

Ten Best Readings Relating to Stem Cells and Transplantation

Clayton Smith, MD, FRCPC

From the Leukemia/BMT Program at the BC Cancer Agency & Vancouver Hospital & Health Sciences Centre, Vancouver, British Columbia

Verfaillie CM, Pera MF, Lansdorp PM. Stem cells: hype and reality. *Am Soc Hematol Educ Program.* 2002;369-391.

This article provides an excellent review of the current status of embryonic stem cells, adult tissue-derived pluripotent stem cells, and the mechanisms of self-renewal and differentiation of hematopoietic cells.

Jiang Y, Jahagirdar BN, Reinhardt RL, et al. Pluripotency of mesenchymal stem cells derived from adult marrow. *Nature.* 2002;418:41-49.

This report describes the isolation of multi-potential adult progenitor cells from bone marrow that can differentiate into mesenchymal cells, hematopoietic cells, and epithelium in a variety of organs. As these cells appear to proliferate extensively without obvious senescence or loss of differentiation potential, they may be an ideal cell source for therapy of inherited or degenerative diseases.

Camargo FD, Green R, Capetenaki Y, et al. Single hematopoietic stem cells generate skeletal muscle through myeloid intermediates. *Nat Med.* 2003;9:1520-1527.

Earlier reports suggested that hematopoietic stem cells can trans-differentiate into muscle cells. This article demonstrates that this is in reality due to cell fusion of circulating myeloid cells to repairing muscle cells. The authors highlight the concerns that reports of "stem cell plasticity" need to be viewed with caution until rigorous experiments are conducted.

Tricot G, Gazitt Y, Leemhuis T, et al. Collection, tumor contamination, and engraftment kinetics of highly purified hematopoietic progenitor cells to support high dose therapy in multiple myeloma. *Blood.* 1998;91:4489-4495.

The authors summarize a clinical trial involving transplantation of purified autologous fluorescence-activated cell sorting (FACS)-sorted CD34⁺ Thy1⁺ Lin⁻ peripheral blood cells in patients with myeloma. The grafts from three patients were tested for tumor contamination and contained no detectable clonal myeloma cells. Engraftment occurred in all patients but was delayed in some. This approach and other strategies involving positive selection of stem cells may be refined in future studies as a method for eliminating tumor cells that may contaminate an autologous transplant.

Storms RW, Trujillo AP, Springer JB, et al. Isolation of primitive human hematopoietic progenitors on the basis of aldehyde dehydrogenase activity. *Proc Natl Acad Sci U S A.* 1999;96:9118-9123.

As an alternative to positive selection of hematopoietic stem cells based on CD34 expression, a method for isolating stem cells and progenitors is described in this report that uses a fluorescent substrate for the enzyme aldehyde dehydrogenase (ALDH). This technique may be useful for isolating stem cells from other tissues as well.

Del Toro G, Satwani P, Harrison L, et al. A pilot study of reduced intensity conditioning and allogeneic stem cell transplantation from unrelated cord blood and matched family donors in children and adolescent recipients. *Bone Marrow Transplant.* 2004 Jan 19. (Epub ahead of print.)

Twenty-one children underwent cord blood transplant following a reduced-intensity conditioning regimen. Seventy-five percent of the recipients demonstrated sustained engraftment. Since cord blood is a near universal source of hematopoietic stem cells and since reduced-intensity regimens are less toxic than traditional myeloablative conditioning regimens, this approach to hematopoietic stem cell transplantation may allow a greater number of transplants to be performed more safely than previously possible.

Devine SM, Lazarus HM, Emerson SG. Clinical application of hematopoietic progenitor cell expansion: current status and future prospects. *Bone Marrow Transplant.* 2003;31:241-252.

The authors provide an excellent summary of the attempts to expand hematopoietic stem cells and the challenges that need to be surmounted to achieve this. Successful expansion of stem cells could revolutionize the practice of bone marrow transplantation by providing a greater number and quantity of acceptable hematopoietic stem cell grafts than currently available.

Uchida N, Dykstra B, Lyons KJ, et al. Different in vivo repopulating activities of purified hematopoietic stem cells before and after being stimulated to divide in vitro with the same kinetics. *Exp Hematol.* 2003;31:1338-1347.

The authors purified murine hematopoietic stem cells (HSCs) to near purity and then demonstrated that growth

factors can differentially affect the ability of HSCs to execute a self-renewal division within a single cell cycle, even when the kinetics of proliferation are the same. These types of studies will be important for defining the environmental and genetic events that govern the developmental fate of stem cells. Understanding these processes is critical to developing techniques for successfully expanding stem cells.

Antonchuk J, Sauvageau G, Humphries RK. HOXB4-induced expansion of adult hematopoietic stem cells ex vivo. *Cell*. 2002;109:39-45.

The Hox family of transcription factors have emerged as important regulators of primitive hematopoietic cell proliferation and differentiation. In this study, the authors found that HOXB4 expression supported high-level ex vivo hematopoietic stem cell (HSC) expansion. HSCs transduced to express HOXB4 retained full lymphomyeloid repopulating potential and had enhanced in vivo regenerative potential, demonstrating the feasibility of achieving significant ex vivo expansion of HSCs without functional impairment. The development of safe pharmacologic versions of HOXB4 or the identification of inducers of endogenous HOXB4 expression might be useful in efforts to expand stem cells for transplantation purposes.

Wang X, Rosol M, Ge S, et al. Dynamic tracking of human hematopoietic stem cell engraftment using in vivo bioluminescence imaging. *Blood*. 2003;102:3478-3482.

Human CD34⁺ subsets were transduced with lentiviral vectors expressing the luciferase gene. The fate and distribution of cells were then followed using a novel in vivo imaging system. The authors used state-of-the-art gene transfer procedures to mark human progenitor cells and then followed the behavior of these over time in a living animal.