the development of ATL-like pathologic features, such as splenomegaly and lymphoma, phenotypically similar to those found in ATL patients.

The observations of Tezuka et al confirm and extend those reported by these previous studies. It is worth noting that Tezuka et al have chosen a different strategy of humanization by performing intra-bone marrow injection (IBMII) of cord blood CD133+ hSCs into 7-week-old NOG (NOD/Shi-scid/IL-2Rγc−/−) null mice. One month after injection, the majority of human CD45+ (hCD45+) lymphocytes present in the bone marrow of these humanized (huNOG) mice consisted of CD19+ B cells. Three to 5 months after engraftment, the number of human CD3+ T cells and the CD4+/CD8+ ratio increased and reached stable levels in the periphery. Likewise, a stable ratio of B cells to T cells in the peripheral blood of these mice indicated the formation of a stable immune system.

Accordingly, Tezuka et al elected to infect huNOG mice 6 to 7 months after engraftment by intraperitoneal injection of lethally irradiated HTLV-1-producing T cells (see figure). As soon as 4 to 6 weeks later, they observed an increased number of hCD45+ cells in the peripheral blood. Then, in about 38% of infected mice, a marked expansion of CD25+ CD4+ T cells in the spleen was found to correlate with a high PVL, ATL-like leukemic features (such as splenomegaly), presence of abnormal leukemic T cells with lobulated nuclei in the periphery, and downregulation of CD3 expression. In addition, they observed an oligoclonal proliferation of human T cells in these infected animals.

Interestingly, the main observation of the study by Tezuka et al concerns the development of HTLV-1–specific adaptive immune responses. First, they observed the presence of restricted cytotoxic T cells (CTLs) against Tax (a major regulator HTLV-1 protein) in IBMII-huNOG mice engrafted with CD133+ hSCs obtained from an HLA-A*24:02 cord blood donor. They show that the frequency of Tax301–309–specific CTLs among in vivo CD8+ T cells was inversely correlated with the PVL of infected cells. Second, the detection of immunoglobulin G antibodies against HTLV-1 antigens in the plasma of 2 infected mice is pleading for a class switching from IgM to IgG, thus supporting the existence of a functional interaction of human T and B cells. It should be emphasized that Tezuka et al are the first to report the development of functional HTLV-1 adaptive immune responses in humanized mice, suggesting that an adequate thymic education has occurred in IBMII-huNOG mice. As a matter of fact, humanized NSG-HLA-A2 mice (created by backcrossing the HLA class I transgene onto the NSG background) infected with EBV displayed human CTLs that recognized EBV-derived peptides in an HLA-restricted manner.9 Nevertheless, it is tempting to speculate that the detection of adaptive immune responses in IBMII-huNOG mice is linked to the use of CD133+ hSCs, to the engraftment procedure, and to the duration of the engraftment period. Indeed, CD133 has been identified as a reliable marker origin of human cord blood CD34+ hSCs and is therefore considered as a specific marker of early hematopoietic progenitor cells.10 Furthermore, when directly injected into the bone marrow cavity, CD133+ hSCs are found to have the right environment for their expansion and their differentiation into CD3+ cells, thus allowing the reconstitution of a functional human immune system.

Clearly, the generation of long-term engrafted immunocompetent mice, as reported by Tezuka et al, is opening a new chapter in the development of optimized humanized mice. Furthermore, their observations reinforce the importance of stem cell models of human viral pathogenesis. More specifically, this animal model raises high hopes for evaluating targeted therapies against ATL and for examining the role of stem cell transplantation in the treatment of ATL and other nonviral-induced leukemias.

Conflict-of-interest disclosure: The author declares no competing financial interests.

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CLINICAL TRIALS & OBSERVATIONS

Comment on Mahlangu et al, page 317

A longer acting rFVIII, safe and effective

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In this issue of Blood, Mahlangu et al describe a well-designed and executed phase 3 multicenter study of a recombinant factor VIII (rFVIII) product fused with the Fc fragment of immunoglobulin G1 (IgG1) in 165 patients with severe hemophilia A.1

