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Changes in the Cell Surface Markers During Normal Hematopoiesis: A Guide to Cell Isolation

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Abstract: Hematopoiesis, the process of hematopoietic cell production, largely takes place in the bone marrow (BM) of humans. This process follows a stepwise manner in which hematopoietic stem cells give rise to progenitor cells and they develop the terminally differentiated cells along each lineage through a sequential series of stages. Consequently, constant changes would occur in the gene expressions leading to morphological or functional changes necessary for different stages of maturation. These changes provide us with guides to differentiate different subsets of hematopoietic hierarchy based on the cell surface antigen markers and will help us to isolate various cells from the hematopoietic hierarchy. Here we have a short review on the changes of these surface markers during different stages of development and we have applied an algorithmic approach for the isolation of all these cells based on our current understandings of this system.

Keywords: Cell surface antigen markers, Hematopoiesis, Progenitor cell, Stem cell.

INTRODUCTION

In humans, the process of hematopoietic cell production (Hematopoiesis) occurs largely in the bone marrow (BM). Only the T-cell differentiation occurs outside the BM, principally within the thymus. This process begins with a quiescent stem cell which is stimulated with various environmental factors and gives rise to progenies differentiating along multiple lineages.

The current model for describing the normal hematopoiesis considers a relatively linear fashion for differentiation along each lineage through a sequential series of stages. The final products are fully functional mature cells which are needed for the performance of routine tasks of the hematopoietic system. The maturation of hematopoietic cells along each lineage is tightly controlled by sequential expression of genes and their products [1]. Consequently, the pattern of genes expression and their resultant products shows constant and reproducible changes during morphological or functional stages of maturation.

A group of these proteins are located on the cell surface. They may have diverse functions such as serving as growth factor receptors, adhesion molecules, extracellular enzymes, and signal transduction molecules. Many of these cell surface proteins were simply identified by their antigenic reactivity and the functions for some of these molecules is not clearly known. Some of these cell-surface antigens are restricted to a specific cell lineage, while others may be more widely expressed but their levels of expression varies with maturational stage or activation state. This may aid us in identification and isolation of different cells within diverse maturational stages based on their patterns of cell surface antigen expression [2].

HEMATOPOIETIC STEM AND PROGENITOR CELLS

Both repair of the injured tissues and formation of new tissues are dependent on the quiescent stem cells localized within specific niches in each organ [3]. Activation of stem cells is closely controlled by environmental stimulations by the surrounding microenvironment and follows a sequence of events at the genetic and epigenetic levels [4]. This tight controlling machine leads to establishment of a hierarchy starting from the slow-cycling stem cell with subsequent transiently amplifying precursors with a high proliferative capacity, but with lineage-commitment properties. At the end of this spectrum are the non-cycling, terminally differentiated cells that carry on the organ functions [5].

During the development of terminally differentiated cells, the stem cells themselves remain undifferentiated, which passes through their unique capacity for self-renewal. When a stem cell divides into two fates, only one of the resulting daughter cells enters the path for increasing specificity and the other one instead remains undifferentiated [6]. This phenomenon keeps the numbers in the overall stem cell pool constant, whereas the proliferation of the descendant progenitors can rapidly provide populations of specific cell types in

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response to changing needs. The capacity of stem cells to recreate themselves is called self-renewality and is one of the most important defining properties of stem cells. This gives them a potential for a nearly unlimited life span. Progenitor cells do have some ability to renew themselves as well, but their ability to reproduce themselves is restricted by an internal counting mechanism and only finite rounds of duplication can be preceded. The ability of the progenitors' offspring to multiply declines steadily as differentiation goes on (Figure **1**). Hematopoietic stem cells (HSCs) are defined as single cells with lifelong ability to self-renew as well as differentiate to produce all blood cell lineages (multipotency).

