Nomenclature of monocytes and dendritic cells in blood*

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Abstract
Monocytes and cells of the dendritic cell lineage circulate in blood and eventually migrate into tissue, where they further mature and serve various functions most notably in immune defense. Over the recent years these cells have been characterized in detail using cell surface markers and flow cytometry and subpopulations have been described. The present document proposes a nomenclature for these cells and defines three types of monocytes (classical, intermediate and non-classical monocytes) and three types of dendritic cells (plasmacytoid and two types of myeloid dendritic cells) in human and in mouse blood. This classification has been approved by the Nomenclature Committee of the International Union of Immunological Societies and we are convinced that it will facilitate communication among experts and in the wider scientific community.
Introduction

The nomenclature of monocytes and dendritic cells (DC) in blood has become quite confusing due to the use of different antibodies for their identification, to the existence of several subpopulations and to the swapping of nomenclature between species. In order to resolve this, a group of experts drafted a nomenclature proposal under the auspices of the International Union of Immunological Societies (IUIS) and the World Health Organisation (WHO). This proposal was discussed at a workshop organized by the DC-THERA European Network of Excellence and the European Macrophage and Dendritic Cell Society (EMDS) in Brescia, Italia, in 2008. After the meeting, the amended proposal was extensively discussed and finally the nomenclature, presented in this paper, was agreed by the panel as a current consensus, acknowledging that it may well require review in the future.

The nomenclature follows the general rule of giving species and tissue, a non-pre-emptive name and informative markers. At this stage the nomenclature proposal refers to the steady state; its application to inflammatory conditions has to be done with care, since inflammation may perturb the expression of markers independent of changes in the composition of cell populations. Knowledge about cells in the blood compartment - due to the ready access - is greatest in man, whereas fewer studies are available for mouse and rat. Because of that man takes the lead in this nomenclature proposal. We propose herein the terminology classical, non-classical and intermediate for the different types of blood monocytes and for cells of the DC lineage we suggest the terms plasmacytoid and myeloid blood DCs, with two distinct types for the latter. These names are combined with informative cell surface markers.

Monocytes

Early studies demonstrated that bone marrow precursors give rise to monocytes in blood, which circulate for a few days before they migrate into tissue where they develop into different types of macrophages [1]. Cells of this lineage are collectively referred to as mononuclear phagocytes or monocytes/macrophages. They are multifunctional with roles in homeostasis, immune defence and tissue repair and they were shown to express an extremely diverse transcriptome [2]. In man monocytes were initially defined based on morphology and cytochemistry (monocyte-specific esterase) and later by flow cytometry based on light scatter properties and on cell surface markers such as CD14. This technology enabled the identification of a CD16-positive subpopulation [3], which is characterized by higher MHC class II expression and following stimulation by TLR-ligands by higher tumor necrosis factor (TNF) production [4; 5; 6]. Also, these cells were shown to expand in inflammatory diseases [7; 8]. The classical CD16-negative monocytes and these CD16-positive cells were shown to share morphology, cytochemistry and many cell surface markers. The more recent approach of expression profiling and hierarchical clustering has substantiated the close relationship of the two types of cells [9;10]. In addition, monocytes with an intermediate phenotype between classical and CD14-low CD16-positive monocyte subsets have been described. These are
found at low frequency but they have unique features and expand with cytokine treatment and in inflammation [11; 12; 13; 14; 15; 16; 17].

It has been demonstrated that monocytes can differentiate into DCs in-vitro and in-vivo [18; 19; 20; 21; 22]. While monocytes therefore might be addressed as DC precursors the panel agreed that these cells still are best called monocytes, since they are not exclusively precursors of DCs but are also the precursors of macrophages.

The use of popular terms such as “inflammatory monocytes,” or “pro-inflammatory monocytes” is not recommended since this leads to confusion as the label inflammatory has been used for different subpopulations in humans and mice. Also these terms may prematurely ascribe functional attributes to cells based on ex-vivo studies while they largely remain to be functionally characterized in-vivo. Earlier, the main monocyte population in man has been called “classical monocytes” [4] and later it was suggested to label the CD16-positive cells “non-classical monocytes” [23]. This approach has been adopted for monocytes in the present nomenclature.

