

ANNUAL REPORT OF THE IUIS NOMENCLATURE COMMITTEE (2014-2015)

by Pablo Engel

Mission:

The mission of the different IUIS Nomenclature subcommittees is to establish a universal and consistent nomenclature for both molecules and cells of the immune system.

Main goal:

The main goal is to create a unambiguous, flexible, informative, neutral nomenclature, and if possible easy to remember and simple, in order to facilitate the communication between scientists in the fields of immunology and biomedicine. It is of key importance to establish a common language for diagnosis and therapy of diseases related to alterations of the immune system and also basic research.

Recent Accomplishments:

The IUIS subcommittees have been establishing the nomenclature of different molecules of the immune system during more than 20 years.

More recently, new committees have been also created for the nomenclature of cells and cellular subsets.

Current Nomenclature Subcommittees and chairs:

Allergen Nomenclature Subcommittee: Chair Richard Godmann

CD Nomenclature Subcommittee: Chair Pablo Engel

IG, TR and MH Nomenclature Subcommittee: Chair Marie-Paule Lefranc

Monocytes and Dendritic Cells in Blood Subcommittee: Chair: Loems Ziegler-Heitbrock

KIR Nomenclature Subcommittee: Chair: Steve Marsh

MALT Nomenclature Subcommittee Chair: Per Brandtzaeg

B cells and plasma cells: Chair Ignacio Sanz

Atypical chemokine receptors Chair Phil Murphy

Complement. Chair: Andrea Tenner

Further Directions

1) Continue the work of current Nomenclature subcommittees.

2) Create new Nomenclature subcommittees to cover all the molecules and cells of the immune system

A new subcommittee should consist of scientists coming from various parts of the world, well known in a specific field, and endorsed by their society or the scientific community.

The new subcommittee has to have a list of members in order to build standing committees.

3) To disseminate the approved Nomenclature to the scientific community using the IUIS web side.

Approval and proposal of new Nomenclature Subcommittees at the 63nd IUIS Council Meeting

1) Innate Lymphocytes. Chair: Marco Colonna (USA)

Borad to be determined.

Publication: Spits H, Artis D, Colonna M, Diefenbach A, Di Santo JP, Eberl G, Koyasu S, Locksley RM, McKenzie AN, Mebius RE, Powrie F, Vivier E. Innate lymphoid cells--a proposal for uniform nomenclature. *Nat Rev Immunol.* 2013;13:145-9

2) Cytokines and interferons

supported by International Cytokine and Interferon Society (formerly ISICR and ICS) (<http://cytokines-interferons.org/>) Chair and board to be determined.

List publications 2014-2015

- Radauer C, Nandy A, Ferreira F, Goodman RE, Larsen JN, Lidholm J, Pomés A, Raulf-Heimsoth M, Rozynek P, Thomas WR, Breiteneder H. Update of the WHO/IUIS Allergen Nomenclature Database based on analysis of allergen sequences. *Allergy*, 2014, 69(4):413-419; is an open access publication.
- Breiteneder H, Chapman MD. Allergen Nomenclature. In *Allergens and Allergen Immunotherapy: Subcutaneous, sublingual and oral*. 5th Edition. Edited by Richard F. Lockey and Dennis K. Ledford. CRC Press, Taylor and Francis Group, Boca Raton, Florida, USA, 2014, pp 37-49.
- Lefranc MP. Immunoglobulin and T Cell Receptor Genes: IMGT(®) and the Birth and Rise of Immunoinformatics. *Front Immunol.* 2014;5:22.
- Lefranc MP. Immunoinformatics of the V, C, and G domains: IMGT® definitive system for IG, TR and IgSF, MH, and MhSF. *Methods Mol Biol.* 2014;1184:59-107.
- Alamyar E, Giudicelli V, Duroux P, Lefranc MP. Antibody V and C domain sequence, structure, and interaction analysis with special reference to IMGT®. *Methods Mol Biol.* 2014;1131:337-81.
- Robinson J, Halliwell JA, Marsh SG. IMGT/HLA and the Immuno Polymorphism Database. *Methods Mol Biol.* 2014;1184:109-21.
- Bachelierie F, Graham GJ, Locati M, Mantovani A, Murphy PM, Nibbs R, Rot A, Sozzani S, Thelen M. New nomenclature for atypical chemokine receptors. *Nat Immunol.* 2014;15:207-8. doi: 10.1038/ni.2812.
- Bachelierie F, Graham GJ, Locati M, Mantovani A, Murphy PM, Nibbs R, Rot A, Sozzani S, Thelen M. An atypical addition to the chemokine receptor nomenclature: IUPHAR Review 15. *Br J Pharmacol.* 2015;172:3945-9.
- Lefranc MP, Giudicelli V, Duroux P, Jabado-Michaloud J, Folch G, Aouinti S, Carillon E, Duvergey H, Houles A, Paysan-Lafosse T, Hadi-Saljoqi S, Sasorith S, Lefranc G, Kossida S. IMGT®, the international ImMunoGeneTics information system® 25 years on. *Nucleic Acids Res.* 2015; 43(Database issue):D413-22.

- Robinson J, Halliwell JA, Hayhurst JD, Flicek P, Parham P, Marsh SG. The IPD and IMGT/HLA database: allele variant databases. *Nucleic Acids Res.* 2015;43(Database issue):D423-31.
- Engel P, Boumsell L, Balderas R, Bensussan A, Gattei G, Horejsi V, Jin BQ, Malavasi F, Mortari F, Schwartz-Albiez R, Stockinger H, van Zelm M, Zola, Clark G. CD Nomenclature 2015. Human Leukocyte Differentiation Antigen (HLDA) Workshops as a driving force in immunology. *J Immunol.* 2015 (in press)

Sub-Committee on CD Molecules

Chair: Pablo Engel (pengel@ub.edu)
University of Barcelona (Spain)

Website: www.HCDM.org

List of current committee members

Pablo Engel
(President HCDM and IUIS Nomenclature Chair)
Georgina Clark (Australia)
(Chair of HLDA10)

Robert Balderas (USA)
Armand Bensussan (France)
Georgina Clark (Australia)
David Fox (USA)
Valter Gattei (Italy)
Bo-Quan Jin (China)
Frank Mortari (USA)
Hannes Stockinger (Austria)
Menno C. van Zelm (The Netherlands)

A new HCDM council will be appointed at the ICI Melbourne 2016.

