Chasing Stem Cells Out of Their Home

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There is increasing interest in human embryonic stem cells (hESCs) as an alternative source of hematopoietic and endothelial cells. These undifferentiated cells, which are derived from fertilized embryos, have the capacity to develop into a variety of cell types of hematopoietic or endothelial potential, for use in cellular or gene therapies. By contrast, hematopoietic stem cells, which are derived from human bone marrow, mobilized peripheral blood, or umbilical cord blood, are limited by quantity and by the availability of matched donors to meet current cell therapy needs. Moreover, hESCs have unlimited proliferative potential and can give rise to erythroid, myeloid, and lymphoid lineages, and cell lines derived from hESCs provide a unique tool to study hematopoiesis, drug discovery, and cell-based therapies.

Dr. Mickie Bhatia, who has authored two recent reviews on this topic *(Ann NY Acad Sci 2007;1106:219-222 and Exp Hematol 2005;33:987-996)*, chaired the Saturday Education Session on Stem Cells. In the first presentation, Dr. Bhatia provided an update on current progress on the translation of embryonic stem cell biology into clinical trials of cell replacement therapies. Among the hot topics in defining the use of hESCs in clinical hematology is the need for standardized, defined stem cell assays that measure both hematopoietic and endothelial development potential. For example, Dr. Bhatia has shown that hESCs that lack pan-leukocyte marker CD45 (but do express PECAM-1, Flk-1, and VE-cadherin), termed $CD45^{neg}$PFV, constitute a population of cells which have both hematopoietic and endothelial cell replacement potential. As these cells can be derived under explicitly defined conditions, it is anticipated that they may provide a potent source for hematopoietic and endothelial replacement and reconstitution, and could potentially be used in induction of immune tolerance, angiogenesis, and tissue vascularization.

The second talk of the session was given by Dr. George Daley, whose studies of ESCs in mouse models have helped define transcription factors and signaling events in hESC differentiation development. He reviewed the recent advances in somatic cell nuclear transfer to develop histocompatible cells and avoid immune rejection during *in vivo* transplantation. Finally, Dr. Irving Weissman elaborated on the conditions necessary for stem cell self-renewal.

Another exciting area of stem cell research is the homing and trafficking of stem cells within bone marrow niches. On Monday, in the Oral Session on Biology of the Stem Cell Milieu, a number of studies were presented on the chemokines and adhesion molecules involved in the regulation, trafficking, and homing of bone marrow stem cells. One of the most exciting clinical applications of this concept is the use of the CXCR4 inhibitor AMD3100 in the mobilization of hematopoietic stem cells in patients with multiple myeloma undergoing autologous stem cell transplant (ASCT). CXCR4 and its ligand, stromal derived factor-1 (SDF1), regulate hematopoietic stem-cell trafficking. AMD3100, a competitive antagonist of CXCR4, disrupts the binding of SDF1, induces rapid mobilization of CD34+ cells, and facilitates stem cell mobilization in healthy volunteers, without significant toxicity.

Although mobilization for ASCT in general results in successful harvest, the mobilization procedure is not always an easy job. Several important predictors of the success of the peripheral blood stem cell yield include the percentage of marrow involvement, prior radiotherapy, and number of prior chemotherapy regimens. The CXCR4 inhibitor AMD3100 has been evaluated in several clinical trials of hematologic malignancies and has been shown to improve the number of CD34+ cells mobilized, including in those in whom mobilization with G-CSF has been unsuccessful. Engraftment of AMD3100-mobilized cells appears to be prompt and durable. The results of a randomized phase III clinical trial of G-CSF plus AMD3100 (Plerixafor) in first or second CR or PR in patients with multiple myeloma requiring ASCT was presented by Dr. DiPersio yesterday. Seventy-two percent of those treated with G-CSF and AMD3100 achieved the primary endpoint, 6 $x10^6$ CD34+ cells/kg in two or fewer apheresis days, as compared with those receiving G-CSF and placebo, 34 percent. The study demonstrated that patients receiving G-CSF and AMD3100 had a statistically significantly higher chance of achieving target collection earlier, compared to those receiving GCSF alone. These data will hopefully help lead to FDA approval of AMD3100 to enhance stem cell collections and likely change the standard of care of stem cell collection in multiple myeloma and other hematologic malignancies.