administration is associated with elevated VWF plasma levels, and it indicates that interleukin-11 and DDAVP modulate VWF plasma levels in a mechanistically distinct manner. Interleukin-11–pretreated dogs indeed still exhibit the characteristic response to DDAVP. Moreover, this response is now much stronger and perhaps not as easily exhausted. Apparently, interleukin-11 treatment not only results in elevated VWF plasma levels but probably also increases the amount of VWF available from DDAVP-responsive storage pools. This raises the question of how this extra VWF is stored: are there more Weibel-Palade bodies per cell, or do more cells contain them?

The promising data justify the initiation of clinical studies of the use of interleukin-11, alone or in combination with DDAVP, and point to new avenues for the exploration of fundamental aspects of VWF and FVIII biosynthesis. Several issues regarding efficacy and safety obviously need to be addressed, and special attention should be given to fluid retention in patients, since both DDAVP and interleukin-11 possess antidiuretic properties.

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Another advance for globin gene therapy

In this issue, Persons and colleagues (page 506) report another advance in the now rapidly moving field of gene therapy for the β-chain hemoglobinopathies, β-thalassemia (β-thal), and sickle cell disease (SCD). The hemoglobinopathies are the most common human inherited diseases, and while the milder forms are increasingly amenable to drug therapies, the only real cure for the severe forms of these diseases has been bone marrow transplantation (BMT). But the scarcity of human leukocyte antigen (HLA)–matched donors and the high morbidity associated with complete myeloablation have limited the use of BMT for the treatment of SCD and β-thal. Recent breakthroughs in vector design allowing stable transfer of globin genes that can be expressed at therapeutic levels in red cells (May et al, Nature. 2000;406:82-86; Pawlick et al, Science. 2001;294:2368-2371) have made the hemoglobinopathies candidates for gene replacement therapy. In mouse models, the introduction of a globin gene (β-globin for β-thal and γ-globin to inhibit sickling in SCD) into a portion of autologous hematopoietic stem cells (HSCs) has led to permanent cures of β-thal or SCD mice receiving transplants (May et al, Blood. 2002;99:1902-1908; Rivella et al, Blood. 2003;101:2932-2939; Persons et al, Blood. 2003;101:2175-2183). Combined with the observations that stable mixed chimerism was associated with the successful cure of severe β-thal or SCD in a subset of human recipients of transplants, it appears that 25% to 50% of corrected cells are sufficient for a full cure. However, the low frequency of gene transfer into human hematopoietic stem cells (about 1%) and the morbidity of full myeloablation in patients with hemoglobinopathies have prevented the application of the recent advances in globin gene therapy to humans.

Persons et al have addressed these problems using 2 different mouse models of stem cell gene transfer. In the first model, they gave β-thal intermedia mice a nonmyeloablative conditioning regimen and transplanted into them a small number of normal bone marrow cells that were transduced with a retrovirus vector containing the *MGMT* gene, which confers resistance to O^6-benzylguanine (BG). The resulting bone marrow chimeras resemble low-level engraftment of HLA-matched normal cells after partial myeloablation and a low frequency of gene transfer. Prior to treatment the animals receiving transplants were indistinguishable from β-thal mice. Following treatment with BG, the level of transduced normal cells rose from less than 10% to 56% in 6 of 10 animals with a concurrent normalization of all red cell indices.

In the second model, Persons et al introduced a lentivirus vector containing both a human γ-globin gene and the *MGMT* gene into mouse bone marrow cells and transplanted them into recipient mice. After BG selection the number of γ-globin producing red blood cells increased from a pretreatment level of less than 1% to more than 60% in 5 of 7 animals.

The 2 studies demonstrate a conservative approach that dramatically lowers the risk of transplantation-related complications to the patient and does not require high rates of HSC transduction. The most pressing issue facing Persons et al and other investigators in this field is to develop vectors that express higher levels of globin per vector copy, so that the maximum amount of globin protein can be produced from the minimum number of insertion events. In addition, while the *MGMT* selection is quite powerful, the frequency of gene transfer to human cells must still be improved to allow the most efficient treatment. I predict that these problems will be solved in the near future and that the first clinical trails for β-thal and SCD will resemble those described in this issue by Persons et al.

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Collagen-mediated platelet activation and PI3K

Phosphatidylinositol 3–kinase (PI3K) is a phospholipid kinase that is involved in diverse cellular events, including the prevention of apoptosis, regulation of glucose metabolism, chemotaxis, and cell proliferation. It is far from obvious what role this enzyme would play in a platelet—a terminally differentiated anucleate cell. Studies using less-than-specific pharmacologic inhibitors have a suggested that PI3K might participate in both collagen-induced platelet activation and the irreversible phase of platelet aggregation (Kovacsovics et al, J Biol Chem. 1995;270:11358-11366; Pasquet et al, Biochem J. 1999;342(pt 1): 171-177).