I. Objective

To establish the nomenclature and validation of monoclonal antibodies against leukocyte cell-surface molecules and other cell-surface molecules of the immune system

II. Recent Accomplishments

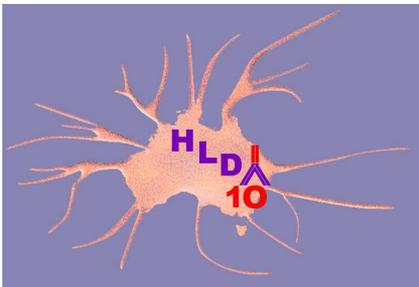
- The HLDA10 Workshop and was organized by Dr. Georgina Clark (Sidney, Australia) and a panel of mAbs preferentially recognizing dendritic markers was analysed.

- Seven new CD were established (CD365-CD371).

CD Number	Gene Name	Full Name (NCBI)	Alternate Names	Gene Family
CD365	HAVCR1	hepatitis A virus cellular receptor 1	TIM-1; HAVCR-1; TIMD1	Immunoglobulin SF
CD366	HAVCR2	hepatitis A virus cellular receptor 2	TIM-3; TIMD3	Immunoglobulin SF

CD367	CLEC4A	C-type lectin domain family 4, member A	DCIR; DDB27; CLECSF6	C-type lectin SF
CD368	CLEC4D	C-type lectin domain family 4, member D	MCL; CLECSF8; CLEC-6; MPCL	C-type lectin SF
CD369	CLEC7A	C-type lectin domain family 7, member A	DECTIN-1; CLECSF12;	C-type lectin SF
CD370	CLEC9A	C-type lectin domain family 9, member A	HEEE9341; UNQ9341; DNGR1	C-type lectin SF
CD371	CLEC12A	C-type lectin domain family 12, member A	CLL-1; MICL; DCAL-2	C-type lectin SF

- HLDA10 Conferences was held in Wollongong (Australia) 1st-2nd December 2014.



- The new HCDM/HLDA web www.hcdm.org has been improved. The contribution of the IUIS is acknowledged at the web page.

III. Ongoing Projects

- The organization of HLDA11 Workshop focused on Seven-span receptors and ion channels.

- Improve the HCDM web page (www.hcdm.org) with information the structure and function of cell-surface molecules, and the application of mAbs for the diagnosis and therapy.

- Publish a special issue with the results of HLDA10 workshop in Clinical & Translational Immunology a new open access journal of the Nature group. This special issue will contain 12 papers.

- The CD Maps project. This project consists of the analysis of the expression of all CD molecules using 8 colour-flow cytometry, and will allow the quantitative determination of the expression of these cell markers in leukocyte and lymphocyte subsets of the blood, tonsil and thymus. This project is done in collaboration with members of *EuroFlow Consortium* (www.euroflow.org/) and the support BD Bioscience, Biogend and ExBio companies. The results corresponding to CD1 to CD100 will be ready for analysis by the end of 2015.

IV. Future Directions

- Continue ascribing CD names to molecules recognized by well validated monoclonal antibodies.
- Generate a data base of actual expression profiles by FACS analysis of all CD molecules on all known leukocyte and lymphocyte subsets. Make this data base freely available to academic groups.
- Start the organization of HLDA11 workshop.
- Prepare guidelines for monoclonal antibody standardization.

V. Publication

Engel P, Boumsell L, Balderas R, Bensussan A, Gattei G, Horejsi V, Jin BQ, Malavasi F, Mortari F, Schwartz-Albiez R, Stockinger H, van Zelm M, Zola, Clark G.

CD Nomenclature 2015. Human Leukocyte Differentiation Antigen (HLDA) Workshops as a driving force in immunology. **Journal of Immunol.** 2015 (in press)

Nomenclature subcommittee on the Immunoglobulins (IG), T cell Receptors (TR) and Major Histocompatibility (MH)

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, UPR CNRS 1142

Web page: www.imgt.org

List of subcommittee members

Donald Capra (USA)

Max Cooper (USA)

Tasuku Honjo (Japan)

Leroy Hood (USA)

Gérard Lefranc (France)

Marie-Paule Lefranc (France)

Fumihiko Matsuda (Japan)

Hans Zachau (Germany)

Cynthia L. Baldwin (USA)

Eva Bengtén (USA)

Pierre Boudinot (France)

Felix Breden (Canada)

Salvatrice Ciccarese (Italy)

Deborah Dunn-Walters (UK)

Jean-Pol Fripiat (France)

Véronique Giudicelli (France)

Evelyne Jouvin-Marche (France)

Sofia Kossida (France)

Véronique Laurens (France)

Serge Muyldermans (Belgium)

Jamie Scott (Canada)

Bettina Wagner (USA)

Corey T. Watson (USA)

I. Objective

The goal of this Sub-Committee and IMGT-NC is the standardization of the immunoglobulins

(IG), T cell receptors (TR) and major histocompatibility (MH) genes and alleles from any

vertebrates with jaws (*gnathostomata*) from fishes to humans.

II. Recent Accomplishments

1) In September 2015, IMGT/GENE-DB, the IMGT® gene database contained 3,570 IMGT genes and

5,267 alleles from 22 species.

