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Preparation of a nomenclature up-date workshop

An extension and up-date of the nomenclature is necessary since over the last couple years there have been several major developments regarding additional cell populations and the precursor cells in blood and bone marrow.
The aim is to arrive at an up-dated nomenclature that

a) Will include blood monocytes and dendritic cells and their precursor cells
b) Will work across different species and
c) Will be applicable to disease including inflammation and malignancy.

The workshop will cover sections on

a) monocyte precursors
b) blood monocyte subsets
c) DC precursors
d) blood DC subsets
e) CD1c+ CD14+ cells: DC or monocyte?
f) omics to define subsets versus different versions of a subset
g) single cell sequencing: How many subsets are there?
h) man, mouse and other species
i) markers in health and disease

For this the nomenclature committee plans on a meeting of 35 leading experts in September 2019. Participants consist of the current member plus experts covering the new topics. These have been selected from the global community based on their crucial contribution.

The meeting works towards agreeing on an extension and up-date of the nomenclature of blood monocytes and dendritic cells. The up-date is targeted to be published in 2020.

Report on the Nomenclature of Monocytes and Dendritic Cells in Blood 2017

Use of the nomenclature

The crucial paper for the new nomenclature is the publication in Blood journal in 2010 (Ziegler-Heitbrock L, Ancuta P, Crowe S, Dalod M, Grau V, Hart DN, Leenen PJ, Liu YJ, MacPherson G, Randolph GJ, Scherberich J, Schmitz J, Shortman K, Sozzani S, Strobl H, Zembala M, Austyn JM, Lutz MB. Blood. 2010 Oct 21;116(16):e74-8)

As of November 30st 2017 this paper has been referenced more than 800 times (see www.researchgate.net/publication/45185387).
The terms “classical monocytes”, “non-classical monocytes” and “intermediate monocytes” are well accepted while for dendritic cells in blood the “CD141 DC” “CD1c DC” nomenclature is still in flux.

Updating the nomenclature: Monocytes

Non-classical monocytes
The monocyte nature of slan+ blood cells has been pointed out already early on Siedlar, Immunobiology, 2000. Others have continued to use the term slanDCs. Compelling evidence based on comparative transcriptomics has confirmed the contention that the slan+ blood cells are monocytes (Hofer et al, BLOOD, 2015, Leeuwen-Kerkhoff, J Leuk Biol 2017). The point to be discussed is whether the slan+ is an adequate marker for the definition of human non-classical monocytes.

The term “patrolling” monocytes for the non-classical monocytes appears to be fading away. This may be due to the demonstration (by the team that coined this term) that the patrolling (=crawling) behavior is equally evident for the classical monocytes in man (Collison, Geissmann, J Immunol 2015) and in the mouse liver vasculature (Dal-Secco, JEM, 2015).

Regarding non-classical monocytes Patel et al (J Exp Med, 2017) have shown using deuterium labelling that the life span of these cells with about 7 days is much longer compared to classical monocytes with about 1 day. Also they have confirmed expression of slan on the non-classicals. The kinetic data in man are in contrast to the mouse where similar studies have shown a half-life of 2 days for the non-classical monocytes (Yona, Immunity, 38, 79–91, 2013). While we propose a unified nomenclature for man and mouse these data again remind us of the fundamental differences we encounter between these two species for monocyte subsets.

Intermediate monocytes
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). 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.
The dissection of intermediate and non-classical monocytes in flow cytometry is not straightforward.
An improvement may come with the use of an additional marker like slan or CCR2 as suggested by Wong et al (Immunological Research, 2012). 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.

On the other hand a recent study has shown a clear separation of these cells from the non-classical monocytes when using the marker slan (Hofer, Blood, 2015). This definition was supported by both molecular data and clinical studies showing an increase of slan- CD14+ CD16+ monocytes in

sarcoidosis. These data await independent confirmation before a recommendation on the definition of intermediate monocytes as slan- CD16+ monocytes can be made.