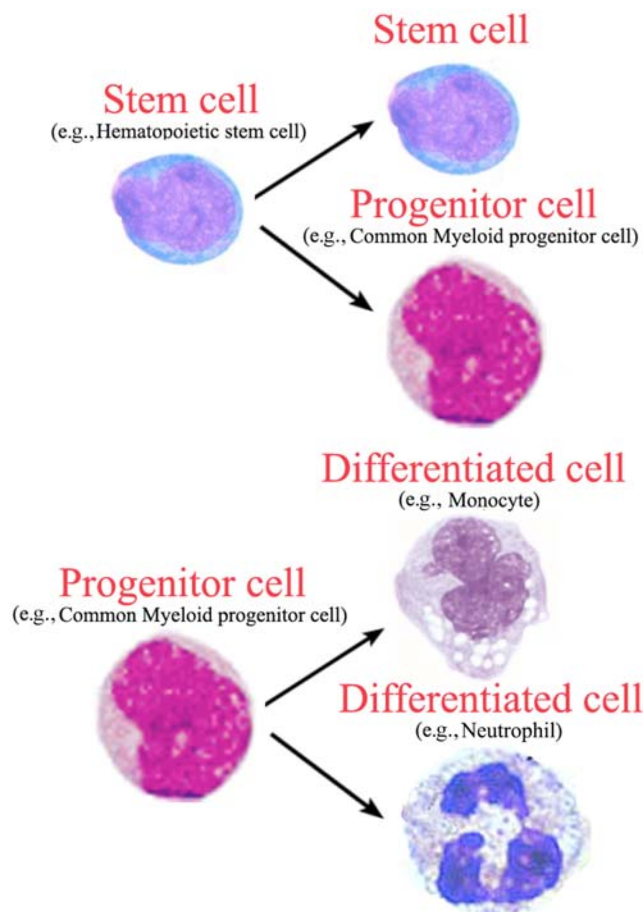

Figure 1: When a stem cell divides into two fates, only one of the resulting daughter cells enters the path for increasing specificity and the other one instead remains undifferentiated. This process is called self-renewality.Consequently the numbers of stem cells remains constant, whereas the descndant progenitors will provide the terminally differentiated cells needed for proper tissue functioning. Progenitor cells do have some abilities to renew themselves as well, which is limited by an internal counting mechanism leading to only finite rounds of duplication.

These hematopoietic cells with repopulating activities have been identified within $CD34^+$ cells [7]. Civin and colleagues in 1981 reported the presence of a marker, at first named as My10, on about 1% to 4% of BM cells which was also present on KG1A leukemia cells and later shown to be CD34 [8]. In 1988, Bernstein and colleagues showed that transplantation of $CD34^+$ cells can reconstitute hematopoiesis in lethally irradiated baboons [9], and the Thomas group in 1990 performed the first human $CD34^+$ enriched autologous graft with successful engraftment in a patient with a brain neoplasm [10]. Primitive hematopoietic cells that tend to lose their self-renewal potential start to express higher levels of the CD38 antigen while becoming more committed to differentiate. Therefore, HSC are found within the $CD34^+CD38^-$ cell fraction [11-13]. In human, two groups of cells can fulfill the definition for HSCs and therefore both can be named as stem cell. But only one can maintain a long-term multilineage reconstitution (LTMR) in allogenic transplants and therefore has been named as long term HSC (LT-HSC). In irradiation-reconstitution experiments, human $CD34^+CD90^+Lin^-$ cells were the only cells in human adult and fetal marrow, cord blood, fetal liver, and mobilized peripheral blood (MPB) that achieved LTMR [14]. So, LT-HSCs are $CD34^+CD38^-CD90^+Lin^-$ cells. These cells can give rise to a progeny, with the phenotype of $CD34^+CD38^-CD90^-Lin^-$, which has a short-term self-renewality potential for 10 weeks despite the ability to produce all blood lineages. They are called short term HSCs (ST-HSC) [14]. In contrast, in the murine system, LT-HSCs are $CD34^-CD38^+$ cells and the more committed progenitors are showing a $CD34^+CD38^-$ phenotype [15, 16]. Therefore, CD38 is a primitive marker in mice and a differentiation marker in humans.

In addition to the mentioned markers, other antigen combinations have been used to discriminate more primitive from more mature $CD34^+$ cells. Some of the combinations used are $CD34^+$c-kit$^+CD38^-CD33^-$Rho-123$^-$ [17], $CD34^+$HLA-DR$^-$Lin$^-$ [18], or $CD34^+CD38^-$Rho-123^{low} Lin$^-$ [19], and $CD133^+$ALDH^{hi}Lin$^-$ [20].