- 718 IG and TR genes and 1,478 alleles for *Homo sapiens*,

- 487 IG and TR genes and 544 alleles for *Macaca* (478 genes and 529 alleles for *Macaca mulatta*),

- 890 IG and TR genes and 1,343 alleles for *Mus* (869 genes and 1319 alleles for *Mus musculus*),

- 560 IG and TR genes and 564 alleles for *Rattus norvegicus*. Other statistics are available at <http://www.imgt.org/genedb/stats>.

2) 2014 marked the 25 years of IMGT®, the international ImMunoGeneTics information system® (<http://www.imgt.org>), creation of which in New Haven in 1989, was at the origin of immunoinformatics.

A publication in *Frontiers in Immunology*, invited by the WHO/IUIS Nomenclature Committee, retraces the development on the immunoglobulin and T cell receptor genes

<http://journal.frontiersin.org/Journal/10.3389/fimmu.2014.00022/abstract> (3,214 views in September 2015).

III. Ongoing Projects

- 1) Collaboration with HGNC, Vega, Ensembl, NCBI.
- 2) Addition of reciprocal links to IUPHAR-DB and to IEDB.
- 3) 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 WHO/IUIS/IMGT nomenclature approved by Human Genome Organization (HUGO) Nomenclature Committee (HGNC).
- 4) IMGT/HighV-QUEST, 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 and T cell receptors in normal and pathological situations, accepts 500.000 sequences per batch and one million sequences for statistical analysis. A novel functionality 'identification and characterization of IMGT clonotypes (AA)' is based on the IG and TR gene and allele names. IMGT/HighV-QUEST promotes the use of the WHO/IUIS/IMGT IG and TR nomenclature for genes and alleles.

III. Future directions

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. We are 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.

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 WHO/IUIS/IMGT nomenclature for new data originating from genome analysis, repertoire next generation sequencing and antibody engineering.

Montpellier, September 28, 2015

Report of the WHO/IUIS Nomenclature Committee for the Killer-cell Immunoglobulin-like Receptors (KIR) –
by Steven March

October 2015

The work of the WHO/IUIS Nomenclature Committee for the Killer-cell Immunoglobulin-like Receptors (KIR) is to provide naming conventions for the KIR genes, alleles and haplotypes. As such, a meeting took place in 2002 that is reported in Marsh *et al.* (2003) that established criteria for the acceptance and naming of KIR genes and alleles and formulated proposals for a KIR haplotype naming systems to be implemented at a point in the future when technologies were adequate. The naming of the KIR genes remains the ultimate responsibility of the HUGO Gene.

Nomenclature Committee (HGNC), and we have worked closely with this group. The IPD-KIR Database has been the official repository for the KIR allele sequences since it's first release in 2003 (Robinson *et al.* 2005, 2013). Since 2002 we have had over 1200 submissions of KIR sequences to the IPD-KIR Database from researchers around the world. These have resulted in 843 officially named KIR allele sequences, with 117 novel sequences being submitted during 2014. A further 48 alleles have been submitted in the first nine months of 2015. The IPD-KIR Database has seen 15 full releases over this period, with the last being in February 2015 [IPD-KIR Release 2.6.1]. This release included 753 publically available KIR allele sequences, derived from 1023 component ENA/GenBank/DDBJ sequence entries, and 925 source cells. The database includes sequences of both the coding regions and also the full genomic sequences from the 5' to 3' UTRs. The technology for defining KIR allele sequences has been slow to progress, meaning that most KIR typing that is being routinely performed relies on defining only the presence or absence of KIR genes, and not their allelic content. This has meant the discovery rate of new KIR alleles has been slow: however, the adoption of next generation sequencing technologies suggests this is due to increase in the near future. The work of the IPD-KIR Database is funded by an NIH/NCI grant [P01 111412]. The IPD website received over 70,000 unique visitors during 2014, viewing over 1 million pages, with the IPD-KIR section remaining one of the most popular sections of the IPD project. The IPD-KIR the home page receives on average over 8,000 views per year, and the IPD-KIR alignment tool performs around 10,000 sequence alignments annually.

Full and co-opted members of the KIR Nomenclature Committee have met biannually at the KIR Workshops to discuss issues around the KIR Nomenclature. At the present time our main aim is to introduce a formal nomenclature for KIR haplotypes, and we are currently working on proposals for discussion. The complexity of the KIR haplotype structure, and the similarity in KIR gene sequences has made this task very difficult to achieve, and almost impossible to implement without access to the sequence of the entire KIR region for each haplotype. We are currently limited by the technology at our

disposal and are mindful not to implement a nomenclature that while elegant and informative, is impossible to use.

Committee

SGE Marsh *Chairman* Anthony Nolan Research Institute, London, UK
M Carrington, Frederick Cancer Research & Development Centre, Frederick, USA

DE Geraghty, Fred Hutchinson Cancer Center, Seattle, USA

D Middleton, Royal Liverpool University Hospital, Liverpool, UK

P Parham, Stanford University School of Medicine, Stanford, USA

J Trowsdale, Cambridge University, Cambridge, UK

Co-Opted Members

P Norman, Stanford University School of Medicine, Stanford, USA

C Hurley, Georgetown University, Washington DC, USA

References:

Marsh SGE, Parham P, Dupont B, Geraghty DE, Trowsdale J, Middleton D, Vilches C, Carrington M, Witt C, Guethlein LA, Shilling H, Garcia CA, Hsu K, Wain H : Killer-cell Immunoglobulin-like Receptor (KIR) Nomenclature Report, 2002. *Tissue Antigens* (2003) **62** 79-86, *Human Immunology* (2003) **64** 648-654, *European Journal of Immunogenetics* (2003) **30** 229-234, *Immunogenetics* (2003) **55** 220-226, *Journal of Immunological Methods* (2003) **281** 1-8

