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Review

Sources of Hematopoietic Stem and Progenitor Cells and Methods to Optimize Yields for Clinical Cell Therapy

Sandhya R. Panch [1,*], James Szymanski [1], Bipin N. Savani [2], David F. Stroncek [1]

[1] Cell Processing Section, Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Bethesda, Maryland
[2] Department of Hematology, Vanderbilt University School of Medicine, Nashville, Tennessee

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Bone marrow (BM) aspirates, mobilized peripheral blood, and umbilical cord blood (UCB) have developed as graft sources for hematopoietic stem and progenitor cells (HSPCs) for stem cell transplantation and other cellular therapeutics. Individualized techniques are necessary to enhance graft HSPC yields and cell quality from each graft source. BM aspirates yield adequate CD34$^+$ cells but can result in relative delays in engraftment. Granulocyte colony-stimulating factor (G-CSF)–primed BM HSPCs may facilitate faster engraftment while minimizing graft-versus-host disease in certain patient subsets. The levels of circulating HSPCs are enhanced using mobilizing agents, such as G-CSF and/or plerixafor, which act via the stromal cell-derived factor 1/C-X-C chemokine receptor type 4 axis. Alternate niche pathway mediators, including very late antigen-4/vascular cell adhesion molecule-1, heparan sulfate proteoglycans, parathyroid hormone, and coagulation cascade intermediates, may offer promising alternatives for graft enhancement. UCB grafts have been expanded ex vivo with cytokines, notch-ligand, or mesenchymal stromal cells, and most studies demonstrated greater quantities of CD34$^+$ cells ex vivo and improved short-term engraftment. No significant changes were observed in long-term repopulating potential or in patient survival. Early phase clinical trials using nicotinamide and StemReginin1 may offer improved short- and long-term repopulating ability. Breakthroughs in genome editing and stem cell reprogramming technologies may hasten the generation of pooled, third-party HSPC grafts. This review elucidates past, present, and potential future approaches to HSPC graft optimization.

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INTRODUCTION

Advances in our understanding of hematopoietic stem and progenitor cell (HSPC) biology has fueled a renewed interest in optimizing HSPC quality and yields from various stem cell sources. Improved yields are of potential value in hematopoietic stem cell (HSC) transplantation and in gene therapy trials, as well as in the field of regenerative medicine, to generate novel third-party products such as HLA-compatible HSCs, universal donor erythrocytes, and platelets. In our review we summarize the various sources of HSPCs and methods to improve stem cell collection from each of these sources.

HISTORICAL PERSPECTIVE

Much of the research related to HSPCs has been driven by the need to transplant hematopoietic cells to treat marrow failure and leukemia (Figure 1). The search for HSCs began in the aftermath of the bombings in Hiroshima and Nagasaki in 1945 when the biologic effects of radiation began to be recognized. Bone marrow (BM) was identified as the source of cells capable of engraftment and hematopoietic recovery after radiation exposure. In 1959, Donnall Thomas and colleagues infused BM cells into 2 patients with advanced leukemia after supralethal doses of radiation and demonstrated hematopoietic recovery even though the patients ultimately succumbed to their leukemia. Subsequently, stem cell characterization studies were pioneered by Till and McCulloch, who studied splenic colony-forming units (CFUs), known today to be short-lived hematopoietic progenitors. The development of flow cytometry and monoclonal antibody technologies further aided cellular phenotyping at a higher resolution and has led to better characterization of HSPCs [1-3].

The presence of HSPCs in peripheral blood was first described by Goodman and Hodgson in murine models [4]. Thereafter, experiments carried out by cross-circulating larger animals provided a means of testing the efficacy of peripheral blood from a donor with normal marrow function in establishing a marrow graft in a recipient animal rendered

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* Correspondence and reprint requests: Sandhya R. Panch, MD, MPH, Cell Processing Section, Department of Transfusion Medicine, Clinical Center, National Institutes of Health, Building 10, 2N-326, Center Drive, Bethesda, MD 20892.
E-mail address: sandhya.panch@nih.gov (S.R. Panch).

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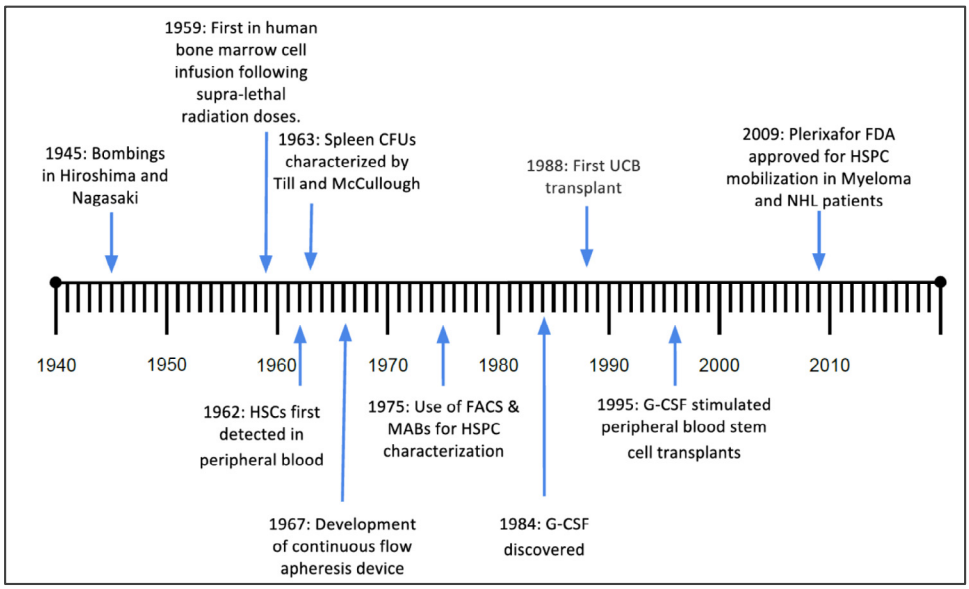

