebra RP, Smith ML, Fofana IBF.
Coupling of single molecule, long read sequencing with IMGT/HighV-QUEST analysis expedites identification of SIV gp140-specific antibodies from scFv phage display libraries.
Front Immunol. 2018 Mar 1;9:329. doi: 10.3389/fimmu.2018.00329. PMID: 29545792

Martin J, Ponstingl H, Lefranc M-P, Archer J, Sargan D, Bradley A.
Comprehensive annotation and evolutionary insights into the canine (*Canis lupus familiaris*) antigen receptor loci.
Immunogenetics. 2018 Apr; 70(4):223-236. doi: 10.1007/s00251-017-1028-0. Epub 2017 Sep 19.
PMID: 28924718

Montpellier, August 28, 2019