Single cell sequencing (SCS) of human cells by Villani et al (Science 2017) picked up two populations within the intermediate gate, one expressing the CSF3R (a typical neutrophil gene) and one expressing the IL2R beta chain, CD2 and CD3zeta (typical T cell genes). The nature of these cells still needs to be determined.

SCS of intermediate mouse monocytes (Mildner et al, Immunity. 2017) has uncovered two cell clusters, one that is in between classical and non-classical monocytes for all genes and one that has unique features with high class II, CD74 and DC-SIGN. This would mean that within this gate we are dealing with cells that are merely in transition and with cells that form a unique population.

The data demonstrate the power of single cell sequencing and the open issues we still face with these early studies. Ultimately this approach should be able to determine how many subsets of monocytes there are. It is expected that we will have solid data and consensus on intermediate monocytes in the next 1 or 2 years.

Tie2-expressing monocytes

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). Since expression of Tie2 is weak it is difficult to define clearly positive and clearly negative cells and the question is whether TIE2-expressing monocytes are a distinct cell population.

Classical monocytes

The definition of classical monocytes is straightforward in man and in the mouse. The human cells can be defined based on the CD14++CD16- pattern and the mouse cells are Ly6C++CD43+ and this has not changed since the 2010 proposal.
A group of cardiologists (European Society of Cardiology) has suggested a variation of the monocyte nomenclature in calling the classical monocytes Mon1 (see Weber et al Thrombosis Hemostasis, 2016). Given that the 2010 nomenclature for monocytes is well established, this unfortunately only adds confusion.

Single cell sequencing has shown these classical monocytes to be homogenous (Milder Immunity 2017, Villani, Science, 2017). Still there have been some attempts to define subsets within the classical monocytes.
Menezes et al (Immunity 2017) looking at mouse bone marrow analyzed CD115+Ly6Chi cells, which, however, included some Ly6C medium cells (Fig1A of that paper). What has not been addressed is whether the R2 cells are intermediate monocytes.

While in man almost all monocytes are HLA-DR+, a large proportion of mouse monocytes does not express Class II cell surface antigen and this applies to both classical and non-classical monocytes (Jakubzick, Immunity, 2013). Whether the differential Class II expression helps in defining additional subset of monocytes remains to be analyzed.

CD14+DR^{low} monocytes (“”myeloid-derived suppressor cells””)

Myeloid-derived suppressor cells (MDSC) are a mixture of cells mainly characterized by their ability to suppress T cell response more so in cancer patients than in healthy controls. They were then subdivided into monocyte-type and neutrophil-type MDSC. The monocyte type cells are defined as CD14high DRlow/- cells (Bronte Nature Comm, 2016). These cells are found increased in cancer and in sepsis and they may represent immature cells or deactivated cells (see Volk, Intensive Care Med, 1996)

Problems that the M-MDSCs face are that the cut-off value for DR is not clearly defined, that cells of this phenotype can be suppressive or not, that studies on side by side comparison with other monocyte subsets are scarce and that comparative transcriptomics are not available (but may be in the pipeline). Also the few single cell sequencing studies “MDSC” has been detected (Villani, Science. 2017;356(6335), Mildner, Immunity. 2017 May 16;46(5):849-862). Taken together the current evidence does not support inclusion of MDSC into a blood monocyte subset nomenclature at this point in time.

Updating the nomenclature: Dendritic Cells

CD141+ DCs

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, Bachem A J Exp Med. 2010;207: 1273). 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 (Vu Manh, Frontiers Immunology, 2015).

Bachem has generated an anti-mouse monoclonal against XCR1 in a knock-out mouse showing expression on 80% mouse CD8+ DCs cells in the spleen (Bachem Frontiers Immunology 2012). Recently, a mouse anti-human XCR1 monoclonal antibody has been patented (Anti-human XCR1 antibodies US 9371389 B2, 2016).