Figure 1. Milestones in HSPC collection and characterization for clinical cellular therapy. FACS indicates fluorescence-activated cell sorting; MABs, monoclonal antibodies; FDA, US Food and Drug Administration; NHL, non-Hodgkin lymphoma.

aplastic by an otherwise lethal dose of whole body irradiation [5]. After the development of a continuous-flow apheresis device by Judson et al. [6], McCredie et al. [7] demonstrated that leukocytes from peripheral blood collected by apheresis contained CFUs. In 1976 Richman et al. [8] demonstrated in a patient studied at weekly intervals during multiple courses of chemotherapy cyclical changes in the concentration of stem cells with maximum values of 20 times baseline. It was estimated that at the time of peak CFU concentrations, a quantity of stem cells equivalent to that present in a bulk BM harvest could be obtained from the peripheral blood by processing 17 liters of whole blood during an apheresis procedure. The serendipitous discovery of granulocyte colony-stimulating factor (G-CSF) by Metcalf and colleagues in 1984 and its isolation and purification led to the application of G-CSF for increasing the concentration of circulating HSPCs or for "mobilization" of HPSCs. The finding that the administration of G-CSF to healthy allogeneic stem cell donors to increase the yield of stem cells that could be collected by apheresis led to the routine use of mobilized peripheral blood HSPCs in clinical autologous and allogeneic transplantation studies [9,10].

Discovery of umbilical cord blood (UCB) as a third source of HSPCs occurred in the wake of another nuclear accident in the 1980s, the Chernobyl catastrophe. Broxmeyer et al. explored the hematopoietic potential of UCB HSPCs for clinical use based on the knowledge that these HSPCs could be maintained in long-term cultures for many weeks, with self-renewal and progenitor cell proliferation potential in vitro. The resulting multi-institutional clinical collaboration led to the first successful UCB transplantation for treatment of Fanconi's anemia in 1988 [11,12].

Today, based on data from the National Marrow Donor Program, all 3 sources, BM, mobilized peripheral blood, and UCB, serve as sources of stem cells for hematopoietic transplantation and other novel cellular therapies. Mobilized peripheral blood has emerged as the most widely used stem cell source over the last decade (see nmdp.org).

HSPC COLLECTION AND CELLULAR AND CLINICAL CHARACTERISTICS

HSPCs collected from different sources vary in cellular characteristics and clinical application as described in Table 1. For marrow HSPC collections, BM aspirates are performed on the donor under general anesthesia. Up to 1.5 liters of marrow aspirate are collected from multiple sites along the posterior iliac crest, using 8- to 11-gauge biopsy needles. No more than 20 mL of marrow per kilogram of donor weight is aspirated at a time. The entire procedure may last up to 2.5 hours. Risks include bleeding, infection, and localized pain. Autologous blood may be collected before the procedure to replace blood lost with the aspirated marrow and to treat periprocedural bleeding requiring resuscitation.

The collection of HSPCs from peripheral blood requires prior mobilization of stem cells from the BM using agents such as G-CSF and/or plerixafor. G-CSF is administered for 4 to 5 consecutive days at doses of 5 to 15 μg/kg/day. In general, G-CSF is very effective an increasing the concentration of $CD34^+$ cells in the peripheral blood, but in some cases mobilization is poor. Plerixafor may be administered at the end of a 4- to 5-day course of G-CSF as a single dose at 240 μg/kg 4 to 6 hours before apheresis collection to improve collection yields for autologous collections. Most centers limit the apheresis collection to the processing of a maximum of 24 liters of whole blood over 1 to 2 days. In donors in whom peripheral veins will not support an apheresis procedure (ie, children, dehydrated adults), a central venous catheter is inserted requiring periprocedural hospitalization. Toxicities associated with collection of G-CSF–mobilized peripheral blood stem cell (PBSC) concentrate are related to mobilizing agents (bone pain, insomnia, flu-like symptoms with G-CSF) and apheresis collection procedures (citrate or other anticoagulant related toxicity-hypocalcemia, bleeding from central venous catheter site).

Donor preferences for the donation of a PBSC concentrate or marrow vary. In a recent multicenter trial with donors