**Report 2018**

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

**67th IUIS Council Meeting, May 12-13, 2018, Cancun**, Mexico, on occasion of the XII Congress of ALAI (Latin American Association of Immunology) and XXIII Congress of SMI (Mexican Society of Immunology) (May 14-18, 2018).

## Chair

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## Members of IMGT-NC

Max Cooper (USA), Founding member 1989
Tasuku Honjo (Japan), Founding member 1989
Leroy Hood (USA), Founding member 1989
Gérard Lefranc (France), Founding member 1989
Marie-Paule Lefranc (France), Founding member and Chair 1989
Fumihiko Matsuda (Japan), Founding member 1989
Cynthia L. Baldwin (USA), 2006
Eva Bengtén (USA), 2006
Pierre Boudinot (France), 2006
Felix Breden (Canada), 2013
Salvatrice Ciccarese (Italy), 2007
Deborah Dunn-Walters (UK), 2006
Jean-Pol Frippiat (France), 2006
Véronique Giudicelli (France), 2014
Evelyne Jouvin-Marche (France), 2006
Sofia Kossida (France), 2014
Véronique Laurens (France), 2012
Ramit Mehr (Israel), 2017
Serge Muyldermans (Belgium), 2006
Mariano Sanchez-Lockhart (USA), 2016
Jamie Scott (Canada), 2013
Bettina Wagner (USA), 2006
Corey T. Watson (USA), 2013

## IMGT Experts

http://www.imgt.org/IMGTindex/IMGTexperts.php

## I. Mission

The IUIS 'Immunoglobulins (IG), T cell receptors (TR) and Major Histocompatibility (MH) Nomenclature SubCommittee (IMGT-NC)' mission is to report to the IUIS Nomenclature committee on the standardized classification and nomenclature of the immunoglobulins (IG), T cell receptors (TR) and major histocompatibility (MH) genes and proteins of any vertebrate species with jaws (*gnathostomata*, from fishes to humans).

IMGT-NC genes and alleles 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.

## II. Members of 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), Fumihiko Matsuda (Japan) and Hans Georg Zachau (Germany) (1930-2017). Members of the SubCommittee are experts and contributors to the field of immunogenetics who in their published work have promoted standardization of the IMGT IG, TR and/or MH genes and alleles. Associated to IMGT-NC are the IMGT Experts who are contributors on a case by case basis for IG, TR and/or MH loci of given species (http://www.imgt.org/IMGTindex/IMGTexperts.php).

Summary reports written by the IMGT-NC are sent on an annual basis to the chair of the WHO-IUIS Nomenclature (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 IMGT-NC events, publications and/or reports since its creation in 1989 are publicly available at http://www.imgt.org/IMGTindex/IUIS-NC.php.

## III. New IG and TR genes and alleles

The biocuration of new IG and TR genes and alleles is done by the IMGT® team. This includes polymorphic genes from humans and genes of newly sequenced genomes of any species of vertebrates with jaws (*gnasthomata*) others than humans.

The complete annotation of new IG and TR genes and alleles is performed based on the IMGT-ONTOLOGY concepts and IMGT Scientific chart rules: standardized identification (keywords), description (labels), classification (genes and alleles nomenclature) and numerotation (IMGT unique numbering).

New IG and TR genes and alleles are entered in the IMGT web resources (IMGT Repertoire Gene tables, Alignments of alleles, Protein displays, etc.), databases (IMGT/LIGM-DB, IMGT/GENE-DB, IMGT/3Dstructure-DB and IMGT/2Dstructure-DB, etc) and tools (IMGT/V-QUEST, IMGT/DomainGapAlign, etc) and are publicly and freely available to the academics.

Following the entry of a new IG or TR gene in IMGT/GENE-DB – which marks its official approval by IMGT® – the IMGT-NC chair informs the Human Genome Organization (HUGO) Gene Nomenclature Committee (HGNC) and the National Center for Biotechnology Information (NCBI Gene) of the new gene and of its IMGT gene name (symbol and definition, reference sequence, genome localization, functionality). Reciprocal links for individual entries are created between the three sites IMGT, HGNC and NCBI Gene.