CD1c+ DCs

For the CD1c+ myeloid DC in human blood it had been noted earlier that there are CD14- and CD14low cells (see the BLOOD-2010 Nomenclature proposal) and these have not been characterized further. A recent study (Bakdash, de Vries Cancer Research, 2016) has described CD1c+ CD14+ cells to be expanded in melanoma patients. The cells were shown to express high levels of PD-L1 and to reduce T cell proliferation more efficiently compared to CD1c+CD14- and to M-MDSC. Transcriptome analysis comparing the CD1c+CD14+cells to CD1c+CD14- cells and to classical monocytes found them to be in between. Comparison to a comprehensive set of blood DCs and monocytes is required in order to define the position of these cells and their assignment to monocytes or DCs.

More recently in a 2017 study the CD1c cells were subdivided into CD5low and CD5high (Yin et al J Immunol. 198: 1553, 2017). The CD5high cells were more potent in antigen presentation and in that are similar to the CD1c+ CD14- cells. Thus we may be dealing two populations of CD1c+ cells a) CD14-CD5hi and b) CD14+ CD5lo. This still needs to be formally shown. The concept of two cell types is supported by recent SCS data (Villani, Science. 2017; 356: 6335), who falsely claimed being the first to describe this subdivision of CD1c cells. The study identified one cell type expressing CD14, S100A9 and S100A8 and one cell type with higher Class II expression. With some more data consolidating this subdivision the Nomenclature Committee may discuss to officially recognize two subtypes of CD1c+ cells. The open question then remains whether the CD1c+CD14+ cells are dendritic cells or monocytes. The expression of MAFB by these cells would support a monocyte nature. Comparative transcriptomics with a large set of prototypic monocytes and dendritic cells may help in making that decision.

CD303+ pDCs

Plasmacytoid DCs have been characterized in man by expression of CD303 and also by high level CD123. Differential CD4 staining has been noted within the population of pDCs (Matsui T, J Immunol. 2009)Also in the rat subsets of pDC have been described and a closer look at heterogeneity of these cells in man is warranted. An indication of such heterogeneity is given in Guilliams (Immunity, 2017) where expression of CD2 and CD5 is shown on a subset of pDCs in human blood pDCs are characterized by high IFNalpha production. When subsets of pDCs fail to produce IFNalpha then the question is whether this disqualifies them as pDCs. In other words what needs to be discussed is whether phenotype or function dominates in the assignment to pDCs.

The 2010 nomenclature proposal suggested a subdivision into two myeloid DC-populations and one pDC population with the markers CD141, CD1c and CD303. The myeloid nature of the former cell types was based on the expression of CD33. On the other hand CD68 a macrophage associated molecule, is clearly expressed by pDCs. So it is unclear whether the term myeloid is appropriate and whether it can be refuted or substantiated with newer data.

SCS candidates

Villani et al (Science, 2017) have search human blood leukocytes for subsets of DCs and they described the pDCs, the CLEC9A+ cells (CD141+, DC1), the two types of CD1c+ cells mentioned under CD1C+DCs (termed DC2 and DC3 by Villani et al). DC4 are CD16-postive and likely are non-classical monocytes contaminating the DC-preparation of cells. A novel population are cells called AS DCs (DC5), which are positive of genes AXL and SIGLEC6. All of this needs confirmation by independent studies but it is expected that over the next 1-2 years, we will definitely know, how many subsets of DCs there are in human and mouse blood.

Nomenclature covering precursors of macrophages and dendritic cells

Monocyte Precursors

After the common monocyte progenitors (cMoPs) had been described as CD117+CD115+CD135low in the mouse (Hettinger, Nature Immunology,2013) more recently a CLEC12AhiCD64hi cMoP has been described in man (Kawamura, Immunity 2017). In addition, a cell termed pre-monocyte has been described in the mouse,(Chong, J Exp Med, 2017), a cell characterized by high CXCR4 expression. Similar CXCR4 hi cells were detected in human samples. Hence, a model emerges with GMPs giving rise to cMoPs that give rise to pre-Monos which in turn develop into classical monocytes (GMP→cMoPs→pre-monocytes→ classical monocytes). When these precursors and their properties have been confirmed by independent studies then their inclusion in a nomenclature proposal can be discussed by the committee.

