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Betting on HSCs

The embryonic stem cell debate has made headlines in major newspapers worldwide. Advocates argue the prospective merits of stem cell therapies to correct tissue and metabolic defects. Likewise, opponents passionately argue against the use of, and even research on, such cells. In a related branch of endeavor, there has been much progress at the interface between transplantation and hematology, currently resulting in the hematopoietic reconstitution of myeloablated cancer patients, for alternative gene- or tissue-replacement therapies that employ the "other stem cell"—hematopoietic stem cells (HSCs)—as the gene-delivery vehicle or source of corrective cells. Many hopes converge on HSCs, and the tissues from whence they come, as less controversial sources for the therapies mentioned above.

In this issue of *Nature Immunology*, we present a Focus on the current state of HSC biology, discussing the hurdles and prospects for the expanded therapeutic use of these cells. HSCs possess two characteristics that make them strong candidates for corrective gene therapies: long-term self-renewal capacity and the pluripotentiality that is necessary to develop into multiple blood cell lineages.

As described in a Commentary by Verfaillie, prospective identification of HSCs is still not possible; rather, they remain operationally defined after *in vivo* transplantation. Successful engraftment depends on long-term proliferation, multipotent potential, proper homing and expression of anti-apoptosis or survival genes. Multiple tissue sources, including bone marrow, umbilical cord blood and peripheral blood, contain HSCs. Geiger and Van Zant note in their Review that, depending on the source and the age of the donor cells, they qualitatively differ in their ability to reconstitute hematopoiesis *in vivo*. An age-related functional decline may limit the use of autologous cells for gene replacement therapies or hematopoietic reconstitution. Identification and manipulation of the underlying mechanism for these age-related differences will no doubt eventually extend the number of potential donors for transplantation.

Despite the ability to culture hematopoietic progenitors (committed to particular lineages), *in vitro* culture of self-renewing pluripotent HSCs has not been yet been achieved. Intense efforts are underway to identify factors, either intrinsic to the individual cell or cues supplied by the external stromal microenvironment, that influence the choice between self-renewal and differentiation. Any application of HSCs for long-term gene therapy, as well as amplification of stem cells from limiting tissue sources—such as cord blood—will require their expansion in *ex vivo* culture.

Perhaps one of the biggest debates in developmental biology today is the question of plasticity, the ability of a cell committed to a particular cell lineage to change course and give rise to cells in another. The plasticity of HSCs also offers the greatest potential for their therapeutic use for correcting nonhematopoietic tissue defects. In his Commentary, Dorshkind discusses how our definition of HSCs may bias interpretation of recent experiments that appear to challenge the germ-layer theory of lineage commitment. Orkin and Zon, in their Review, extend this discussion on stem cell plasticity to differences between embryonic and adult hematopoiesis. Critical to the debate on cellular plasticity is whether genetic reprogramming occurs in a clonal population. Unfortunately, our definition of the earliest stem cell population is limited by the lack of markers that can be used to distinguish their future potential. Indeed, HSCs are defined as lineage-negative. Exploring whether and/or how tissue environments influence or induce specific lineage potentials of these stem cells will guide potential applications for nonhematopoietic therapies.

The range of diseases or conditions that may be amenable to HSC delivery of gene therapies and potential number of patients who stand to benefit is great. In their Commentary, Bordignon and Roncarolo discuss the therapeutic applications envisioned for HSCs and the hurdles and limitations that currently restrict clinical application.

Although we can confidently predict that current research endeavors will lead to future therapeutics, we are sobered by the significant hurdles that still exist for many of these applications. For the clinician who must counsel anxious families today, whatever the future may bring may be too late. However, because of the dedication and hard work of many who have contributed—and still contribute—to our basic understanding of HSCs, thousands of transplant recipients survive. Our reward is that with a greater understanding of stem cell biology, more will benefit tomorrow.

The online version of this Focus on HSCs (http://immunol.nature.com/special_focus/hsc) is free, to all who register, until 1 July 2002. The website contains additional features, such as free-access links to hematopoietic papers published by the Nature Publishing Group and regularly updated Round-ups of the latest publications in HSC research. Our Web Focus also provides viewers with an annotated section devoted to selected classic papers in HSC biology. We express our gratitude to the Focus authors and to I. Weissman, A. Bernstein, N. Iscove and J. Dick for their invaluable help in selecting those landmark papers that have contributed substantial insight into the biology of HSCs.