Robinson J, Waller MJ, Stoehr P, Marsh SGE : IPD – the Immuno Polymorphism Database. *Nucleic Acids Research* (2005) **33** D523-D526

Robinson J, McWilliam H, Lopez R, Marsh SGE : IPD – the Immuno Polymorphism Database. *Nucleic Acids Research* (2013) **41** D1234-D1240

2015-08-19

Executive Summary of Nomenclature of Blood Monocytes and Dendritic Cells

by Prof L. Ziegler-Heitbrock

This report covers the current status of a) the Nomenclature of Blood Monocytes and Dendritic Cells, b) the Nomenclature initiative for tissue macrophages and DCs and the c) Nomenclature for the precursors of monocyte/macrophages and DCs

a) For blood monocytes the subdivision into classical, intermediate and non-classical monocytes is now well established in the community. For dissection of intermediate and non-classical monocytes the slan marker can be recommended. An emerging subset is the FcεRI+ monocyte.

For blood DCs the subsets CD1c+ DC, CD141+DC and the CD303+ plasmacytoid DCs are consolidating. A potential addition is the precursor for CD1c+ and CD141+DCs that is found in blood.

A meeting of the Committee is prepared for the 2017 EMDS conference in Spain.

b) Nomenclature initiative for tissue macrophages and DCs

A discussion group has formed on this and based on a suggestion by Pablo Engel I have joined that group. We have generated 16 papers in Frontiers in Immunology and a consensus document will be put together. Some contribution of ontogeny is emerging in that monocyte/macrophage-derived dendritic cells are to be separated from bona fide dendritic cells.

A separate issue is the M1 and M2 macrophage concept, on which I had exchanges with Alberto Mantovani. M1 and M2 describes the extremes of a spectrum of macrophages activated by cytokines like IFNγ and IL4 and cells with such signatures may occur in various tissue macrophages. These tissue macrophages will have their tissue specific signature and on top of that a cytokine-specific signature. However, the marriage of the two concepts needs to be substantiated with experimental data.

c) Nomenclature for the precursors of monocyte/macrophages and DCs

The definition of precursors has led to the description of cMoPs (to date only in the mouse), to MDPs in the mouse, the existence of which in careful studies has been disputed, and in man to the definition of precursors for all DCs and precursors for CD1c+ and CD141+ DCs. The field is still in flux and is complicated by different types of data in man and mouse. A consensus on this may emerge with more data on cloning, fate mapping and transcriptomics.

Report on the nomenclature for monocytes and dendritic cells in blood, Update August 2015

We have extended the previous document rather than drafting a new one, in order to have a complete compilation of the new aspects in a single document for committee discussions.

The previous text is given in grey. Additions for the Update put together in August 2015 have been added **black**.

Loems Ziegler-Heitbrock, Helmholtz Zentrum Muenchen, Robert-Koch-Allee 1, 82131 Gauting, Germany, e-mail LZH@monocyte.eu

Use of the new nomenclature

The crucial paper for the new nomenclature is the publication in BLOOD journal in 2010¹

As of April 30th, 2013 this paper has been referenced more than 130 times².

As of August 19th, 2015 this paper has been referenced more than 400 times².

In order to reflect the use of the new nomenclature for monocytes we searched in Google Scholar for publications that use the terms “nonclassical monocyte or classical monocyte” and this revealed 179 publications. For the intermediate monocytes a series of about 20 articles has appeared since its delineation in the original nomenclature document. Hence the new terminology for monocytes has been widely accepted. A Google Scholar search for the term classical monocyte revealed 443 publications. For intermediate monocytes more than 100 publications have appeared by August 2015. Apparently the definition of these cells in the nomenclature proposal has drawn attention to a type of cell that previously remained unrecognized because scientist did not know how to interpret the staining pattern of what now is called intermediate monocytes. In that sense the nomenclature has had a clear impact on the development of science in the field of monocytes.

As a criterion to track the use of the new nomenclature for DCs we performed a search in Google Scholar for “CD1c+ myeloid DC” and this revealed 33 publications. What was used more commonly was the term CD1c+ DC (156 times). It appears that the DC terminology has not been used as much when it comes to the word “myeloid”. This is fine since this additional term is not necessary as long as CD1c+ is used to unequivocally define this DC subset as compared to the CD141+ DCs (mentioned 63 times).

As of August 2015 the term “CD1c myeloid DC” was used in 59 publications and “CD1c DC” was used in 282 publications.

Hence it appears that the new nomenclature is spreading in the community.

This indicates that the new nomenclature is now well established.

Promoting the new nomenclature

The nomenclature had been initially published in BLOOD (*Blood*.2010;116:e74-e80) and under the IUIS home page

(<http://www.iuisonline.org/iuis/images/stories/docs/monosdc.pdf>). In order to publicise

the new nomenclature further we have entered a brief description under Wikipedia.org. Here under monocyte the section “monocyte subpopulations” was introduced and under the dendritic cell section we added a paragraph with the title “dendritic cells in blood”. This was done along with the relevant references. For your information please see: <http://en.wikipedia.org/wiki/Monocyte> and http://en.wikipedia.org/wiki/Dendritic_cell.

New activities in 2012 included a solicited review on monocyte subsets in *Frontiers in Inflammation* (Ziegler-Heitbrock, L, Hofer, TPJ: Toward a refined definition of blood monocytes, *Frontiers in Inflammation*, 4: 23, 2013).

New activities up to Aug 2015 includes

1. a review on monocytes in different species (Ziegler-Heitbrock, L : Monocyte subsets in man and other species *Cellular Immunology* 289 (2014) 135–139) and
2. a *Frontiers in Immunology* contribution Ziegler-Heitbrock, L: Blood monocytes and their subsets: established features and open questions in (August 2015 | Volume 6 | Article 423)

For details see further below.