DC Precursors

In the mouse, a macrophage dendritic cell precursor (MDP) has been postulated. However, the existence of these cells has 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.

A novel blood subset belonging to the human DC family has been described (Breton, J Exp Med, 212: 401-13, 2015). What they have described is a DC precursor for both the CD141+ DCs and the CD1c+ DCs. This may be an important new finding and a confirmation of these data by other teams is awaited.

In a study by the Reis e Sousa team it was shown that the CD141+ Clec9A+ DCs can be generated from the common myeloid progenitor (CMP) and with high efficiency from multipotent lymphoid early progenitors (MLPs) (Helft, Cell Reports, 20, 529–537, 2017). Cell generated from the two progenitors show an identical transcriptome (convergent differentiation).The study by Breton et al has described cell termed hpre-CDC-like which is found in human blood and bone marrow, has the phenotype Lin-CD34-CD117+ CD135+ CD116+ CD115- . In clonal analysis 90% of these cells can give rise to CD1c+ (DC2) and CD141+ (DC1) myeloid DCs but only 10% lead to production of monocytes (Breton, J Exp Med, 212: 401-13, 2015). These studies also reported on CDPs (common dendritic cell precursors which has similar features as the GMPs =granulocyte monocyte progenitor) to give rise to pDCs and pre-CDCs which can generate DC1 and DC2. In addition, single cell sequencing analysis (See *et al*., *Science* 2017) has proposed a separate pre-DC for DC1 and DC2 each. Here pre-DC1 (CD123loCADM1+CD1c-) and pre-DC2 (CD123loCADM1-CD1c+) that are committed to generate DC1 and DC2, respectively.

Other species: monocytes and DCs in blood of non-human primates

As mentioned in the original nomenclature document most of the anti-human reagents can be used directly for non-human primates and they give similar patterns for blood leukocytes in old world monkeys. The CD16-positve monocyte subset was originally reported for Macaca fascicularis by Munn et al (Blood 1990) and Otani (AIDS Res Human Retro viruses 1998) expanded on this in the context of retrovirus infection.
For Macaca mulatta the Williams team also reported on monocyte subsets and they identified and characterized the intermediate monocytes (Kim, JLB, 2011). Monocyte subsets could be properly identified based on CD14 and CD16 in rhesus macaques, cynomolgus macaques and pigtail macaques (Sugimoto, J Immunol, 2015). The same study using BrdU injection demonstrated consecutive appearance of label in classical, intermediates and non-classical monocytes, similar to the developmental sequence after bone marrow transplant (Dayyani, JLB, 2002), and after deuterium glucose injection in man (Patel, JEM, 2017). Also injection of the R848 TLR7/8 ligand into rhesus monkeys a strong increase of intermediate monocytes could be demonstrated (Kwissa, Blood, 2012).
For DCs it was noted that anti-human CD141 antibodies do not identify a CD141-high population in rhesus monkeys but stains at a low level all mDCs and monocyte subsets (Autissier, J Imm Methods, 2010). Still the three DC subsets can be identified using antibodies against CD1c and CD123+for pDCs (Sugimoto, J Immunol 2015) and against CADM1 for the CD141+ homologue in rhesus macaques (Dutertre, J Immunol,2014).
Also for new world marmosets cross-reactivity for CD14, CD1c and DR has been demonstrated
These findings support a suggestion to recommend the human nomenclature also in non-human primates, albeit different reagents may be needed at times.

Other species: monocytes and DCs in blood in the mouse
There are no new data on characterization of mouse monocyte subsets but rather on the biology of these cells. The subsets are still being defined via Ly6C and CD43 expression and CD115 or F4/80 are used to identify all monocytes. Based on an intermediate level of Ly6C intermediate mouse monocytes are being confirmed in several publications (e.g. Lessard Cell Reports, 2017, Makinde, JIM, 2017, Wolf, JEM, 2017).