The CD133 marker, also known as prominin-1 or AC133 antigen, is also co-expressed on most of the $CD34^+$ cells, and can characterize stem cells in humans [21-23]. Investigations have shown the presence of very rare undifferentiated cells with stem cell properties within the $Lin^-CD34^-CD38^-$ cell fraction which expresses CD133 [24-26]. It seems that CD133 describes the most primitive human hematopoietic cells more precisely than CD34 [7].

Table 1: Expression of Surface Antigens during Different Stages of Granulopoiesis (Neutrophilic Maturation)

	GMP	Myeloblast	Promyelocyte	Myelocyte	Metamyelocyte	Band Cell	Neutrophil
CD10	−	−	−	−	−	−	++
CD11a	++	+/++	+/++	+/++	+/++	+/++	+/++
CD11b	−	−	−	+/++	++	++	++
CD11c	−	−	−	++	++	++	++
CD13	++	++/+++	++/+++	+	+/++	++	+++
CD14	NA [b]	−	−	−	−	−	+
CD15	−	+	+++	+++	+++	+++	+++
CD15s	++	+++	+++	++	+	+	+++
CD16	−	−	−	−	+	++	+++
CD18	++	++	+	+++	++	−	−
CD24	−	−	−	++	++	++	++
CD29	+++	++	++	++	+	+	+
CD31	+++	++	++	++	+	+	+
CD32	++	++	++	++	++	++	+++
CD33	+++	+++	+++	++	+	+	+
CD34	+	++	−	−	−	−	−
CD35	−	−	−	−	−	++	++
CD44	+++	+++	++	+	+	++	+++
CD45	NA [a]	+/++	+/++	++	++	++	++
CD45RA	++	+	+	−	−	−	−
CD45RO	−	−	−	+	+	++	+++
CD49d	+++	++	++	++	+	−	−
CD49e	+++	++	++	++	+	+	+
CD54	++	++	++	+/−	+/−	+/−	+/−
CD55	+++	+++	+	+	+++	+++	+++
CD59	+++	+++	+++	+++	+++	+++	+++
CD62L	++	++	++	++	++	++	++
CD64	++	+	+	++	++	−	−
CD65	+	+	++	++	++	+++	+++
CD66a	−	−	−	++	++	++	++
CD66b	−	−	+++	+++	++	++	++
CD82	+++	++	++	++	++	++	++
CD87	−	−	−	−	−	++	++
CD117	NA [a]	++	+	−	−	−	−
CD162	+++	+++	+++	+++	+++	+++	+++

[Modified from Elghetany MT: Surface Antigen Changes during Normal Neutrophilic Development: A Critical Review. Blood Cells Mol Dis 2002; 28: 260-74].
GMP means granulocyte monocyte progenitor cell; +++ means strong expression; ++ means moderate expression; + means weak expression; +/− means very weak expression; − means no expression; NA means Data Not Available; a means possible expression; b means possible not expressing.

Human hematopoietic progenitors have also been characterized. Manz *et al*. described the characteristics of the "Common Myeloid Progenitor Cell (CMP)", "Granulocyte Monocyte Progenitor Cell (GMP)", and "Megakaryocyte Erythrocyte Progenitor Cell (MEP)" within the $CD34^{+}CD38^{+}$ fraction of hematopoietic cells from both the adult bone marrow and cord blood by the differential expression of CD45RA and IL3Ra (CD123)

[27]. They showed that CMP ($CD123^{+}CD45RA^{-}$) can give rise to both the GMP ($CD123^{-}CD45RA^{-}$) and the MEP ($CD123^{low}CD45RA^{+}$). None of these cells contained a lymphoid developmental potential [14]. Instead, in 1995, Galy *et al.* described $CD34^{+}CD\text{-}38^{+}Lin^{-}CD10^{+}CD45RA^{+}$ cells within human BM that could give rise to T, B, natural killer (NK), and dendritic cells and are common lymphoid progenitor cells [28].