IG and TR alleles are under the entire responsibility of IMGT® since its creation in 1989 (Human Gene Mapping 10 workshop, New Haven). They were published for the first time in the Immunoglobulin FactsBook (2001) and in the T cell receptor FactsBook (2001). The IG and TR alleles are currently managed in IMGT/GENE-DB and displayed in Alignments of alleles. There are fully annotated and entered in the IMGT® web resources, databases and tools as described above.

On April 29, 2018, IMGT/GENE-DB, the IMGT® gene database, contained 4,944 IMGT genes and 6,878 alleles from 26 species.
• 706 IG and TR genes and 1,360 alleles for *Homo sapiens* (462 IG genes and 935 alleles; 244 TR genes and 425 alleles) as well as 11 RPI and 135 alleles
• 686 IG and TR genes and 746 alleles for *Macaca* (478 genes and 529 alleles for *Macaca mulatta*),
• 892 IG and TR genes and 1,345 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.

Updates of the IMGT reference directories are reported in the Documentation of the corresponding IMGT® tools.

**IV. Recent accomplishments**

1) Major individual external submissions to IMGT-NC (since Report 2017, November 22)

Acknowledgement to Catherine Scheepers (Sandringham, South Africa) for her submission of 36 genomic sequences with INSDC accession numbers on 15/12/17. The sequences were found in 1, 2 or 3 individuals (total 47 sequences), or found twice in the same individual. The submission concerns 11 different genes (not including the duplicated genes), 17 known alleles; 8 new alleles (1 IGHV1-8 (*03), 2 IGHV1-69 (*15, *16), 2 IGHV2-26 (*02, *03), 3 IGHV2-70 (*15, *16, *17) (Results from IMGT-NC 26/12/17).
Following the classical IMGT procedure, these alleles led to:
1. Entry of the sequences in IMGT/LIGM-DB and IMGT annotation
http://www.imgt.org/ligmdb/view?format=IMGT&id=MG719328
2. Update of GeneTable
http://www.imgt.org/IMGTrepertoire/index.php?section=LocusGenes&repertoire=genetable&species=human&group=IGHV
3. Update of Alignments of allele
http://www.imgt.org/IMGTrepertoire/Proteins/alleles/index.php?species=Homo%20sapiens&group=IGHV&gene=IGHV1-69%20and%20IGHV1-69D
4. Update of the IMGT reference directories (nucleotide and amino acid sequences)
Lefranc et al. Nucleic Acids Res. 2015;43:D413-22. PMID: 25378316

2) Entry of 107 *Homo sapiens* IG variable genes in UniProt

IMGT/GENE-DB reference sequences of 107 *Homo sapiens* IG genes were provided by IMGT to UniProt and the translation of these genes entered in the database by the UniProt team. They include 37 IGHV, 38 IGKV and 32 IGLV. Reciprocally, cross-references were added from IMGT/GENE-DB to UniProt for these entries.
This collaborative work between IMGT and UniProt on the sequences of the IGHV, IGKV and IGLV genes is a major step, at the international level, based on the IMGT gene nomenclature (IMGT gene names approved by HGNC in 1999 and endorsed by NCBI in 2000).
The IMGT alleles of the IG genes are defined at the nucleotide levels, and allele query should be done in IMGT/GENE-DB, however for completeness and correspondence between the databases, the IMGT allele of the sequence provided by IMGT is reported in UniProt.

Announced in the Report 2017, November 22, this entry of IMGT IG variable genes in UniProt has led to two communications:

Poux S, Argoud-Puy G, Breuza L, Lefranc M-P, IMGT®, the international ImMunoGenetics information system® and UniProt Consortium.
*Representative functional immunoglobulin (IG) genes in UniProtKB/Swiss-Prot.*
Comm. Poux S. 11th International Biocuration Conference (IBC).
Shanghai, China, April 8-11, 2018.