Hemarthrosis is the clinical hallmark of hemophilia and can lead to long-term musculoskeletal problems. Left untreated, joint hemorrhages can progress to chronic synovitis, with loss of cartilage, loss of joint space, and loss of joint function. In an attempt
to prevent this vicious sequence of events, Nilsson et al, in Malmö, Sweden, began attempts at prophylaxis in the 1960s, and prophylaxis soon became the standard of care in Sweden. As more experience was gained, the Malmö group began regular prophylaxis at 1 to 1.5 years of age, before the onset of joint bleeds. FVIII (25-50 IU/kg/dose) was administered 3 times weekly or every other day. Such frequent dosing was needed, as the half-life of FVIII is only 8 to 12 hours. Many other centers in Europe and in North America began using prophylaxis in the early 1990s. However, cost was often a major issue because of the increased use of FVIII concentrates for prophylaxis compared with episodic treatment. Despite this, many subsequent studies documented the benefits of prophylaxis beginning at an early age, including far fewer bleeding episodes; much less joint damage than seen in children on episodic treatment; decreased disability, hospitalization, and time lost from school; and improved quality of life. However, such frequent intravenous dosing often necessitated the use of a central line (with its potential complications), and compliance with prophylaxis often decreased in teenagers and young adults.

A longer-lasting FVIII was needed to reduce prophylactic injection frequency. Mahlangu et al demonstrate, in a phase 3 pivotal study, that a novel rFVIII Fc fusion product has a longer half-life than standard rFVIII, which resulted in a lower annualized bleeding rate when dosed prophylactically, 1 to 2 times weekly. Safety, efficacy, and pharmacokinetics were evaluated in 165 males with severe hemophilia A, aged ≥12 years. The rFVIII Fc fusion product was well tolerated and effective, and no subject developed an inhibitor to FVIII.

Fc fusion technology uses a naturally occurring recycling pathway that delays the destruction of FVIII and cycles it back into the bloodstream, resulting in a longer circulating half-life. Fc fusion technology is also used in ≥7 US Food and Drug Administration–approved products for other chronic diseases, such as rheumatoid arthritis and platelet disorders. rFVIII Fc is a recombinant fusion protein composed of a single molecule of B-domain deleted rFVIII linked to the human IgG1 Fc domain. This technology has the potential to have a major impact on the worldwide use of prophylaxis for severe hemophilia, which could ultimately prevent bleeding episodes and their sequelae.

Although it would be even more beneficial to have a product with a longer half-life than rFVIII Fc, Mahlangu and colleagues note the obstacles in developing such a product. These center on the protective effects of von Willebrand factor (VWF) on circulating FVIII, with VWF protecting FVIII from proteolytic degradation and binding to FVIII clearance receptors. However, this beneficial interaction between VWF and FVIII also limits further extension of FVIII half-life beyond that of VWF (16-17 hours). At present, no longer-lasting FVIII or FIX products are yet licensed. Only Biogen Idec’s rFVIII Fc and rFIX Fc are under regulatory review. Other pharmaceutical manufacturers are pursuing other methodologies, including glycopegylation, pegylation, and albumin fusion.

This is, indeed, an exciting time, with great promise for longer-acting FVIII and FIX products that could benefit persons with hemophilia around the globe.

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**LYMPHOID NEOPLASIA**

Comment on Turesson et al, page 338

**Determining the significance of MGUS**

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In this issue of *Blood*, Turesson et al study the risk of progression of monoclonal gammopathy of undetermined significance (MGUS) to lymphoplasmacellular and myeloid malignancies in a large population, validating current risk factors and adding immunoparesis as a predictor of progression.

MGUS is one of the most common premalignant disorders in the general population, occurring in over 3% of individuals ≥50 years old. It is predominantly diagnosed incidentally and is characterized by the presence of a serum monoclonal (M) protein in the absence of symptoms, with an unrelenting annual risk of progression to multiple myeloma (MM) or related plasma cell (PC) disorders of approximately 1%. Although virtually all patients with MM have a previously recognized MGUS, most cases of MGUS do not progress toward malignancy. Differentiating low-risk patients, who may not need further follow-up, from high-risk patients, who warrant close monitoring, is challenging.

Multistep genetic and microenvironmental changes lead to the transformation of MGUS into smoldering myeloma (SMM), MM, and, finally, to extramedullary myeloma or related malignancies. Intense research is ongoing to identify biologically relevant markers differentially expressed throughout this progression, which could be exploited to predict evolution or suggest therapeutic strategies that would prevent or delay progression. Despite important progress, we still lack reliable biological markers to predict which patients will progress and which will not, and MGUS is currently risk stratified based on clinical variables identified through epidemiologic studies. Both the Mayo Clinic

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