For human blood monocytes a subdivision into three subsets, i.e. classical, intermediate and non-classical, is suggested (Table 1).

Since for the monocyte / macrophage system the term monocyte is reserved for the cells in blood, it was felt that it is not necessary to always use the label blood when referring to monocytes. Classical monocytes are the cells known to hematologist as monocytes based on morphology for a century, whereas the somewhat smaller, non-classical monocytes, which account for only 10% of all monocytes, have been described only 20 years ago. There appears to be a developmental relationship between these cells (from classical via intermediates to non-classical) in that during the course of an infection or with M-CSF treatment there is an increase first of the intermediate cells followed by an increase of the non-classical CD14+CD16++ monocytes [13]. Here + denotes an expression level that is about 10 fold above the isotype control and ++ is about 100-fold above the isotype control. With a gradual development from classical to non-classical monocytes it may be difficult at times to determine the boundaries between the subpopulations. As with any immunofluorescence analysis, isotype controls are to be used for proper determination of subpopulations.

The CD14 and CD16 markers have proven useful in many studies in the literature and their use is recommended for determination of subpopulations. For human monocytes CD14 and CD16 antibodies targeting different epitopes are available. For CD14 we suggest the use of antibodies directed against the lipopolysaccharide-binding domain and for CD16 those that bind to the Fc-binding domain. In order to exclude granulocytes CD66b can be helpful but intracellular lactoferrin is also a robust marker for exclusions of neutrophils [24].
exclusion of NK cells CD56 is recommended and staining for MHC class II expression and for low level CD4 on monocytes can also be helpful.

CD43, while showing a strong differential staining in mouse monocytes subsets (see further below), gives only a weak difference for the human subsets and is not recommended for standard staining. CCR2/CD192 staining, however, distinguishes human subsets very clearly and there is also differential expression in the mouse [25; 26]. CCR2 may well become a marker for definition of subpopulations in the future but its usefulness for this purpose still needs further study.

There is published evidence for further subsets including proliferating monocytes and 6-sulfo LacNAc⁺ and FcεRI⁺ monocytes [27; 28; 29; 30; 31]. Once more information from different research groups is available, these subpopulations can potentially be incorporated in this nomenclature. Taken together, we recommend to subdivide human monocytes into three subsets based on the expression of CD14 and the CD16 receptors: The classical monocytes show high CD14 expression but no CD16 (CD14⁺CD16⁻), the intermediate monocytes show a high level of CD14 together with low CD16 (CD14⁺⁺CD16⁻) and the non-classical monocytes express a low level of CD14 together with high CD16 (CD14⁻CD16⁺⁺), (Table 1). When the intermediate and the non-classical monocytes are not separately defined then we propose to address them collectively as CD16-positive monocytes.

For mouse blood monocytes a subdivision into three subsets similar to man is proposed, i.e. classical, intermediate and non-classical (Table 1).

Markers CD43 and Ly6C have proven to be informative with respect to differential expression. Reagents detecting the Gr-1 epitope, which is present on both Ly6C and Ly6G, are available but the use of specific anti-Ly6C antibodies is to be preferred. Also, models using transgenic mice have been highly informative for definition of monocyte subpopulations like mice with differential expression of CX₃CR1-promoter driven marker genes [26; 32; 33]. Such studies on chemokine receptor expression have revealed that the classical monocytes in the mouse are CCR2high and CX₃CR1low while the non-classical monocytes are CCR2low and CX₃CR1high.

Since none of the markers used for subset definition is monocyte-specific additional markers such as CD11b or CD115 (M-CSF receptor) have been used to define monocytes as such. The M-CSF receptor has been used since it clearly discriminates monocytes from granulocytes. The disadvantage of this marker is that the CD115 protein can be cleaved under conditions of inflammation. This can be obviated using M-CSF-R promoter driven GFP but unfortunately such animals show strong GFP-expression also in granulocytes [34]. Also, while CD14 is expressed by mouse monocytes, the signal is too weak to serve as a monocyte marker in this species. Therefore a single optimum defining marker for mouse monocytes is still needed.
Cell depletion studies demonstrate a developmental relationship between classical and non-classical monocytes [35] in that the non-classical monocytes in mouse blood are more mature and derived from the classical monocytes. Since this relationship is also found in man, these data support the concept that the non-classical Ly6C+ CD43++ monocytes in mouse blood are homologous to human non-classical CD14+CD16++ monocytes. Furthermore, studies on cytokine expression after stimulation with TLR-ligands have shown higher levels of TNF protein per cell in the non-classical monocytes as compared to the classical monocytes both in man and mouse [4;36]. Similar to man intermediate cells in the mouse were shown to have unique features [37].