Argoud-Puy G, IMGT®, the international ImMunoGeneTics information system®, and The UniProt Consortium
*Representative functional immunoglobulin (IG) genes in UniProtKB/Swiss-Prot*
Poster 13th [BC]² - the Basel Computational Biology Conference.
Basel, Switzerland, September 12-15, 2017.

3) Nomenclature and next generation sequencing (NGS) of IG and TR

IMGT/HighV-QUEST, http://www.imgt.org/HighV-QUEST/login.action the web portal created in October/November 2010, and currently the only online tool freely available for academics for the analysis of Next Generation Sequencing (NGS) data for the study of repertoires of immunoglobulins (IG) and T cell receptors (TR) in normal and pathological situations, 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 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.

4) 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 structure 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. This long-term collaboration for standardization has recently been formalized between IUIS and WHO.

5) 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
The publication has reached 11,307 views on April 29, 2018.
UniProt has made a link to that publication in the abstract of the files of the 107 IG variable genes. HGNC has quoted this reference in the two introductory pages on the IG and TR.

**V. Ongoing projects**

1) Collaboration with HGNC, Ensembl, NCBI, UniProt.
2) Collaboration with the European Research Initiative on CLL (ERIC).
3) Collaboration with the EuroClonality-NGS consortium.
4) Collaboration with 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 the 2012 Sub-Committee report.
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).

**VI. Challenges and opportunities in 2018**

**Large scale genome sequencing**

1) IMGT/GENE-DB biocuration and nomenclature of IG and TR genes and alleles of species from newly sequenced genomes.
A landmark is represented by the approved IMGT nomenclature of the IG and TR loci of *Canis lupus familiaris* (Martin et al. 2018) which will be used as a benchmark for other species. The *Canis lupus familiaris* reference sequences have been entered in IMGT/HighV-QUEST reference directories allowing NGS repertoire analysis

2) IMGT-NC is currently developing the concept of localization to annotate and manage the copy number variations (CNV) and polymorphisms by insertion/deletion in the *Homo sapiens* IG and TR loci.

3) A working group (WG) within AAIR intends to analyse the criteria for defining inferred alleles from NGS (the procedure would include a submission of inferred alleles validated by the WG to a generalist database, before submission to the IMGT-NC). If IMGT data quality requirement is preserved, inferred

alleles could be considered in the IMGT reference directories of IMGT/V-QUEST and IMGT/HighV-QUEST.

**Pespectives**

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.

**VII. Selected recent publications derived from the work of the committee**


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

Baliakas P, Mattsson M, Hadzidimitriou A, Minga E, Agathangelidis A, Sutton L-A, Scarfo L, Davis Z, Yan X-J, Plevova K, Sandberg Y, Vojdeman FJ, Tzenou T, Chu CC, Veronese S, Mansouri L, Smedby KE, Giudicelli V, Nguyen-Khac F, Panagiotidis P, Juliusson G, Anagnostopoulos A, Lefranc M-P, Trentin L, Catherwood M, Montillo M, Niemann CU, Langerak AW, Pospisilova S, Stavroyianni N, Chiorazzi N, Oscier D, Jelinek DF, Shanafelt T, Darzentas N, Belessi C, Davi F, Ghia P, Rosenquist R, Stamatopoulos K.
No improvement in long-term survival over time for chronic lymphocytic leukemia patients in stereotyped subsets #1 and #2 treated with chemo(immuno)therapy.
Haematologica. 2017 Dec 21. pii: haematol.2017.182634. doi:10.3324/haematol.2017.182634. [Epub ahead of print] No abstract available. Free Article.
PMID: 29269523

Hemadou A, Giudicelli V, Smith ML, Lefranc M-P, Duroux P, Kossida S, Heiner C, Hepler NL, Kuijpers J, Groppi A, Korlach J, Mondon P, Ottones F, Jacobin-Valat M-J, Laroche-Traineau J, Clofent-Sanchez G.
Pacific Biosciences sequencing and IMGT/HighV-QUEST analysis of full-length single chain Fragment variable from an *in vivo* selected phage-display combinatorial library.
Front. Immunol. 2017 Dec 20 8:1796. doi: 10.3389/fimmu.2017.01796. Free PMC Article.
PMID: 29326697