GRANULOPOIESIS

The process of Granulocyte maturation (Granulopoiesis) starts from myeloblasts through a linear process into morphological stages historically termed promyelocytes, myelocytes, metamyelocytes, bands, and neutrophils. Only the last fates within this lineage (band/neutrophils) are fully functional and have bactericidal potentials. The antigenic changes during these stages have been widely studied from an immunophenotypic perspective. [2].

Among the CD markers, CD15 needs special attention in granulocyte maturation charts. Early studies suggested the expression of CD15 from GMP through the segmentation phase of neutrophils [29]. In other studies, expression of CD15 was shown at the blast stage but not on $CD34^{+}$ cells [30-32]. More recent studies indicate that a small portion of $CD34^{+}$ bone marrow precursor cells do expresses CD15 and this expression increases significantly with sequential maturation from promyelocytes to neutrophils [33, 34]. So it seems that expression of CD15 is the only key to differentiate between myeloblast and GMP [35]. A summary of antigen expression during different developmental stages of neutrophils is shown in Table **1.**

MONOCYTE MATURATION

Monocytes maturation starts from monoblasts as a continuum through one intermediate stage termed the promonocyte [32, 36]. With maturation of monoblasts from GMPs, expression of CD4 begins and increases with more differentiation. In contrast, CD34 expression stops with transition from monoblasts toward promonocytes. The expression of CD64, HLA-DR, and CD33 are retained at relatively high levels on maturing monocytes unlike the myeloid counterparts and may serve as useful monocytic markers [2].

In general, the presence of CD4 on monoblast and its progenies can help differentiate them from myelocytic lineages and also GMP. The presence of CD33 makes them different from T-cell subtypes [2]. A summary of antigen expression during different developmental stages of Monocytes is shown in Table **2.**

Table 2: **Expression of Surface Antigens during Different Stages of Monocytic Maturation**

	GMP	Monoblast	Promonocyte	Monocyte
CD4	−	−/+	+	+
CD11b	−	−	++	+++
CD13	++	++	+/++	++/+++
CD14	NA [b]	−	+/++	+++
CD15	−	−	++	+
CD16	−	−	−	−/+
CD33	+++	+++	+++	+++
CD34	+/++	+	−	−
CD36	−	−	++	+++
CD45	NA [a]	+	++	+++
CD64	++	−	++	+++
HLA-DR	++	++	+++	++/+++

[Modified from Wood B: Multicolor immunophenotyping: human immune system hematopoiesis. Methods Cell Biol. 2004; 75: 559-76.]

GMP means granulocyte monocyte progenitor cell; +++ means strong expression; ++ means moderate expression; + means weak expression; +/− means very weak expression; − means no expression; NA means Unknown Data Not Available; a means possible expression; b means possible not expressing.

ERYTHROPOIESIS

Erythropoiesis is the process of formation of red blood cells. The maturational stages of this process have historically been divided into proerythroblasts, basophilic erythroblasts, polychromatophilic erythroblasts, and erythrocytes based on their morphological appearance. The morphological changes have shown reasonable correlations with the observed immunephenotypes [37-40]. The expression of CD34 is high on MEPs but low on proerythroblasts. The expression of CD38 also decreases with maturations. Proerythroblasts show high levels of CD71 and CD235a, both of which being absent on MEPs. It should be noted that the preparations of BM samples for evaluating maturational stages during erythropoiesis differ from those for other lineages. For example, usage of lysing reagents such as NH_4Cl generally leaves only proerythroblasts for evaluation [2]. A summary of antigen expression during different developmental stages of erythrocytes is shown in Table **3.**

MEGAKARYOPOIESIS

Megakaryopoiesis is the process that leads to the production of the platelets. The development of the

Table 3: Expression of Surface Antigens during Different Stages of Erythropoiesis (Erythrocyte Maturation)

	MEP	Proerythroblast	Basophilic Erythroblast	Polychromatophilic Erythroblast	Erythrocyte
CD34	++	−/+	−	−	−
CD36	−	++	+++	++	−
CD38	++	+	−/+	−	−
CD45	++	+	−/+	−	−
CD45RA	−	NA	NA	NA	NA
CD71	−	+++	+++	+++	−
CD117	++	++	−	−	−
CD123	−	NA	NA	NA	NA
CD235a	−	+/++	+++	+++	+++
HLA-DR	++	++	+	−	−
Hemoglobin	−	−	−/+	+	+++

[Modified from Wood B: Multicolor immunophenotyping: human immune system hematopoiesis. Methods Cell Biol. 2004; 75: 559-76.]