Also, in the mouse non-classical monocytes show lower CD14 and higher CD16 staining compared to the classical monocytes [38], further supporting the concept that the non-classical monocytes in man and mouse are homologous cell types. Finally, transcriptional profiling of mouse subsets has provided further evidence for the homology of the non-classical blood monocytes in man and mouse [38; 39].

Again, it may be difficult to determine the boundaries between the mouse monocyte subpopulations especially when it comes to the intermediate cells. Unique markers for these intermediate cells are required. Taken together, we suggest a subdivision of mouse monocytes similar to man based on the expression of Ly6C and CD43: The classical monocytes show high Ly6C expression and low CD43 (Ly6C++ CD43+), the intermediate monocytes show a high level of Ly6C together with high CD43 (Ly6C++ CD43++) and the non-classical monocytes express a low level of Ly6C together with high CD43 (Ly6C+ CD43++), (Table 1).

For rat blood monocytes a few groups have addressed subpopulations [40; 41; 42]. While there is evidence for heterogeneity, a nomenclature for blood monocytes subsets in the rat is considered premature at this point in time. It is interesting to note, however, that also in the rat, CD43 is differentially expressed among monocyte subsets, and transfer of CD43+ monocytes gives rise to CD43++ cells in vivo [42]. This suggests a similar developmental relationship between subsets as has been observed in man and mouse. However, a definite description of rat monocyte subsets awaits further study with an appropriate set of markers and with functional analyses. In any case, we suggest that the terms “classical” and “non-classical” might be used in other species besides human and mouse when the appropriate counterparts have been identified.

**Blood dendritic cells**

Dendritic cells were first identified as a discrete cell type in lymphoid organs in the mouse [43]. Cells assigned to the DC lineage in blood have been characterized mainly in man with a few studies available for the mouse and no data for the rat. Again the human system takes the lead when it comes to nomenclature for cells in blood. The panel recognizes the difficulty of defining a DC as compared to a monocyte/macrophage since these two cell types are closely
related, as evidenced by the findings that blood monocytes can differentiate into DCs [18; 19; 20; 21; 22] and that DCs from human blood can differentiate into macrophages [44]. Also, the expression of individual markers such as the commonly-used CD11c is not restricted to DCs; 90% of human monocytes and approximately 40% of mouse monocytes are CD11c+ [45; 35] and alveolar macrophages in the mouse are also CD11c+ [46]. In fact, it is very difficult at present to identify a single marker that can be used to clearly assign a cell to either the monocyte or the DC lineage. When taking an unbiased approach and analysing the entire transcriptome of the two monocyte subsets (classical CD14++CD16− and non-classical CD14+CD16++) as compared to three types of DCs (HLA-DR-positive cells negative for markers of other leukocyte lineages) in human blood, then hierarchical clustering demonstrates that three blood DC populations cluster together and are clearly separated in their expression profile from the two monocyte populations [9]. Therefore, we can group the three cells of the DC lineage together and can assign them collectively to the DC lineage.

Still these blood cells do not have typical characteristics of DCs as seen in tissue: it is apparent that they lack dendrites and also lack markers of mature DCs like CD83. Also in blood they most likely do not present antigen to T cells since this would require close cell-cell contacts, which is unlikely to occur under flow conditions. Rather these DC-lineage cells appear to be in transit and they mature into functional DCs only after entering the tissue.