Updating the new nomenclature

For monocytes the original nomenclature document has listed proliferating monocytes and 6-sulfo LacNAc+ and FcεRI+ monocytes as potential future additions. To date no additional manuscripts, which characterise FcεRI+ monocytes, have appeared.

Regarding the FcεRI+ monocytes a substantial number of these cells (2.5% of all monocytes) was noted to occur in children (Dehlink, E, Relationships between levels of serum IgE, cell-bound IgE, and IgE-receptors on peripheral blood cells in a pediatric population. *PLoS One* (2010)) and these cells were shown to be involved in clearance of serum IgE (Greer AM, .Serum IgE clearance is facilitated by human FcεRI internalization *J Clin Invest* (2014) **124**:1187–98, Shin&Greer, *Cellular and Molecular Life Sciences*, June 2015, Volume 72, Issue 12, pp 2349-2360). While there is little activity in this field the FcεRI+ monocyte is consolidating and its inclusion among the monocyte subsets can be discussed at the next Committee meeting and nomenclature update. For this, the enumeration of these cells in a large cohort of cases and controls with a standardized flow cytometry approach and the molecular characterization of these cells by e.g. transcriptome analysis would be desirable. In this context I have contacted Dr. J.S. Shin from UCSF).

For the 6-sulfo LacNAc+ monocytes two papers have appeared and both continue to address these cells as dendritic cells (Dobel, *Blood*, 2013 , Micheletti, *JLB*, 2013) although the reagent used is mentioned as MDC8+ monocyte isolation kit (see Micheltti, *JLB*, 2013). What would be required for the nomenclature committee in order to make a statement on the nature of the SLAN+ cells as monocytes is a publication defining with additional technology the monocyte features of these cells. This would extend the previous single report (Siedlar, *Immunobiology*, 202:11, 2000) on this issue.

There have been a couple more papers addressing slan positive monocytes as DCs (Bsat, J Leuk Biol, 2015, Thomas [Neurol Neuroimmunol Neuroinflamm.](#) 2014 Sep 18;1(3):e33, Rutella, [J Transl Med.](#) 2014 Sep 2;12:240, Brunner [J Allergy Clin Immunol.](#) 2013 Nov;132(5):1184-1193, Jähnisch, [Cancer Lett.](#) 2013 Jul 10;335(1):119-27). On the other hand expression of slan on CD16 monocytes has been confirmed (Dutertre, Blood. 2012 Sep 13;120(11):2259-68.). Finally the similarity of non-classical monocytes and slan-positive cells has been extended to the depletion by glucocorticoids (Thomas [Neurol Neuroimmunol Neuroinflamm.](#) 2014 Sep 18;1(3):e33).

We have conducted a comprehensive study into the use of slan to define non-classical monocytes versus intermediate monocytes and this is in press with BLOOD (Hofer et al, BLOOD, in press). This paper demonstrates that the slan marker can be used to clearly and unequivocally dissect the non-classical and the intermediate monocytes.

Based on this the next Committee Meeting may be able to decide on the allocation of slan-positive cells to the non-classical monocytes.

A new candidate has emerged with cells showing high CD14 and no CCR2, i.e. CD14⁺⁺CD16⁻ CCR2⁻ monocytes (Gama et al JLB, 2012). These cells increase with immunodeficiency virus infection and they are functionally distinct from the CD14⁺⁺CD16⁻ CCR2⁺ monocytes. They will be considered for inclusion pending confirmation and further characterization by independent groups. **No further publication on CCR2-negative CD14^{high} monocytes has appeared.**

For the intermediate monocytes a series of publications has appeared since its delineation in the original nomenclature document. This included transcriptome studies which show unique signatures (Wong, Blood, 2011, Zawada, Blood, 2011) and several reports on their increase in clinical settings and a study of their induction by TLR7/8 ligands in non-human primates (Kwissa Blood, 2012). While it appears that these cells are, in fact, in transition, their definition as a separate cell population also for clinical purposes is warranted. Several clinical reports have shown the increase the CD14⁺⁺CD16⁺ intermediate monocytes in inflammatory conditions.

A list of 37 papers which use the term “intermediate monocyte” in the abstract has been compiled (see Table 1). The definition of intermediate monocytes is easy with respect to CD16 expression since here an isotype control can be used to define the cut-off versus the classical monocytes. The cut-off versus the non-classical monocytes is to some extent arbitrary and it often cuts right through what appears to be a homogenous cell population (see Figure)

