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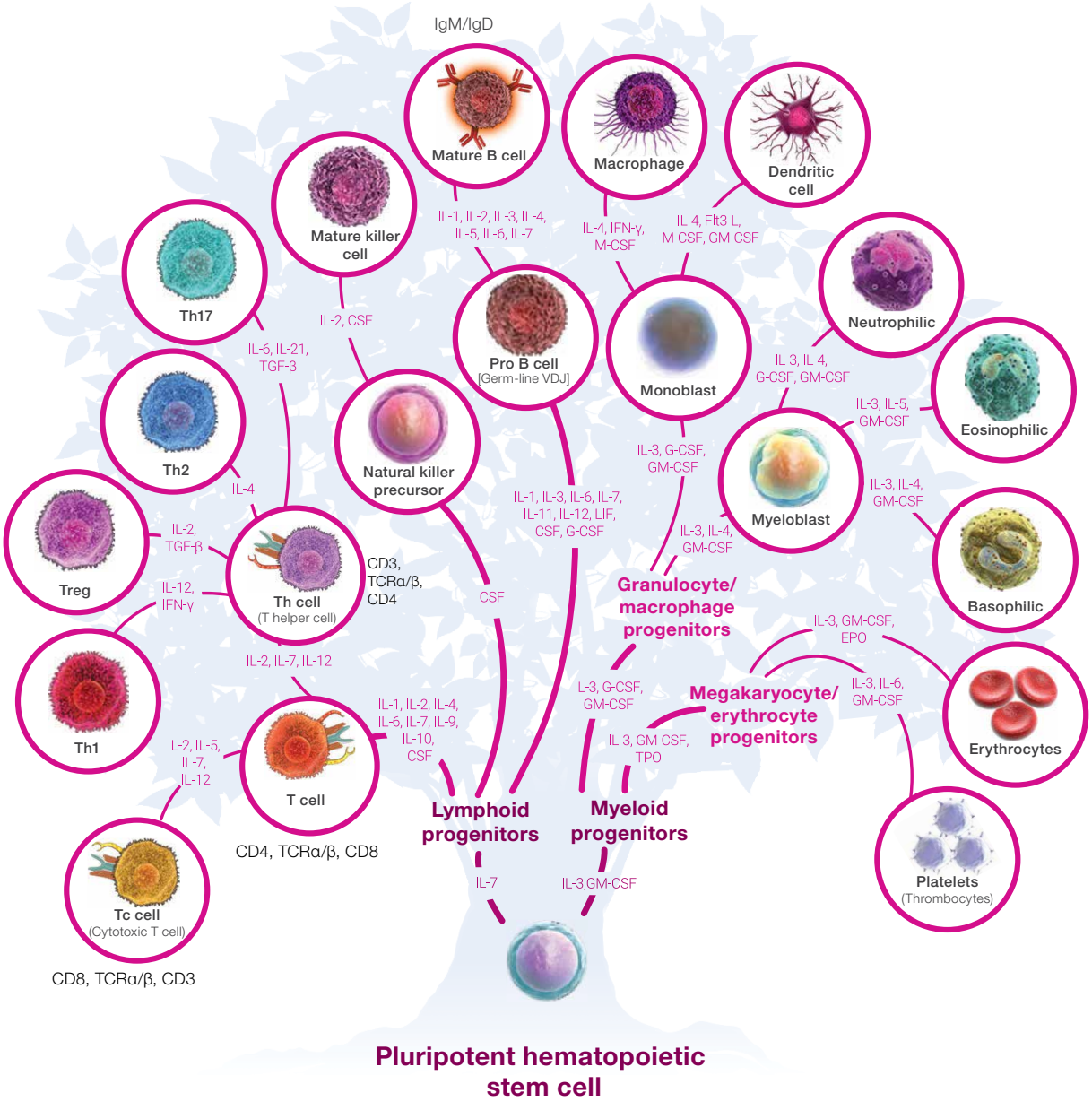
Hematopoietic stem cell differentiation

Hematopoietic stem cells (HSCs) are the basis of hematopoiesis, or the process by which undifferentiated cells propagate mature blood cell lineages. Through hematopoiesis, hundreds of billions of blood cells are produced daily in order to maintain normal blood circulation [1]. HSCs are rare, multipotent, self-renewing cells that are mainly found in the bone marrow (BM) but can also be found in umbilical cord blood and peripheral blood [1-4].