So far, three cell types assigned to the DC lineage have been identified in human blood. Among these the plasmacytoid DC subset might be addressed as being at an immature DC stage rather than a precursor, since they have properties of circulating sentinel cells that, after receiving a maturation signal such as virus contact, can enter the lymph node through high endothelial venules to prime T cells immediately [47]. By contrast, the CD1c+ and CD141+ DC lineage cells show features of both DC precursors (“preDCs”) and of immature DCs. Similar to immature DCs they have the potential to act as sentinel cells since in-vitro they secrete cytokines when activated, they effectively stimulate T cells and they rapidly mature in response to Toll-like receptor agonists [48; 49]. On the other hand, the CD1c+ and CD141+ DC lineage cells fail to mature in response to TNF and they express early myeloid markers like CD33 at high levels, features that would suggest a classification as DC precursors [50; 48]. A nomenclature that reflects such distinct maturational stages of the DCs in blood would be confusing. Therefore the panel agreed on the term “blood DCs” for the entire collection of cells. This terminology goes along with the connotation that a blood DC is not a mature cell of this lineage.

For **human DC lineage cells** in blood a subdivision into three subsets is suggested, i.e. plasmacytoid DCs and 2 types of myeloid DCs.

Plasmacytoid DCs in tissues were originally described as T associated plasma cells, plasmacytoid T cells, or plasmacytoid monocytes [51; 52; 53] When these cells were first
is isolated from human tonsils, they were shown to have the ability to differentiate into mature DCs in culture with IL-3 [54]. In parallel research a subpopulation of human blood cells enriched in cells expressing MHC class II and CD4, was found to have the capacity to produce high levels of IFN-α in response to viruses and these cells were named natural type 1 interferon producing cells [55; 56]. In crucial experiments it was revealed that these interferon-producing cells are, in fact, the plasmacytoid DCs [57; 47]. The CD68 marker can discriminate the plasmacytoid DCs from the two types of myeloid DCs, but this requires combination with additional markers since CD68 is also strongly expressed on monocytes [58]. While CD123 expression is only incrementally higher on plasmacytoid DCs as compared to monocytes, CD303 is a marker with good signal to noise ratio for the plasmacytoid DCs [59].

Both the CD1c+ and CD141+ myeloid blood DCs express myeloid markers CD13 and CD33, suggesting their direct derivation from the myeloid lineage. While earlier studies relied on exclusion of all other lineages of leukocytes combined with high level MHC class II expression in order to study these blood DCs, the CD1c and CD141 markers available now only require exclusion of a few cell types that co-express these markers.

For proper identification of the CD1c+ DCs in blood CD19+CD20+ B cells need to be excluded, because the latter cells also show strong expression of the CD1c molecule. A fraction of the CD1c+ blood DCs expresses low level CD14 [60]. No comparative data are available on the CD14+ and CD14- subsets of the CD1c+ cells at this point in time. In support of their uniqueness functional studies on CD1c+ cells have demonstrated a specific pattern of chemokine production in these cells [61].

The CD141+ DCs represent a very minor subset of blood leukocytes. Co-staining with CD14 is recommended in order to exclude low level signals from monocytes. These CLEC9A+ CD141+ cells (but not CD1c+ blood DCs) are also major producers of IFN-β and cross-present antigen for CD8 class 1 restricted CTL responses in response to TLR-3 / CD283 ligation: these and their other properties suggest that they are homologous to the mouse CD8+ DC subset. [62; 63; 64; 65].

It is recommended that the CD1c+ and CD141+ blood DCs are defined separately and are not addressed as one population of myeloid blood DCs.

Taken together, we recommend to define human blood DCs as MHC class II-positive, lineage-marker negative cells and to subdivide them into three subtypes. These are the plasmacytoid CD303+ DCs, the myeloid CD1c+ DCs and the myeloid CD141+ DCs (Table 2).
For **mouse DC lineage cells** in blood little information is available. Still, a subdivision into plasmacytoid and myeloid DCs appears to emerge.

Regarding plasmacytoid DCs blood cells with a high capacity to produce IFN-α in response to CpG stimulation have been defined as CD11c<sup>low</sup>, CD11b<sup>-</sup> CD45RA<sup>high</sup> cells [66]. Anti-bone marrow stromal cell Ag 2 (BST2) antibodies have been described to stain mouse plasmacytoid DCs in spleen and staining of mouse blood cells has demonstrated a strong signal for BST2 [67; 68]. However, expression of the BST2 antigen on plasma cells under steady state conditions and on many other cells after induction by type I interferon needs to be considered.