MEP means megakaryocyte–erythrocyte progenitor cell; +++ means strong expression; ++ means moderate expression; + means weak expression; +/− means very weak expression; − means no expression; NA means Data Not Available.

platelet passes through megakaryoblast, promegakaryocytes, and megakaryocytes. Production of the platelets from mature megakaryocytes needs cytoplasmic fragmentation occurring through a dynamic and regulated process, called proplatelet formation. This process consists of pseudopodial elongations with final breaking into the blood.

The hallmarks of this lineage are CD41 and CD61. CD41 is present on about 3% of marrow CD34$^+$. These CD34$^+$CD41$^+$ cells are enriched in megakaryoblasts. The expression of CD41 precedes the detection of CD42 [41]. Thus, CD34$^+$CD41$^+$CD42$^−$ cells correspond to true megakaryoblast whereas CD41$^+$CD42$^+$ cells give rise to promegakaryocytes and the expression of CD42 accompanies late differentiation steps. CD61 expression starts with passing through MEP to megakaryoblast and can help differentiate these two cells. As the maturation of cells increases, the CD34 antigen disappears [42].

Table 4: Expression of Surface Antigens during Different Stages of Megakaryopoiesis (Platelet Maturation)

	MEP	Megakaryo-blast	Promega-karyocyte	Mega-karyocyte
CD34	++	−/+	−	−
CD38	++	−/+	+	++
CD41	++	+	+	++
CD42	−	−	−/+	+
CD61	−	+	+	++

MEP means megakaryocyte–erythrocyte progenitor cell; +++ means strong expression; ++ means moderate expression; + means weak expression; +/− means very weak expression; − means no expression.

A summary of antigen expression during different developmental stages of megakaryocytes is shown in Table **4.**

CONCLUSION

Although, to the best of our knowledge, no study has evaluated all the CD markers together simultaneously, the sum of previous investigations can logically be mixed to reach the final picture of the whole hematopoietic hierarchy (Figure **2**).

Our current knowledge from the widely popular model of describing the hematopoietic hierarchy, the “sequential determination model”, provides us with guides to isolate different cells within different stages of maturation (Figure **3**) and helps us differentiate various subsets of hematopoietic hierarchy based on cell surface antigen markers. However, there are still some missing parts; for instance, the status of CD38 expression on the Myeloblasts and Monoblasts is not determined.

Unlike the classical sequential determination model, two human cord blood derived cell populations (CD34$^+$CD45RA^{high}CD10$^+$Lin$^−$ and CD34$^+$CD45RA^{high-}CD7$^+$Lin$^{−)}$ have been described by Haddad and colleagues to contain robust myelomonocytic differentiation potentials despite being primed to

