

Stem Cells and Transplantation

Stem cells are celebrities these days. They have been touted as potential cures for diseases ranging from cancers to heart attacks. They may provide ways to regenerating aging or ill body parts. Like all good celebrities, they have been embroiled in controversies, some technical and some involving politics, ethics, and religion. Some stem cells and stem cell properties are well characterized and are being used to treat diseases as we speak. Other stem cells or stem cell properties remain in the realm of conjecture or outright hype. The purpose of this issue of *Cancer Control* is to shed some light on the stem cells of the blood system and give some examples of how they are being used to understand and treat blood diseases. Before embarking on these reviews, it may be helpful to define the different types of stem cells that are currently known or conjectured:

Embryonal Stem (ES) Cells — These cells are derived from early developing embryos and can be maintained and expanded in culture while retaining their ability to generate virtually any tissue in the body. Mouse ES cells have been studied for over 2 decades while human and primate ES cells have been established and studied only since the late 1990s. ES cells are controversial because they are derived from embryos; however, they are also the stem cells with the most promise to repair and regenerate tissues and organs. There are substantial scientific and technical hurdles for human ES cells to be used clinically. However, even in well-studied and relatively simple mouse models of human diseases, it is difficult to transplant ES cells and have them successfully engraft and form the appropriate tissues.

Multipotential Adult Stem Cells (MAPCs) — MAPCs were recently isolated from adult bone marrow and are characterized by their ability to differentiate into virtually any body tissue under the appropriate conditions. The promise of MAPCs is that they could have the functionality of ES cells but could be collected from a technically simple and ethically acceptable source such as adult bone marrow. Much more needs to be learned about these cells to determine if this promise is realistic.

Tissue-Specific Stem Cells — It is now clear that many, if not all, tissues are continually turning over and regenerated from stem cells that reside in that tissue. Stem cells have been found for the blood system (hematopoietic stem cells), skin, gut, liver, and perhaps brain and pancreas. These stem cells exist in small numbers but have enormous self-renewal potential so that they can divide

and give rise to a large number of daughter cells that progressively differentiate into mature cells of the particular tissue.

Hematopoietic Stem Cells (HSCs) — HSCs are the longest studied and best known examples of tissue specific stem cells. Every day, billions of new blood cells are formed, all generated from a small number of HSCs. In the mouse, a single HSC can regenerate every cell in the blood system including neutrophils, lymphocytes, red blood cells, and platelets for the lifespan of the animal. HSCs generate these differentiated cells through a progressive series of intermediates, termed *progenitors*, that have limited self-renewal capacity and a restricted ability to give rise to cells of the different cell lineages. For example, in contrast to an HSC, which can give rise to every blood cell type, a common lymphoid progenitor (CLP) has been identified that can give rise to only lymphoid cells and not myeloid cells.

Peripheral Blood Stem Cells (PBSCs) — PBSCs are HSCs that are circulating in the blood. HSCs circulate at low levels in the blood all the time but can increase in number dramatically when a person is treated with certain cytokines such as G-CSF or when hematopoietic recovery occurs following chemotherapy. PBSC transplants tend to engraft faster than bone marrow transplants presumably because they have greater a proportion of mature progenitors. When patients hear and talk about “stem cell transplants,” they are typically referring to peripheral blood stem cell transplants.

Cancer Stem Cells — Many cancers, if not all, are now believed to be generated and sustained by a small number of malignant stem cells that are analogous to normal tissue stem cells. Understanding the biology of these stem cells may be crucial to curing many cancers since it is the malignant stem cells that may survive chemotherapy and then cause relapse.

Stem Cell Plasticity — The possibility that tissue-specific adult stem cells can trans-differentiate into other tissue types has received much attention in the scientific and lay press over the last few years. For example, if hematopoietic stem cells possessed sufficient developmental plasticity, they could regenerate muscle, neurons, liver, and other tissues. If this were correct, stem cells that could easily be obtained from an adult's bone marrow could be used to correct muscular dystrophy, myocardial infarctions, strokes, hepatitis, and other diseases. Currently, it appears that many of the early reports of stem cell

plasticity were due to processes including fusion of donor stem cell progeny with mature cells of the tissue in question, leading to the appearance of donor markers in mature recipient cells. Other technical issues may also have contributed to an overestimation of the ability of tissue-specific stem cells to trans-differentiate into other tissues. However, since entire animals can be cloned from the nucleus of an apparently completely differentiated cell, it appears that every cell, including stem cells, may have an extraordinary amount of plasticity. Perhaps if we could identify the factors that promote trans-differentiation, a whole new generation of tissue regeneration and repair therapies could be developed.

The brief summary above gives only a glimpse of stem cells and their biology. The study of stem cells has become such a broad subject in the last several years that it has become difficult to encapsulate it in a single journal issue. To provide more insight into the exciting developments in stem cell biology, this issue includes a list of "Ten Best Readings" that summarizes current thinking about ES cells, MAPCs, stem cell plasticity, and efforts to expand stem cells in culture. The individual reviews in this issue of *Cancer Control* focus on the following topics:

Dr. Elwood discusses the biology of HSCs with a focus on the role that telomerase and telomere length plays in HSC growth and in the development. Understanding how telomeres are maintained and how telomerase may interact with other stem cell processes including cell proliferation and differentiation pathways may be key to achieving successful expansion of HSCs and other stem cells. Interrupting telomerase activity in leukemic stem cells may provide a novel antitumor strategy.

Dr. Goggins and Dr. Rizzieri review an exciting new form of allogeneic HSC transplantation, termed *nonmyeloablative transplantation*. For the last 3 decades, it was believed that allogeneic transplants would successfully engraft only if very high doses of chemotherapy or radiotherapy were administered to patients prior to transplant. Recently, it has become clear that engraftment can occur with relatively low doses of immunosuppressive therapy and that the engrafted cells can exert potent graft-vs-tumor effects against some cancers including chronic myeloid leukemia and chronic lymphocytic leukemia. This form of transplantation may become even more widely used in the future as more is learned about the biology and technical aspects of this treatment.

Dr. Guzman and Dr. Jordan summarize our current understanding of leukemic stem cells and how they may be distinguished from their normal HSC counterparts. Understanding these differences may allow us to design more effective chemotherapy regimens and, more importantly, may point the way to developing novel targeted therapies against leukemia.

Dr. Muench and Dr. Bárcena summarize the experience in transplanting HSCs in utero to correct congenital

disorders. While some patients have been successfully treated with this approach, much remains to be learned about how to optimize engraftment and minimize graft rejection. Lessons learned from studying in utero transplantation may have great importance for performing HSC transplants in children and adults as well.

Lastly, Dr. Gasparetto describes the state of the art of HSC transplantation in multiple myeloma, the most widely used indication for stem cell transplantation. Evidence documenting the rationale and use of autologous PBSC and allogeneic HSC transplantation in this disease is presented. In addition, Dr. Gasparetto describes how other strategies including immunotherapies and novel drugs may be incorporated into HSC transplant-based approaches to treat myeloma.

Together, these reviews provide insight into some of the exciting developments in our understanding of HSC biology and transplantation, and they highlight the challenges we must address to further improve stem cell therapies. Many of the lessons learned in the study of HSCs will undoubtedly help to guide basic and clinical research into other types of stem cells as well. We live in an exciting time in stem cell research, and transplantation holds great promise. While some stem cell celebrities may have only 15 minutes of fame, others will be stars for years to come, and a few will undoubtedly change our lives.

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The next issue of *Cancer Control* will focus
on topics in neuro-oncology.
Look for your issue in May 2004.