Deiss TC, Vadnais M, Wang F, Chen PL, Torkamani A, Mwangi W, Lefranc M-P, Criscitiello MF, Smider VV.
Immunogenetic factors driving formation of ultralong VH CDR3 in *Bos taurus* antibodies.
Cell Mol Immunol. 2017 Dec 4. doi: 10.1038/cmi.2017.117. [Epub ahead of print].
PMID: 29200193

Rubelt F, Busse CE, Bukhari SAC, Bürckert JP, Mariotti-Ferrandiz E, Cowell LG., Watson CT, Marthandan N, Faison WJ, Hershberg U, Laserson U, Corrie BD, Davis MM, Peters B, Lefranc M-P, Scott JK, Breden F; AIRR Community, Luning Prak ET, Kleinstein SH
Adaptive Immune Receptor Repertoire Community recommendations for sharing immune-repertoire sequencing data
Nat Immunol. 2017 Nov 16; 18(12):1274–1278. doi:10.1038/ni.3873.
PMID: 29144493

Breden F, Luning Prak ET, Peters B, Rubelt F, Schramm CA, Busse CE, Vander Heiden JA, Christley S, Bukhari SAC, Thorogood A, Matsen IV FA, Wine Y, Laserson U, Klatzmann D, Douek DC, Lefranc M-P, Collins AM, Bubela T, Kleinstein SH, Watson CT, Cowell LG, Scott JK, Kepler TB
Reproducibility and reuse of Adaptive Immune Receptor Repertoire data
Front Immunol. 2017 Nov 1;8:1418. doi: 10.3389/fimmu.2017.01418. eCollection 2017. Free PMC Article Open access
PMID:29163494

Giudicelli V, Duroux P, Kossida S, Lefranc M-P.
IG and TR single chain Fragment variable (scFv) sequence analysis: a new advanced functionality of IMGT/V-QUEST and IMGT/HighV-QUEST
BMC Immunol. 2017 Jun 26;18(1):35. doi: 10.1186/s12865-017-0218-8.
PMID: 28651553

Prieur A, Cappellini M, Habif G, Lefranc M-P, Mazard T, Morency E, Pascussi J-M, Flacelière M, Cahuzac N, Vire B, Dubuc B, Durochat A, Liaud P, Ollier J, Pfeiffer C, Poupeau S, Saywell V, Planque C, Assenat E, Bibeau F, Bourgaux J-F, Pujol P, Sézeur A, Ychou M, Joubert D.
Targeting the Wnt pathway and cancer stem cells with anti-progastrin humanized antibodies: a major breakthrough for K-RAS mutated colorectal cancer treatment
Clinical Cancer Res. 2017 Sep 1;23(17):5267-5280. doi: 10.1158/1078-0432.CCR-17-0533. Epub 2017 Jun 9.
PMID: 28600477

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Chronic lymphocytic leukemia with mutated IGHV4-34 receptors: shared and distinct immunogenetic features and clinical outcomes
Clin Cancer Res. 2017 Sep 1;23(17):5292-5301. doi: 10.1158/1078-0432.CCR-16-3100. Epub 2017 May 23.
PMID: 28536306

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Immunoglobulin gene sequence analysis in chronic lymphocytic leukemia: updated ERIC recommendations
Leukemia. 2017 Jul;31(7):1477-1481. doi: 10.1038/leu.2017.125. Epub 2017 Apr 25.
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High-throughput immunogenetics for clinical and research applications in immunohematology: potential and challenges.
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PMID: 28416603

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Mol Cell Proteomics. 2017 May;16(5):824-839. doi: 10.1074/mcp.M116.064733. Epub 2017 Mar 6.
PMID: 28265047 Free Article.

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Novel structural parameters of IG - Ag complexes yield a quantitative description of interaction specificity and binding affinity
Front. Immunol. 2017, 8:34. doi: 10.3389/fimmu.2017.00034
PMID: 28232828 Free PMC Article
http://journal.frontiersin.org/article/10.3389/fimmu.2017.00034/abstract

Montpellier, April 29, 2018