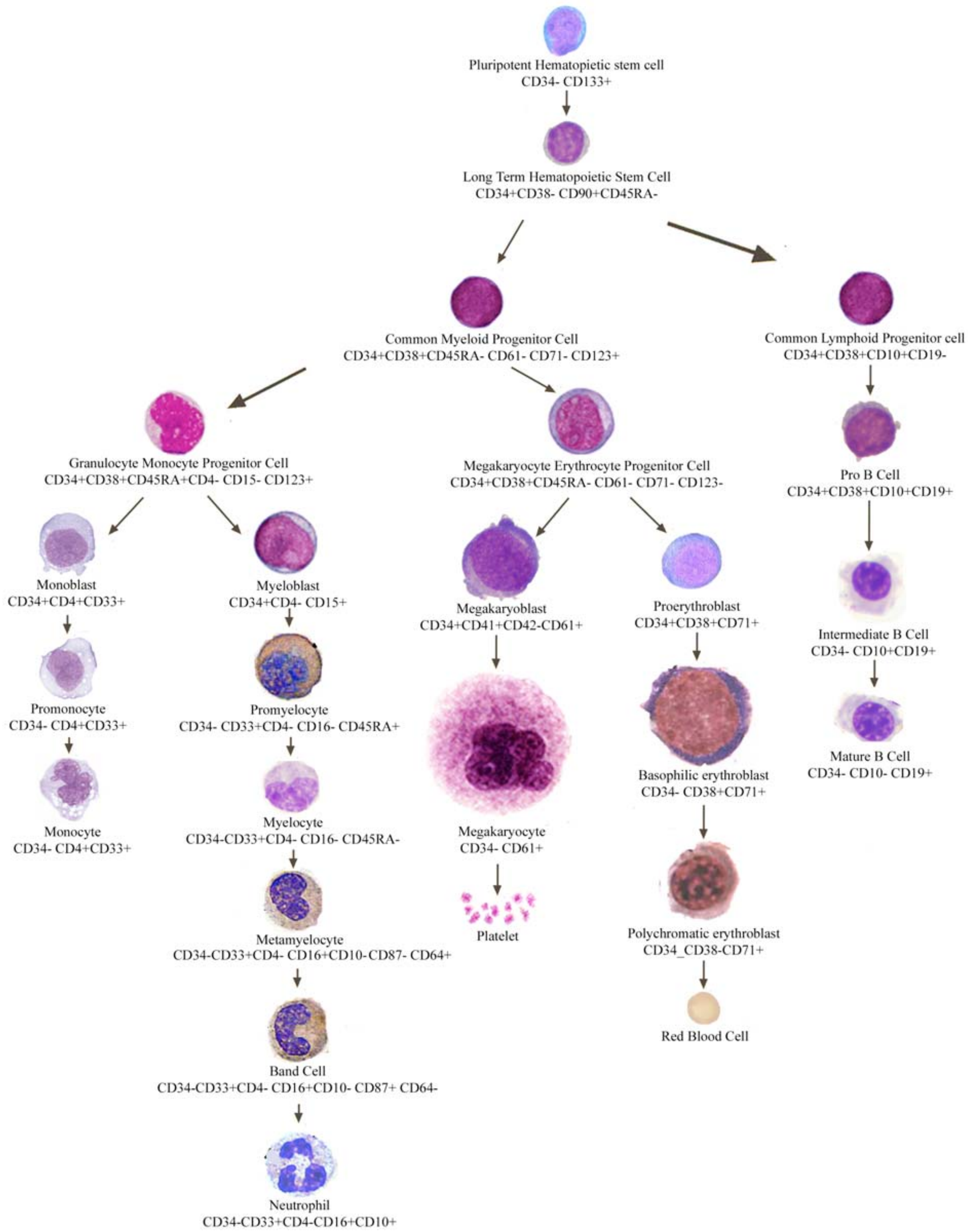

Figure 2: A schematic representation for how different cells within hematopoietic hierarchy express various cell surface markers.

develop the T-cell and NK cell or the B-cell lineage, respectively [43]. However, this $CD34^+CD38^-CD7^+$ population does not exist in the adult bone marrow [14]. Similarly, $CD34^+CD10^-CD19^-$ cells are known to be committed to early B-cell development do still have the capacity to differentiate into NK-cells, T-cells and macrophages [44]. Additionally, $CXCR4^-CD34^+CD19^+$ B-cell progenitor cells have been shown to have potentials for granulocyte, macrophage, and red blood cell development [45].

