Hematopoietic-cell expansion represents a much-sought-after therapeutic goal of the biomedical sciences. With the cloning and characterization of a large and growing number of hematopoietic growth factors, a mechanism for hematopoietic expansion seemed to be at hand. However, ex vivo expansion strategies using cocktails of cytokines have failed to expand transplantable hematopoietic stem cells (HSCs). In contrast, most such approaches lead to the differentiation and extinction of the most primitive cells in the cultures. The explanation for these results is the requisite coupling of cell proliferation and differentiation that results when hematopoietic growth factors bind their cognate receptors.

The work of Abdel-Azim and colleagues in this issue of *Blood* has used a previously described cell-expansion strategy in a new target-cell population to massively expand hematopoietic cells of multiple lineages, including, apparently, the HSC. The approach involves chemically inducing dimerization of the cytoplasmic domain of the thrombopoietin receptor (c-Mpl) in highly purified, primitive human marrow cells. The rationale for this approach began with the discovery that c-Mpl and its ligand, thrombopoietin, provide important and nonredundant support for HSC survival and proliferation.

Hematopoietic growth factors act by binding to their cognate receptors, altering the conformation of the latter, resulting in cross-phosphorylation of 2 tethered Jak signaling kinases. Once phosphorylated, Jak kinases phosphorylate the receptors themselves as well as several secondary survival and proliferation signals, including signal transduction and activator of transcription 3 (STAT3) and STAT5, phosphoinositide-3-kinase (PI3K), and mitogen-activated protein kinases (MAPKs). Ultimately, some of these same signals lead to signal extinction, by inducing receptor internalization and STAT-induced expression of suppressors of cytokine signaling (SOCS) molecules, which block further Jak signaling.

Identification of the FK506 binding protein (FKBP), the target of the commonly used immunosuppressant drug FK506, and the demonstration by Spencer et al that a chemically synthesized dimeric form of FK506, FK1012, could artificially dimerize 2 molecules of FK506,\(^1\) led to the first chemical inducer of dimerization (CID) strategy. Following a minor modification in FKBP (F36V) to render it responsive to the nonimmunosuppressive AP20187 compound, the stage was set to use this CID to mimic cytokine-induced cellular signaling. By transducing marrow cells with an FKBP (F36V)–c-Mpl fusion protein, Jin et al first established the ability of the CID approach to influence hematopoietic-cell proliferation.\(^4\) These efforts expanded mature blood cell production both in vitro and

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<table>
<thead>
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<th>Number of family members with reduced VWF*</th>
<th>Likelihood ratio</th>
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<tr>
<td>1</td>
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<td>4</td>
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Likelihood ratios for VWD in a nuclear family, based on the number of siblings in the family and on the number of family members with reduced VWF levels (below the 25th percentile). *Including propositus. See the complete figure in the article beginning on page 3998.

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**Comment on Abdel-Azim et al, page 4064**

**Cell expansion and maintenance of stemness**

Kenneth Kaushansky  UNIVERSITY OF CALIFORNIA AT SAN DIEGO

Manipulation of hematopoietic cells to expand output while maintaining stem-cell potential has been an elusive goal of experimental hematology. The development of a system using a chemically induced dimerizer and modified thrombopoietin receptor has now allowed the expansion of primitive hematopoiesis without sacrificing stem cells.

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**REFERENCES**


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AIDS, T cells, chemotherapy: HAART-breaking?

Richard F. Little  National Cancer Institute

Chemotherapy depletes T cells in AIDS patients on HAART, but preexisting lymphopenia limits the scale compared with non-AIDS patients. Thus T-cell recovery time to baseline may be rapid, but the risk of additional AIDS-related complications persists.

Treatment advances for AIDS-related lymphoma (ARL) have largely been predicated on highly active antiretroviral therapy (HAART). Before HAART, the combined immune injury of AIDS and chemotherapy made effective cancer treatment impossible. Chemotherapy is now more well-tolerated secondary to immune preservation with HAART. Conventional wisdom stresses that successful administration of anticancer therapy is dependent on concomitant HAART. This inference is challenged by data indicating favorable outcomes in patients who stopped HAART until completion of cancer therapy. A study of 105 ARL patients reported by Bower and colleagues in this issue of Blood does not resolve this debate, but the authors do detail virological and immunological changes seen in a subset of 68 patients treated concomitantly with HAART and chemotherapy who survived 3 months or longer.

Importantly, the fact that analysis of lymphoid recovery was restricted to survivors favors selection of subjects with a higher number of CD4+ cells. However, this selection bias is justified because it reduces spurious results that may occur when subjects with low numbers of CD4+ cells die disproportionately early in the study timeline, shifting the mature data set to represent the remaining subjects—mainly those with higher numbers of CD4+ cells. In such a scenario, the appearance of later CD4+ cell increases could be unrelated to any actual changes in individual patient counts. The analysis by Bower and colleagues likely has avoided this confounding element. Consequently, the data they present inform important concepts regarding AIDS, T cells, and chemotherapy.

To better appreciate the issue at hand, recall that lymphocytotoxic chemotherapy is a more potent T-cell destroyer than is HIV by several orders of magnitude. HIV-seronegative adults typically lose approximately 600 cells/mL within 2 treatment cycles, reaching a nadir at 150 to 600 cells. Recovery from this degree of depletion usually takes well over 12 months. Importantly, most patients with ARL have far fewer than 600 CD4+ cells/mL at the time of lymphoma diagnosis—a consequence of years, not weeks, of ongoing HIV replication. In this study, the survivors’ median baseline CD4+ cell count was 178 cells/mL, and ranged from 8 cells/mL to 636 cells/mL. Thus, when starting with a damaged immune system, even minor additional CD4+ cell loss can be life-threatening. Conversely, small, rapid CD4+ cell increases can substantially reduce morbidity. As with febrile neutropenia, opportunistic illness (OI) risk is, in part, dependent on the depth and duration of T-cell depletion.

Comment on Bower et al, page 3986
Cell expansion and maintenance of stemness

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