and are again detected in adult liver after hypoxia or anemic stress. Further investigation to determine the extent to which endogenous human Epo expression parallels these observations of mouse Epo in the kidney and liver is warranted.

Increasing evidence suggests physiologic function of Epo beyond erythropoiesis. For example, Epo expression in the brain, and its apparent neuroprotective activity in culture and animal models, have led to investigation of the use of Epo therapy for ischemic stroke.4 Localization and enumeration of Epo-expressing cells in the brain under normal and ischemic conditions would offer insight into endogenous Epo activity in this organ. Obara and colleagues observe GFP-expressing cells only in the kidney and liver: either additional sequences are required for Epo production in other tissues, or GFP expression is below the level of their detection method. Increased understanding of the nature and function of Epo-producing cells in the kidney, liver, and other organs may be useful in broadening cell-type specificity for new therapeutic strategies designed to enhance endogenous Epo expression.3 Examination of the GFP transgenic mouse may also provide new insight into factors that affect endogenous Epo production, such as the fate of kidney Epo-producing cells in renal disease.

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REFERENCES
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“Regulating” rheumatoid arthritis via autotransplantation

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Using a mouse model of inducible autoimmune arthritis that mimics some aspects of the human disease, Roord and colleagues identify a role for regulatory T cells (Treg) both for modulation of disease and as a therapeutic component of autologous bone marrow transplantation (aBMT).

Since 1996, more than 1000 patients worldwide have undergone autologous hematopoietic stem cell transplantation (HSCT) as therapy for refractory autoimmune diseases, including systemic sclerosis, multiple sclerosis, systemic lupus, Crohn disease, and rheumatoid arthritis (RA). Although autologous HSCT yields 5-year disease-free survival in 30% to 50% of patients, current therapies are likely not curative.1 Importantly, post-HSCT disease responses in RA patients are very common, but unfortunately, relatively short-lived. As such, one critical question investigators must address is how HSCT can be modified to induce sustained disease-free survival and, ideally, cure most patients with autoimmune disease. Clearly, it is desirable to elucidate the mechanisms whereby autologous HSCT controls autoimmunity. In this respect, the contributory role of Treg reconstitution identified by Roord et al points to a promising future for the field.

The proteoglycan-induced RA model used in this report appears to invoke both B-cell and T-cell immunity, and to produce a relapsing and remitting disease natural history that is perhaps clinically relevant. The investigators’ discovery that in vivo depletion of CD25+ cells yielded a 100% incidence of the arthritic syndrome strongly supports the protective role of naturally occurring Treg in this model. With respect to the authors’ transplantation results, it was determined that Treg were reconstituted after transplantation in an initial wave of functionally quiescent memory cells and a second wave of naive, competent, Foxp3+ Treg. This latter Treg population represented an immunotherapeutic subset because in vivo antibody depletion resulted in disease relapse. Such cells appear to be analogous to thymus-derived Treg, known to suppress graft-versus-host disease after murine allogeneic HSCT.2 Several points of discussion are of interest. First, similar to the clinical context, the arthritis syndrome in mice that underwent transplantation was ameliorated but not completely resolved (see figure). It will be of interest to determine whether methods to further improve Treg reconstitution, such as adoptive cell therapy3 or pharmacologic methods such as rapamycin,4 may consolidate the autoimmune arthritis remissions in this model. Second, further murine studies to compare and contrast the efficacy of autologous versus allogeneic transplantation would be informative in light of the potential role of allogeneic HSCT as an autoimmune therapy.5 Finally, in an attempt to evaluate a potentially more stringent model more analogous to the clinical context, it would be of interest to observe the therapeutic effect of transplantation in thymectomized murine hosts.

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REFERENCES