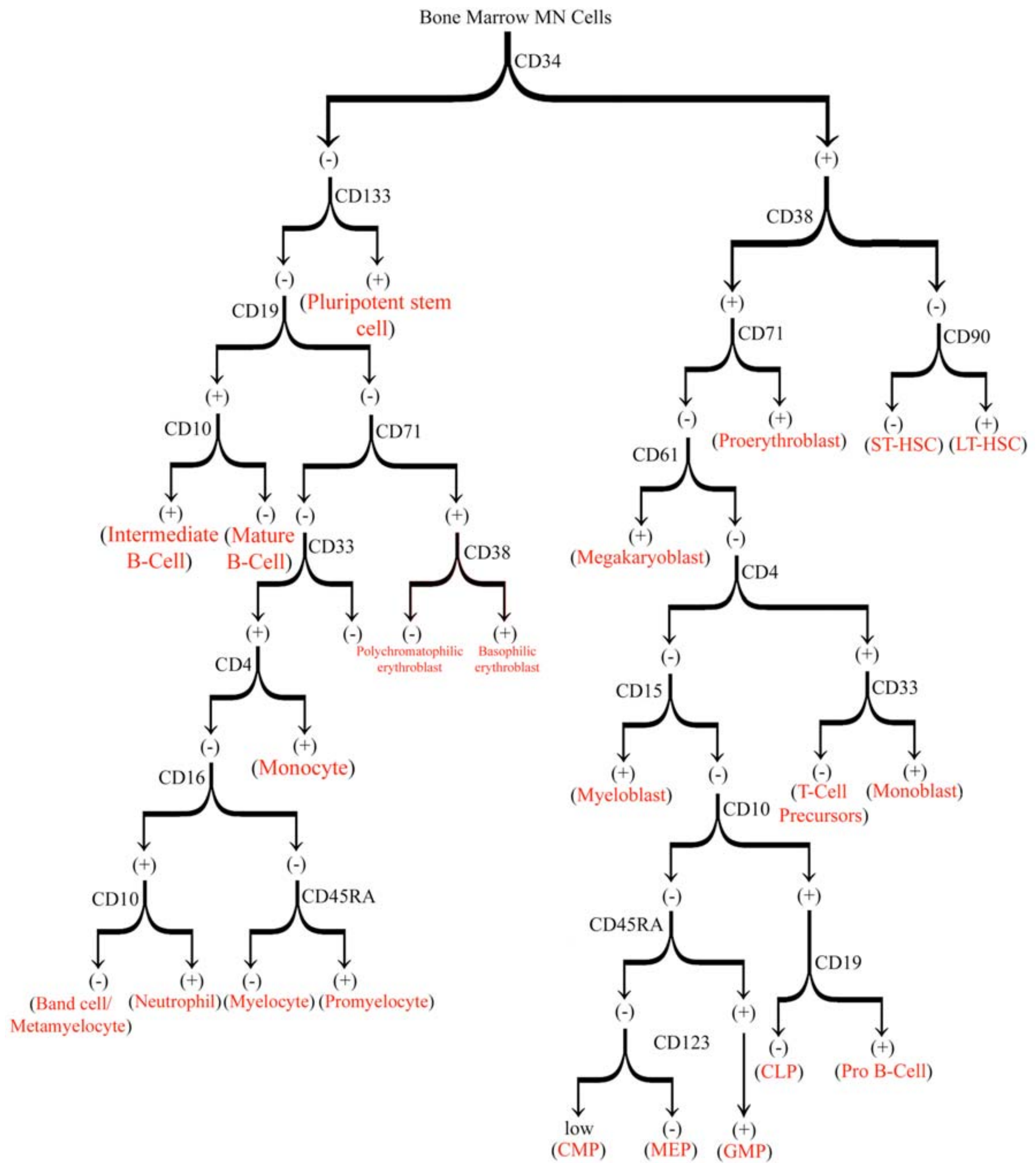

Figure 3: A proposed algorithmic chart for isolation of cells within hematopoietic hierarchy based on the cell surface antigen markers. (Abbreviations: CLP=Common Lymphoid Progenitor cell, CMP = Common Myeloid Progenitor Cell, GMP = Granulocyte Monocyte Progenitor Cell, LT-HSC = Long Term Hematopoietic Stem Cell, MEP = Megakaryocytic Erythroid Progenitor Cell, MN = Mononuclear Cell, ST-HSC = Short Term Hematopoietic Stem Cell.).

The identification of progenitors with diverse cell fates has prompted new models of hematopoiesis [46-50]; however, most of these models lack the consensus for a lineage branching map. A revised model to depict the developmental relationships between hematopoietic cell lineages has been proposed by Ceredig and collegues. This model involves grouping the pairwise relationships between lineage fates around a broken circle, and considers the hematopoietic hierarchy as continuum other than a branched stepwise model [51].

Although these new models may be more realistic, because the differentiation of hematopoietic cells is a continuous rather than a step-wise process, they models cannot help us in isolating cells from this spectrum and the classical models seem to be more practical for this purpose.

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