Non-classical monocytes had been called “patrolling” and it was proposed that their main function is to monitor and clean up the endothelium (Auffray, Science, 2007) rather than going into tissue as is the standard fate of monocytes. However, already in the Auffray publication it was shown that these very cells rapidly go into tissue after injury, but disregarding this many follow up papers maintained that it is the classical monocytes that exclusively go into tissue. Recently several reports have shown that non-classical monocytes go into inflamed joint, normal mesenteric tissue and inflamed skin (Misharin, Cell Reports, 2014, Saja Cell Reports, 2015, Olingy, Scientific Reports, 2017).

Single cell sequencing has identified two types of mouse intermediate monocytes, one with intermediate expression of all DEGs and one with unique features like high class II, CD74 and DC-SIGN (Mildner, Immunity 2017 May 16;46(5):849-862).

Mouse blood DCs
For the PDCA-1-(CD317, BST2) positive pDCs two subsets (CD8+ CD8-) have been described (Sharma Infection Immunity, 2016). Also, it has reported that there are PDCA-1hi pDCs compared to PDCA-1lo CD11chi DCs in blood (Kim, Scientific Reports, 2016). Björk described CD9+Siglec-Hlo pDCs as the main IFNalpha producers (Björk, JIM, 2011). So subsets of pDCs in the mouse (and also in man) will have to be addressed.
For the human CD1c myeloid DCs the homologous blood DCs in the mouse 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+ (Sirpalpha+, 70%) and CD172a- (Sirpalpha-, 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.
With a focus on DCs in tissue there is discussion on the use of surface markers other than CD8, like XCR1 and CLEC9A for the definition of what might be termed DC1 (vu Manh, Frontiers in Immunology, 2015).
Guilliams (Immunity, 2016) has compared man and mouse for DC subsets. Looking at mouse spleen cells CD11c+CD26+XCR1high CD72alow cells (DC1) and CD11c+CD26+ XCR1low CD72ahigh cells (DC2) could be identified.
The former can, in addition, be defined as CADM1hi and the latter as CADM1low and the two subsets are characterized by mutually exclusive intracellular staining for IRF8 and IRF4 for what is termed DC1 and DC2 (Guilliams, Immunity 45, 669–684, 2017). Mouse pDCs are defined as $D11b^{lo}120G8^{hi}$ $CD172a^{int}$ $B220^{int}$ $Ly6C^{int}CD11c^{int}$ in that study. In an IRF4 IRF8 staining the pDCs from mouse spleen overlap with DC1 cells.
These data still need to be confirmed for mouse blood samples.

Other species: monocytes and DCs in rat and pig and cow and horse

Rat:
For the rat monocyte subsets have been defined based on high or low expression CD43 expression in cells defined as monocytes via CD172a or CD68. Ahuja (Cell Immunol, 1995) demonstrated high CD4 on the CD43++ cells. Infusion of IFNgamma into rats was shown to lead to a strong increase of CD43+ CD4 low monocytes (Scriba, JLB, 1997). The CD43++ monocytes were then demonstrated to below for CCR2 and high for CX3CR1 (Yrlid, J Immunol, 2006). Also the CD43++ cells were low to negative for CD62L.
More recently the classical-non-classical nomenclature was applied to the rat by several groups. Work involving the Marijke Fass laboratory reported on CD172a+ CD43+ classical and CD172a+ CD43++ non-classical monocytes and showed an increase of non-classical monocytes during pregnancy in the rat. (Melgert PLOSone, 2012, Groen, PLOSone, 2013, Spaans, Am J Reprod Immunol 2014).
Grad et al (Drug Deliv. and Transl. Res. 2017) described CD68+CD43low classical and CD68+CD43high non-classical monocytes, with classicals being CD4 low and non-classicals CD4high confirming earlier work by Ahuja (Cell Immunol, 1995). Also Barnett (PLOSone 2016) has recently characterized CD43 high and low rat blood monocytes with the phenotypes CD43hi His48lo and CD43lo His48hi. The two cell types were differential for CD4 and CD161. It appears that CD4 may assist in differentiation classical and non-classical monocytes in the rat. Taken together, while some homologies to man and mouse are evident the amount of knowledge on rat monocytes is still limited. Notably there are no comprehensive analysis of functional and molecular data without and with stimulation and the intermediate monocytes have not been delineated.