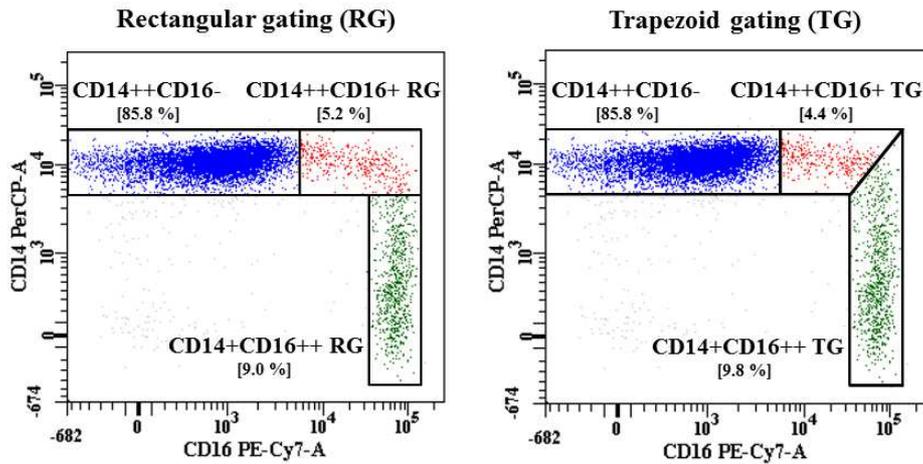


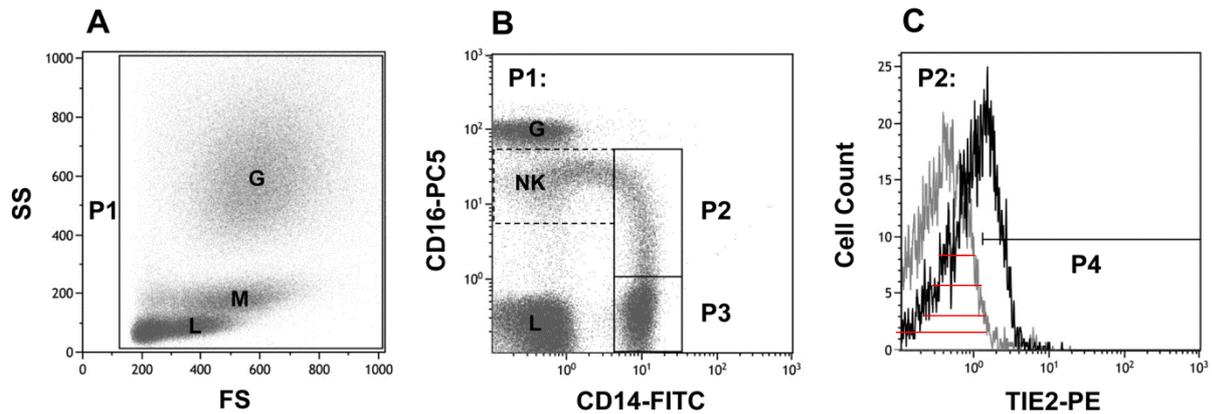
Figure 1

When an oblique line is used to dissect the non-classical and intermediates then this can slightly improve the predictive power of the intermediates (Zawada, *Cytometry A*. 2015 Aug;87(8):750-8). However, the difference is too small in order to suggest this as the appropriate strategy. What may provide a substantial improvement is the use of slan to define intermediate monocytes as slan- CD14++CD16+ cells.

An alternative approach that uses of CCR2 has been tested in a series of studies on cardiovascular disease (Shantsila, *Thromb Haemost.* 2013;110:340-8., *J Thromb Haemost.* 2011;9:1056-66). However, no relevant advantages of this approach have been demonstrated and molecular studies that document a superior separation when using CCR2 are lacking.

Tie2-expressing monocytes have been defined earlier in man and mouse (Da Palma 2005) and here Tie2 expression was found in CD16-positive monocytes (Venneri *Blood*, 2007) and more specifically in the intermediates (Murdoch *JIM* 2007). The recent study by Zawada et al has shown that the intermediate monocytes are the cells with a higher tie2 protein expression. An update of the nomenclature will draw attention to this finding and may suggest the use of the term intermediate monocyte for the Tie2 expressing monocytes.

Recently several additional papers on the Tie2 cells have appeared (Schauer, *Plosone* 7: e4450, 2012; Matsubara, *Hepatology*, 57:1416, 2013; Goede, *Cancer Invest*, 30:225, 2012, Patel, *EMBO Mol Med*, in press). Schauer (*Plosone* 7: e4450, 2012) noted that intermediate monocytes and not TIE2+ monocytes can be used for diagnostics of colon cancer. Here TIE2 expression was determined within the intermediates and only the cells, which localize to the right of the isotype control, were taken as positives (see below). This is, however, a misconception since also the cells overlapping with the isotype control are positive (see red shaded area).



In this context the committee chair has had discussions with the Zawada team and strategies to confirm the identity of the cells defined either as Tie2⁺ or intermediate monocytes have been discussed. No further clarification has emerged as to whether Tie2 can serve as a marker for a distinct monocyte subset.

Among dendritic cells the CD141⁺ myeloid blood DCs have been further characterized and the expression of markers like XCR1, Clec9A and the transcription factor IRF8 have strengthened the view that these DCs and the mouse CD8-positive DCs are homologous cells and share the property to cross-present exogenous antigen to CD8 T cells (Contreras J Immunol. 2010;185:3313-25. Crozat K. J Exp Med. 2010;207:1283-92. Bachem A J Exp Med. 2010;207:1273-81). Of note, in blood the respective mouse DCs do not express the CD8 antigen on the cell surface. XCR1 has been recently identified as a conserved universal marker for these DCs across tissues and species (for review see Villadangos and Shortman, JEM 2010). Studies using monoclonal antibodies against XCR1 are required in order to determine the usefulness of this marker for definition of these cells in flow cytometry.

For the CD1c⁺ myeloid DC in human blood it had been noted earlier that there are CD14⁻ and CD14^{low} cells and these have not been characterized further.

In the mouse the homologous blood DCs appear to be the CD11c⁺CD11b⁺CD45RA⁻ cells, which are the CD8⁻ DCs in the spleen. Splenic CD8⁻ DCs can be subdivided into Clec12A^{high} DCIR2 (Clec4a4)^{low} and the Clec12A^{low} DCIR2(Clec4a4)^{high} (Kasahara, JLB, 91:437, 2012). Also, in mouse blood the CD11c⁺CD11b⁺CD45RA⁻ DCs can be subdivided into CD172a⁺ (Sirpα⁺, 70%) and CD172a⁻ (Sirpα⁻, 30%) DCs (Proietto PNAS 2008). Hence it appears that for mouse blood DCs a further subdivision emerges but better and selective markers are needed to support this.

Two papers (Meredith, JEM, 2012 and Satpathy, JEM, 2012) have described the Zbtb46 molecule as marker expressed by mouse CD4⁺ and CD8⁺ DCs but not by plasmacytoid DCs in blood and spleen. Interestingly this marker was also found with the same pattern in human blood DCs.

Here discussions are underway as to whether a consensus on the mouse blood DCs and their preferred markers can be reached. However, the Zbtb46 protein is a transcription factor and therefore not readily accessible by flow cytometry. To this end a working cartoon has been used (see below).