Looking at myeloid DCs the CD11c<sup>-</sup>CD11b<sup>+</sup>CD45RA<sup>-</sup> cells identified in mouse blood share features with the splenic CD8<sup>-</sup> DC subset [66] and they may be homologous to human CD1c<sup>+</sup> myeloid blood DCs [9].

The CLEC9A<sup>+</sup> DC in mouse blood also stain for CD24 and may thus be representative for the CD8<sup>+</sup> splenic DC subset. Since anti-CLEC9A also strongly stains the human blood CD141<sup>+</sup> cells [65] and since human CD141<sup>+</sup> blood DCs and mouse CD8<sup>+</sup> spleen DCs share specific transcriptional signatures [9], the CLEC9A<sup>+</sup> mouse blood DCs are potential homologues of the human CD141<sup>+</sup> CLEC9A<sup>+</sup> myeloid blood DCs. Taken together, it is clear that there are plasmacytoid and two types of myeloid DCs in mouse blood, but the optimum markers await to be defined. Therefore, the nomenclature proposal for the mouse does not give identifying markers at this point in time (Table 2). For the time being it is suggested to define the myeloid subsets with the compilation of markers, for example mouse myeloid CD11c<sup>-</sup>CD11b<sup>+</sup>CD45RA<sup>-</sup> blood DCs.

Differentiation of bone marrow plasmacytoid DCs into CD11b<sup>+</sup>CD45RA<sup>-</sup> myeloid DCs demonstrates the close relationship of the plasmacytoid and myeloid DC types [69]. Also transcriptional profiling and hierarchical clustering of mouse spleen DCs has demonstrated that the mouse plasmacytoid DCs and the CD8<sup>+</sup> and CD8<sup>-</sup> DCs cluster together in a similar manner to what has been shown for human blood DCs. Also the same analysis revealed co-clustering of the human and mouse plasmacytoid DCs [9]. For further consolidation of the mouse blood DCs it will be important to analyse expression of orthologues of informative human cell surface markers. Also, transcriptional profiling of purified mouse blood DCs is required for comparison to man.

Taken together, we recommend to define mouse blood DCs similar to man and to subdivide them into three subtypes. These are the plasmacytoid DCs and two types of myeloid DCs. Since specific markers for these cells in mouse blood are still to be identified they currently have to defined using combinations of cells surface markers.
For rat DC lineage cells in blood no data are currently available. It is expected that homologues of the three types of human blood DCs can be defined in the future using reagents that target the same or novel DC-specific molecules.

Technical aspects
The analysis of monocytes and blood DCs requires special attention since the frequency of some of these cells can be very low. Therefore contamination of the population of interest by unwanted events needs to be excluded. For flow cytometry analysis, we therefore suggest to use un-processed blood, exclusion of dead cells, gating on CD45 and no gating on scatter whenever possible and to use reagents with high signal to noise ratio. Also, high numbers of total events need to be acquired in order to obtain sufficient numbers of specific events for a meaningful analysis.

When reporting on monocytes and blood DCs in lectures and publications we recommend that flow cytometry plots of representative examples are given initially in the paper or as supplementary data in online publications, and these need to define the cells based on isotype controls to demonstrate the signal compared to noise. For optimum assessment the isotype control and the specific antibody need to be derived from the same manufacturing process with the same fluorochrome to protein ratio. For multicolour flow cytometry analysis the “fluorescence minus one” principle needs to be followed, i.e. only one antibody is exchanged for an isotype control at a time [70].

Concluding remarks
The present nomenclature proposal avoids the use of functional terms like “pro-inflammatory” for monocyte and blood DC subpopulations. Such terms may be very stimulating and make integration of the cells into mechanistic concepts easier. On the other hand such a nomenclature can lead our thinking and our research into wrong directions such that we disregard anti-inflammatory properties of a cell dubbed pro-inflammatory. Therefore, a neutral nomenclature is proposed for monocytes and blood DCs.

For monocyte subpopulations the nomenclature based on the classical versus intermediate and non-classical approach allows for other markers to be employed for the 3 subsets in the future. When new markers are used for human monocytes subsets then their validity needs to be demonstrated with reference to the CD14 and CD16 dot plots and a combination with these established markers is always recommended. The same applies to Ly6C and CD43 dot plots in the mouse. Also, the nomenclature proposal for blood DCs is open to additional subpopulations.