Dendritic cells
Hubert (J Immunol, 2006) has described CD103+ DCs in the spleen with a CD4+ and CD4- subset. They noted a differential expression of TLRs and selective production of IFNalpha by pDCs. CD4+ and CD4- subsets were confirmed in spleen (Stojić-Vukanić Biogerontology, 2013)
More recently a monoclonal antibody against rat pDCs (85C7) Anjubault (PLOSone, 2012) described a CD4low and a CD4 high subset. Such pDCs expressed E2-2 mRNA but CD103 DCs did not. Most of this is spleen data but it is shown that CD4lo pDCs can be found in rat blood.

Pig: The original nomenclature proposal has not covered the pig. Here early work had shown that antihuman CD14 antibodies can stain pig monocytes (Ziegler-Heitbrock Scand J Immunol 1994; 40:509-14) and there were monocytes with high and low CD14.
A clear demonstration of monocyte subsets was provided by the Dominguez lab, which described CD14+CD163+ MHC Class II+ and CD14++CD163- MHC class II- subsets (Sanchez, 162:5230, 1999). Also, Ondrackova et al (Vet. Res. (2010) 41:64) have found two subsets based on CD14 and CD163 and Fairbairn et al (JLB 89:855, 2011) have confirmed subdivision of porcine monocytes based on CD14 and CD163 with a CD14+CD163+ and a CD14++CD163- subset.

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 non-classical monocytes in man.

Of note, the CD14+CD163+ MHC ClassII+ monocytes in the pig show the reverse expression pattern for CD163, since the non-classical 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, Immunupathol, 2013). Recently the monocyte subset definition was confirmed for porcine bone marrow (Fernandez, Dev Comp Immunol, 2017).
The impact of M-CSF on the development of non-classical monocytes has been reported for the pig (Sauter, Am J Physiol Gastrointest Liver Physiol.2016). Further characterization

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

Regarding blood dendritic in the pig CD172low CD4+ DCs and CD172low CD4- interferon type I producing plasmacytoid DCs have been described (Summerfield, Immunology 2003, Balmelli, EJI 2005). Also, using a labelled XCR1 ligand (=XCL1) the respective DCs were detected in pig blood and skin (Deloizy, Dev Comp Immunol, 2016).

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).

Other species: monocytes and DCs in the cow
Hussen (Plosone 2015) and Corripio-Miyar (Vetenary Res, 2015) using CD14 and CD16 antibodies have defined the three monocyte subsets in Holstein cattle with high variation between individuals. The cell surface phenotype was similar to man and intermediate monocytes showed highest class II expression and non-classical monocytes lowest CD163. Also the non-classical monocytes showed highest levels of TNF and IL12 and lowest for IL-10 also matching the patterns in man. However, IL-1 was found lowest in non-classical monocytes by Hussen (2015). In addition DC-Sign may be informative in dissection of monocyte subsets in this species (Elnaggar, Vet Imm Immunopathol 2016).

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

Looking at dendritic cells in cattle blood a homologue of the human CD141+DCs has been described as CD26+CADM1+CD205+MHCII+CD11b- cells, which express mRNA for XCR1 and for CLE9A and these cells migrate in response to XCL1 (Li et al PLOSone 0170575, 2017). CD209 cells have been described as DCs in the cow but with expression of CD14 it is also possible that these DC-SIGN+ cells are monocytes (Park PLOSone, 0165247, 2016). pDCs with the markers CD4 MHC II CD45RB CD172a CD32 were reported to produce high levels of IFN type I (Reid, J Virol, 85: 4297, 2011). It remains to be shown whether these cells can be further narrowed down with additional markers. Taken together there are indications for a similar subdivision of blood DCs in the cow, but a clearer definition of subsets is required.