In functional analysis Sanchez et al (1999) reported for the CD163+ subset a higher antigen presenting activity, a higher production of TNF and a lack of IL-10 production. More recently the same team has demonstrated that the CD163+CD14+SLA-II+ monocyte subset lacks CCR2 and shows a preferential expression of CX3CR1 (Moreno, Veterinary Research, 2010), which further strengthens the homology to the nonclassical monocytes in man.

Of note, the CD14+CD163+ MHC ClassII+ monocytes in the pig show the reverse expression pattern for CD163, since the nonclassical monocytes in man are essentially CD163 negative. Also in the pig CD16 is expressed by both subsets albeit higher in the CD163+ cells. Still, all the other features studied show a similar pattern for the non-classical CD14+CD16++ monocytes in man and the CD14+CD163+ MHC ClassII+ monocytes in the pig. There is also evidence for the existence of intermediate cells. New data have been provided by the Dominguez team on staining with a new TLR4 antibody and here stronger signal was seen on the non-classical monocytes with intermediate levels on the intermediate monocytes (Alvarez, Vet Immunol, Immunopathol, 2013)

A proposal for the use of the classical-intermediate-nonclassical nomenclature for pig monocytes will be put on the agenda for the next meeting of the nomenclature committee.

Regarding blood dendritic cells no data are available on the rat, while for the pig CD172low CD4+ DCs and CD172low CD4- interferon type I producing plasmacytoid DCs have been described (Summerfield, Immunology 2003, Balmelli, EJI 2005). Other than that data on blood DCs in these species are scarce.

For horse monocytes a CD16 antibody has been described and was shown to identify CD16-positive blood monocytes (Noronha, Veterinary Immunol Immunopathol 146: 135, 2012).

We plan on a meeting of the Blood Monocyte and Dendritic Cell Nomenclature Committee Members at the 2017 EMDS congress in Spain. For this we try to convince members to attend the conference and then participate in a workshop on nomenclature update.

We will invite additional scientist, who have contributed novel aspects for presentation and discussion at the workshop.

¹ Nomenclature of monocytes and dendritic cells in blood

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Manuscripts using the term "intermediate monocyte" in the abstract	
Chelombitko MA, Shishkina VS, Ilyinskaya OP, Kaminnyi AI, Pavluni	Acta Naturae. ;6:80-8.
A cytofluorometric study of membrane rafts in human monocyte su	2014
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Vereyken EJ, Kraaij MD, Baan CC, Rezaee F, Weimar W, Wood KJ, Le	PLoS One. ;8(7):e70152
A Shift towards Pro-Inflammatory CD16+ Monocyte Subsets with Pre	2013
Hearps AC, Martin GE, Angelovich TA, Cheng WJ, Maisa A, Landay AL	Aging Cell. ;11(5):867-875
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Braesch-Andersen S, Paulie S, Smedman C, Mia S, Kumagai-Braesch	PLoS One. ;8:e79908.
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Krychtiuk KA, Kastl SP, Pfaffenberger S, Lenz M, Hofbauer SL, Wonne	PLoS One. ;10:e0123367
Association of small dense LDL serum levels and circulating monocy	2015
Traunecker E, Gardner R, Fonseca JE, Polido-Pereira J, Seitz M, Villig	Eur J Immunol.;45:1414-25
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Surdacki A, Sulicka J, Korkosz M, Mikolajczyk T, Telesinska-Jasiowka	J Rheumatol.;41:481-9
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Klimek E, Mikolajczyk T, Sulicka J, Kwaśny-Krochin B, Korkosz M, Osr	Biomed Res Int.;2014:736853
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CD14(bright)CD16(low) intermediate monocytes expressing Tie2 are	2014
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Nomenclature covering macrophages and dendritic cells in tissue 2015-09-25

There has been an interest resolving some of the nomenclature issues for tissue macrophages and dendritic cells. Here a core group consisting of Florent Ginhoux, Marc Dalod and Martin Williams has suggested to consider ontogeny, i.e. to address cells with different precursors separately.

As suggested by Pablo Engel I have started discussions with these colleagues via detailed e-mail exchange (Florent Ginhoux, (e-mail 01.11. 2014), Marc Dalod (e-mail 22.10. 2014), Martin Williams (e-mail 10.11. 2014)). And we have made substantial progress.

Important issues in these discussions:

When we want to use ontogeny as a central point in the nomenclature then we have to keep in mind that a common progenitor is not sufficient to assign common names to the progeny. An informative example is the megakaryocyte-erythrocyte-progenitor (MEP) cell, which gives rise to either megakaryocytes and their platelet progeny or to erythroblasts and their red blood cell progeny (Debili, Blood 88 (1996) 1284-96. Klimchenko, Blood 114 (2009) 1506-17). Megakaryocytes and erythroblasts have a distinct transcriptome (Macauley, Blood 109 (2007) 3260-9) and they are involved in distinct functions, i.e. in blood clotting and oxygen transport, respectively. Therefore, although having a common ontogeny, these cells belong to clearly separate lineages.

On the other hand different precursors may give rise to similar progeny and it may not be relevant to distinguish such cells. With respect to macrophages in various tissues it is unclear whether an embryonic/fetal origin of these cells as opposed to a derivation from immigrating monocytes will make a relevant difference: these two types of cells have been shown to have a similar enhancer landscape. There are differences in the transcriptome of such cells and it is unclear whether this is a meaningful feature (Steffen Jung, Rehovot, personal communication).

Much of the concept is based on mouse data and before a nomenclature can be agreed there is an absolute need to confirm it in man or non-human primates. I have pointed out that there are many examples of an entirely different biology between man and mouse and have introduced into the discussion the slogan "avoid the mouse trap". Scientists who restrict themselves to mouse studies but extrapolate the findings to all mammalian species are caught in the mouse trap. I continue to make a strong point of this.