At this stage the nomenclature applies to man and mouse. It may be applicable directly to non-human primates, while for the bovine, porcine and rat system much more experimental
work is needed. We expect that the comprehensive analysis of gene expression (transcriptome, proteome, metabolome etc.) in subpopulations of blood monocytes and of blood DCs will refine this nomenclature and will help in consolidating homologues in the different species.

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Author Contributions

All authors contributed to the discussion of the nomenclature, all were involved in writing and all agreed with the proposal presented herein.

Disclosure of Conflicts of Interest

Jürgen Schmitz is employed by Miltenyi Biotec, a company that sells reagents to identify monocyte and dendritic cell subsets, DNH is a consultant for TransBio Ltd, Bundoora VIC 3083 Australia, PJML's institution has received royalties for commercially available anti-mouse monocyte antibodies from AbD Serotec, 40477, Düsseldorf, Germany, BMA Biomedicals,-4302 Augst, Switzerland, Santa Cruz Biotechnology, Santa Cruz, CA 95060 USA and Hycult Biotechnology, 5405 PB Uden, NL. The other authors declare no conflict of interest.
References


### Tables

#### Table 1 Nomenclature of Blood Monocytes*,**,***

<table>
<thead>
<tr>
<th></th>
<th>man</th>
<th>mouse***</th>
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<tbody>
<tr>
<td>classical</td>
<td>CD14++CD16-</td>
<td>classical Ly6C++ CD43+ monocytes</td>
</tr>
<tr>
<td>intermediate</td>
<td>CD14++CD16+</td>
<td>intermediate Ly6C++ CD43++ monocytes</td>
</tr>
<tr>
<td>non-classical</td>
<td>CD14+CD16++</td>
<td>non-classical Ly6C+ CD43++ monocytes</td>
</tr>
</tbody>
</table>

*The CD markers given are considered most appropriate at this point in time. They may be superseded by superior reagents in the future. **Here + denotes an expression level that is about 10 fold above the isotype control and ++ is about 100-fold above the isotype control. *** Additional markers have to be used to define the cells under study as monocytes (see text).

#### Table 2 Nomenclature of Blood Dendritic Cells*

<table>
<thead>
<tr>
<th></th>
<th>human</th>
<th>mouse</th>
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</thead>
<tbody>
<tr>
<td>plasmacytoid</td>
<td>CD303+ blood DCs</td>
<td>plasmacytoid blood DCs</td>
</tr>
<tr>
<td>myeloid</td>
<td>CD1c+ blood DCs</td>
<td>myeloid blood DCs</td>
</tr>
<tr>
<td>myeloid</td>
<td>CD141+ blood DCs</td>
<td>myeloid blood DCs</td>
</tr>
</tbody>
</table>

*The CD markers given are considered most appropriate at this point in time. They may be superseded by superior reagents in the future. CD303 is the official name for the commercial antibody BDCA-2, CD1c is BDCA-1 and CD141 is BDCA-3.
Legend to Figure 1

Ziegler-Heitbrock et al. Nomenclature of monocytes and dendritic cells in blood

The 6 types of cells are shown with different symbols, which represent the crucial markers of the respective cells.

= CD14,  = CD16,  = CD303,  = CD1c,  = CD141

A higher number of a given symbol indicates a higher density of a given receptor. The arrows in the upper part represent the developmental relationship. This does not necessarily indicate that development is actually occurring in the blood compartment. The location of the non-classical monocytes closer to the vessel wall is to indicate that these cells preferentially localize to the marginal pool, a concept supported by the intra-vital microscopy data for the mouse homologue. The two types of myeloid DCs are depicted closer to each other since both are closer related to each other as compared to the plasmacytoid DCs.
Human blood monocytes
- classical CD14++ CD16-
- intermediate CD14++ CD16+
- non-classical CD14+ CD16++

Human blood DCs
- plasmacytoid CD303+
- myeloid CD1c+
- myeloid CD141+

CD16-positive monocytes

Figure 1 Ziegler-Heitbrock et al. Nomenclature of monocytes and dendritic cells in blood
Nomenclature of monocytes and dendritic cells in blood