Haploidentical stem cell transplantation (HSCT) has become a favored approach for patients with marrow failure states and high-risk malignancies who lack a suitable HLA-matched donor [1]. To overcome severe acute graft-versus-host disease (GVHD) as well as graft failure anticipated with the mismatched HLA antigens, the initial approach was to use T lymphocyte-depleted grafts and mega-doses of high CD 34+ numbers [2]. Several groups have since resorted to monoclonal antibody-based in vivo T lymphocyte immunodepletion using antithymocyte globulin or alemtuzumab [1-3], while others resorted to post-transplantation cyclophosphamide [4,5] to achieve in vivo T lymphocyte cyto-reduction. This approach capitalizes on the rapid proliferation of donor-derived alloreactive T lymphocytes, sparing natural killer cells and aldehyde dehydrogenase–rich regulatory T cells [6], thereby providing the much needed graft-versus-leukemia effect while reducing the incidence of severe acute GVHD. Emerging strategies for the prevention of GVHD, such as T cell depletion, mammalian target of rapamycin (mTOR) inhibition, the use of chemokine–cytokine antagonists or novel regulators, such as atorvastatin and bortezomib, epigenetic modulators with histone acetylase antagonists or novel regulators, such as atorvastatin and bortezomib, are currently being evaluated in preclinical GVHD models and introduced in allogeneic hematopoietic stem cell transplantation clinical trials [7-9].

Granulocyte colony–stimulating factor (G-CSF) is a recombinant cytokine with pleotropic activities [10], affecting proliferation and expansion of myeloid-committed progenitor cells, hematopoietic as well as leukemic stem cell proliferation and paradoxical quiescence [11], as well as CD34+ stem/progenitor cell mobilization [10] and acute myeloid leukemia chemosensitization [12-14]. G-CSF is also recognized as a tolerance-inducing cytokine, as it promotes the mobilization of T helper 2–inducing dendritic cells [15] and has a tolerance-promoting action independent of IL-10 [16]. Di Bartolomco et al. have recently shown a beneficial effect of G-CSF–primed bone marrow in the unmanipulated haploidentical transplantation setting, with improved engraftment, incidence of GVHD, and survival in patients with high-risk malignancies using a chemotherapy-based conditioning regimen and GVHD prophylaxis with antithymocyte globulin, cyclosporine, methotrexate, mycophenolate mofetil, and anti-CD25 antibody [17]. This report set the stage for Gao et al. [18], who determined the outcome of haploidentical stem cell transplantation in high-risk malignancy patients using a combination of G-CSF priming during the chemotherapy conditioning regimen as well as G-CSF–mobilized peripheral blood (>6.0 × 10^6/kg CD34+ cells) and bone marrow nucleated cells (>4.0 × 10^6/kg). GVHD prophylaxis in this study used antithymocyte globulin (Thymoglobulin, Genzyme Cambridge) at 2.5 mg/kg for 4 days (days −5 to −2). G-CSF at 5 μg/kg daily was administered subcutaneously on days −10 to −7 of the chemotherapy-based conditioning regimen, which consisted of cyclohexyl nitrosourea 200 mg/m^2 orally on day −9, high-dose cytarabine 4 g/m^2 daily on days −8 to −7, busulfan 3.2 mg/kg daily on days −6 to −4, and cyclophosphamide 1.8 g/m^2 daily on days −3 to −2 [18]. Based on the known activities of G-CSF [10-16], the use of G-CSF-mobilized peripheral blood stem cells and the enhanced leukemic chemosensitization with the combination of high-dose cytarabine plus G-CSF priming in the conditioning regimen [12-14] allows one to anticipate decreased GVHD and leukemia relapse.

However, another novel property of G-CSF has been elucidated in the report of Boyd et al. [19] showing niche displacement of human leukemic stem cells, thereby
allowing the more efficient and nimble normal hematopoietic stem cells to home and repopulate the hematopoietic stromal niches. The combined use of G-CSF priming and augmented peripheral blood and marrow haploidentical stem cell transplantation was associated with improved cumulative leukemia-free survival and cumulative survival. Although these findings are excellent in the context of high-risk hematologic malignancies, they require corroboration from ongoing and/or future studies. The concept of hematopoietic stem cell competition and displacement of residual leukemic stem cells by G-CSF priming is a testable hypothesis in preclinical transplantation models. These advances from our colleagues in China are welcome, as fully matched HLA identical donors are not always available, especially in minority populations and some ethnic groups. Thus, modified haploidentical HSCT will increasingly become the favored technique to provide a fully ablative and/or nonmyeloablative transplantation to high-risk patients with hematologic malignancies [18,20]. The pioneering work of EJ Fuchs has enabled future application of HSCT to nonmalignant disease as well as solid organ transplantation. Finally, "designed" grafts containing appropriate ratios of conventional T lymphocytes and T regulatory cells, natural killer cells, and other accessory cells will pave the road to better immune reconstitution and less GVHD, eventually avoiding the toxicity and expensive monitoring of post-transplantation pharmacological prophylaxis [21,22].

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REFERENCES