HSCs are non-homogeneous and can be divided into two populations—long-term self-renewing cells, which are ideal for transplantation, and short-term self-renewing cells. Additionally, HSCs can also be categorized based on their biases toward lymphoid and myeloid lineages: separating into those that produce a balance of lymphoid and myeloid cells, those that produce very few lymphoid cells, and those that produce very few myeloid cells [4,5].



HSCs undergo a series of changes in order to produce the mature blood cells found in circulation. These progeny gradually lose their capabilities of self-renewal, becoming more restricted in their differentiation potential and generating lineage-committed progenitor cells [2].

The proliferation, self-renewal, and differentiation of HSCs into various blood cells are dependent on the involvement of certain cytokines and growth factors. Stem cell factor (SCF) and thrombopoietin (TPO), for example, have been found to be important factors in the development and self-renewal of HSCs. While interleukins, such as IL-2, IL-3, IL-4, IL-6, IL-7, and IL-12, influence proliferation and maturation [3], colony-stimulating factors (CSFs), including granulocyte CSF (G-CSF), macrophage CSF (M-CSF), and granulocyte-macrophage CSF (GM-CSF), specifically stimulate differentiation of HSCs into committed cells [6].

In addition to cytokines and growth factors, small molecules are becoming an important tool in stem cell research and application, as demonstrated by several studies examining their potential in manipulating HSCs [7]. Several small molecules have been shown to effect various aspects of HSC expansion including self-renewal, apoptosis inhibition, and differentiation inhibition. Some examples include increased self-renewal by UM171, SR1, P18IN003, 6-bromoindirubin-3′-oxime (BIO) and garcinol, the inhibition of differentiation by diethylaminobenzaldehyde (DEAB), and the inhibition of apoptosis by Z-VAD-FMK and 5-HT [7].

Decades of research have established that, upon transplantation, HSCs have the ability to entirely reconstitute the hematopoietic system. They are currently the only type of stem cells used regularly in clinical applications. HSC transplantation is most commonly used to replenish hematopoietic systems destroyed by chemotherapy or radiation therapy during treatment of patients with blood or bone marrow malignancies. The HSCs that are used for transplantation are derived from bone marrow, peripheral blood, or umbilical cord blood, and can be either autologous (the patient's own cells) or allogeneic (from a genetically matched donor). Allogeneic HSC transplantation is still considered a dangerous procedure because of various associated complications, such as graft-versus-host disease (GvHD) [4,8].

Although HSC transplantation is well established, there are still many remaining challenges that need to be addressed in order to optimize success. These challenges include improving the access of HSC transplantation to patients in less-developed countries, improving the understanding of the immunological basis behind graft rejection and GvHD, and identifying both new sources of HSCs and new techniques for obtaining sufficient cell numbers [8].

Transplantation of BM containing HSCs is predominantly used to treat blood cancers, but also other hematopoietic related diseases, such as thalassemia and various anemias [4]. Most of the clinical trials using BM/HSCs transplantations aim to deal with hematopoietic diseases. There are also trials that investigate the ability of BM/HSCs transplantations to regenerate other tissues, such as liver and heart; however, the feasibility of this approach is yet to be determined [8]. Another avenue that is explored for the use of HSCs is gene therapy, whereby cells are manipulated *ex vivo* and then transplanted. BM transplantation contains heterogeneous fractions of cells, and there are indications that using purified HSCs for various applications is advantageous [4].

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