Most cells have multiple isoforms of PI3K that are composed of a regulatory subunit and a catalytic subunit. Using cells obtained from genetically modified mice,

investigators have begun to understand the role of different PI3K isoforms in hematopoietic cells. For example, mice lacking the p110γ catalytic subunit of PI3K have a defect in ADP-mediated platelet aggregation (Hirsch et al, FASEB J. 2001;15:2019-2021), while mice lacking the p85α regulatory subunit of PI3K have impaired B-cell development. In this issue, Watanabe and colleagues (page 541) have studied the effects of the p85α knockout on platelet function. They found that in the absence of p85α there was a defect in signaling events initiated by the platelet collagen receptor, GPVI, whereas there was no defect in platelet activation following stimulation by other platelet agonists such as ADP or thrombin.

It is noteworthy that GPVI signaling pathways are similar to those emanating from the B-cell antigen receptor, as well as other members of the immunoglobulin supergene family of receptors. Does the work by Watanabe et al suggest that therapeutic targeting of p85α would be a useful way to disrupt platelet activation following exposure to subendothelial collagen such as occurs during coronary plaque rupture? Given the ubiquitous expression and diverse functions of PI3K, such speculation is premature.

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The biology and treatment of ITP: what's next?

Immune thrombocytopenic purpura (ITP) is the result of 2 pathologic processes: loss of tolerance to self-antigen accompanied by sustained autoantibody production, and antibody effector mechanisms that destroy platelets in excess of their production. There is a considerable challenge to hematologists treating the chronic, severe, refractory subset of patients. IVIG has many putative mechanisms of action in treating ITP. These include "blockade" of phagocytic Fc receptors, anti-idiotype effects, reduction of antibody production, reduced survival of the autoantibody in the circulation (Hansen and Balthasar, Blood. 2002;100:2087-2093), and, finally, stimulation of inhibitory FcγRIIb. In this issue, Crow and colleagues (page 558) follow up on the seminal observations of Samuelsson et al (Science. 2001;291:484-486) concerning how IVIG's efficacy in ITP depends on the inhibitory FcγRIIb on macrophages. FcγRIIb counters the phagocytic signal provided by the activating Fcγ receptors (I/γ and IIIa/γ in mice; I/γ, IIIa/γ, and IIA in humans) on splenic macrophages. Crow et al confirm that IVIG's effects in vivo depend on expression of FcγRIIb. They then explore the potential downstream signals of FcγRIIb used in B cells and mast cells that would explain IVIG's role in macrophages. Using germ line knockout of SHIP1, SHP1, or BTK in their ITP mouse model, Crow and colleagues found IVIG to be effective despite the absence of these individual signaling molecules. Functional redundancy among the known phosphatase families, or an as-yet undiscovered mechanism specific to macrophages, may explain their observations. The mechanism sought by Crow et al may yield new molecular targets for therapy. Equally of interest to the field is the mechanism by which IVIG increases FcγRIIb expression in the first place. Current data favor an indirect effect, in which IVIG causes a subset of splenic cells to secrete one or more substances—perhaps cytokines—that act on the phagocyte to increase the relative proportion of inhibitory FcγRIIb versus phagocytic Fcγ receptors. Elucidation of this pathway may also yield new molecular targets of therapy.

There are unanswered questions in the development of the ITP autoantibodies and in the antibody effector mechanisms. How is tolerance broken? Do dendritic cells, B cells, macrophages, or platelets themselves present antigen? Is there an intrinsic genetic predisposition for loss of tolerance and sustained autoantibody production? Are there genetic differences, for example in the Fcγ receptor endowment, that have an impact on disease course or response to therapy? Now that Fcγ receptor crystal structures have been solved, will small molecule inhibitors of IgG ligand binding be useful? Can we block receptor signaling, as this family of activating receptors prefers lipid microdomains (rafts) in which to initiate signals via members of the src and syk protein tyrosine kinase families? Will additional ways be discovered to alter the balance of activating and inhibitory receptors to allow platelets to survive in circulation? The next step in the biology and therapy of ITP is more precise understanding of the origins of the disease and the promise of molecularly targeted therapy.

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Angiopoietin expression in multiple myeloma

Multiple myeloma demonstrates a progressive, and usually fatal, course, with current treatments generally producing only temporary remissions. Antiangiogenic therapies represent a potential new approach to treating this cancer. While it is well established that growth in solid tumors is dependent on angiogenesis, the role of this process in hematopoietic tumors is not fully appreciated. There is a strong correlation between increased angiogenesis and poor survival in myeloma patients. Furthermore, both cellular and circulating levels of vascular endothelial growth factor (VEGF) are often elevated in hematologic malignancies, including myeloma, and have been shown to predict for a poor outcome, lending additional support to the concept that angiogenic cytokines are involved in the growth and progression of these malignancies.

In this issue, Giuliani and colleagues (page 638) extend our knowledge of marrow angiogenesis with their report on the expression of angiopoietin-1 in myeloma cell lines and patient samples. Angiopoietin-1 (Ang-1) was found to be expressed in 47% of the patient samples examined. Bone marrow angiogenesis was examined and found to be elevated in 12 of 15 patients examined (80%), and there was a significant correlation between Ang-1 expression and