It has become clear that unbiased -omic data are an important adjunct for the definition of cells. For instance, transcriptomics is an informative tool to learn more about the nature of different cells and here proteomics, glycomics, metabolomics and epigenomics will have to be studied.

One helpful notion that has emerged from these discussions is that monocyte-derived dendritic cells need to be separated from bona fide dendritic cells. Transcriptomic analyses have shown that MoDCs have a transcriptome akin to monocytes and not to dendritic cells (Mabbott, [Immunobiology](#). 2010 ;215:724-36). Defining MoDCs as high APC macrophages will be an important step and will settle much debate in the field.

I have participated in this nomenclature initiative, which has materialized in the topic “Dendritic Cell and Macrophage Nomenclature and Classification” in FRONTIERS IN IMMUNOLOGY. The topic includes a set of 16 papers including my article

“Blood monocytes and their subsets: established features and open questions”, which highlights some of the issues explained above.

The contributions for this topic will be summarized in a consensus statement and this may lead to a nomenclature proposal, which is not comprehensive but suggests a few landmarks. I see my role in this is to make sure that this proposal is balanced, meets the IUIS standards and takes into account the points raised above.

A different initiative on the issue of M1 and M2 macrophages has been summarized in a consensus statement (Murray et al, Immunity, 41: 14, 2014). M1 and M2 cells are macrophages that have been activated by IFN γ and IL-4, respectively. As such they are not different macrophage cell types but just cells that have been activated by different signals.

In essence it has been agreed that M1 and M2 rather represent extremes of a spectrum of monocyte derived cells that have been stimulated with different sets of cytokines with the prototypic examples of IL-4 and IFN γ . This consensus statement does not lead to a nomenclature that can be easily married with the above initiative to define tissue macrophages. Rather the endpoint will be that an IL-4 signature or an IFN γ signature or an IL-10 signature can be detected with omic approaches in the various types of tissue macrophages.

Nomenclature covering macrophages and dendritic cells precursors

There are currently different models of the precursors for these cells in bone marrow. Also there are data from the two species man and mouse. And there are the changes in precursor cells during ontogeny, i.e during embryonic and adult life. These models are currently in flux. In the mouse, for instance, has the existence of the macrophage dendritic cell precursor (MDP) been disputed (Sathe, Immunity, 41: 104, 2014). More data with clonal analysis and fate mapping are required until a solid consensus can be reached in this field of precursors. This topic also includes the precursors for CD1c+ and CD141+ DCs that have been covered above.

Report of the Human B cell Nomenclature Sub-Committee

by Iñaki Sanz

ADD here comment form email

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Jen Anolik (Jennifer.Anolik@urmc.rochester.edu) proposed Co-Chair
Immature, Transitional and naïve B cells

I. Objective

The main goal of this committee is to establish a nomenclature on B cell and plasma subsets.

II. Ongoing Projects

- establish the general mandate, vision and specific goals of the subcommittee;
- proposed working classification of human B cell populations:

Working Nomenclature of human B cell populations.

<i>B cell population (CD19+ unless otherwise noted)</i>		<i>Markers</i>	<i>Function/Properties</i>
Transitional	T1/T2	CD24++CD38++CD10+CD27-IgM++	Developmental precursor
	T2-MZP	CD24++CD38++CD10+CD27-IgM++CD21+	Regulatory (IL-10) MZ precursor
	T3	CD24+CD38+CD10+/-CD27-IgM++IgD+	Developmental precursor
Naïve	Resting	CD24+/-CD38+/-CD27-IgM++/+IgD++CD21+ CD95-	Developmental precursor
	Activated	CD24-CD38-CD27-IgM++ IgD++CD21-CD95+MTG+	Precursor of short-lived PB and GC reactions
	Anergic	CD24-CD38-CD27-IgMlow/- IgD+	Hypo-responsive. Maintenance of tolerance
Memory	Unswitched	IgD+IgM+CD27+CD1c+	Natural memory MZ equivalent
	Pre-switched	IgM+IgD-CD27+	Pre-switch memory Early IgM memory

			IgG memory precursor
	Switched	Resting	IgG/IgA+CD27+CD21+ CD95-
		Activated	IgG/IgA+CD27+CD21- CD95+CD86+
	Atypical memory		IgM/IgG/IgA+CD27-FcRL4+
B1 cells	CD11b+ (B1orc)		IgM+IgD++CD43+CD27+ CD70- CD5+ CD11c+ CD14+
	CD11b- (B1sec)		IgM+IgD++CD43+CD27+ CD70- CD5+ CD11c- CD14+
Marginal zone	Spleen		IgD+IgM+CD27++ CD21++CD1c+
	Circulating		IgD+IgM+CD27+CD1c+
Antibody secreting cells	Circulating	Pre-PB	CD38++CD27+/-CD138-Ki67+
		PB	CD38++CD27++CD138-Ki67+
		PC	CD38++CD27++CD138+Ki-67+
	Bone marrow	Immature	CD38++CD27++CD138-Ki67-
		Mature	CD19+CD38++CD27++ CD138+Ki-67-
		Long-lived PC	CD19-CD38++CD27++ CD138+Ki67-
B regulatory cells	CD24hiCD38hi transitional cells		CD24++CD38++CD27-
			CD24++CD38++CD27-CD1d+
	B10 (no unique markers; defined by IL-10 production)		CD24hiCD27+ CD38+/- CD48++CD148++ IgM+/-IgD+/-
Proposed classification of human B cell subsets with surface phenotypic markers derived from multiple studies and our own work ¹⁻¹⁴ . Functions ascribed to these populations (or equivalent ones) in the literature are shown. Numeric or functional alterations demonstrated in at least some SLE studies are indicated.			

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