

DMS may trigger actin polymerization via the WASp/WAVE pathway.

Reports over the past 5 years have significantly advanced our understanding of the structural and mechanical aspects of proplatelet formation.^{4,5} Schulze and colleagues provide initial insights into the formation and function of the DMS, including its role in platelet biogenesis, furthering our understanding of this most mysterious cell, the megakaryocyte. Dr Wright should be pleased, but I suspect he is wondering what took so long. ■

REFERENCES

1. Wright JH. The origin and nature of the blood plates. *Boston Med Surg J*. 1906;154:643-645.
2. Yamada F. The fine structure of the megakaryocyte in the mouse spleen. *Acta Anat*. 1957;29:267-290.
3. Italiano JE, Lecine P, Shivdasani RA, Hartwig JH. Blood platelets are assembled principally at the ends of proplatelet processes produced by differentiated megakaryocytes. *J Cell Biol*. 1999;147:1299-1312.
4. Hartwig JH, Italiano JE. The birth of the platelet. *J Thromb Haemost*. 2003;1:1580-1586.
5. Richardson JL, Shivdasani RA, Boers C, Hartwig JH, Italiano JE. Mechanisms of organelle transport and capture along proplatelets during platelet production. *Blood*. 2005;106:4066-4075.

● ● ● GENE THERAPY

Comment on Gangadharan et al, page 3859

Bringing home the bacon for hemophilia

Katherine P. Ponder WASHINGTON UNIVERSITY SCHOOL OF MEDICINE

Hematopoietic stem cell–directed gene therapy with a retroviral vector expressing the pig fVIII gene cured hemophilia A without inhibitor formation in mice. This approach holds promise for prevention of bleeding or tolerance induction in patients.

Hemophilia A is due to factor VIII (fVIII) deficiency and results in bleeding in 1:5000 males. Although it can be treated with infusions of human fVIII, this costs more than \$100 000 per year for patients with less than 1% of normal activity.

A feared complication of human fVIII replacement therapy is the development of inhibitors, which occurs in 25% of patients with severe disease.¹ Inhibitors can be eradicated in

70% of patients with immune tolerance induction, which involves frequent injections of high doses of human fVIII and costs \$1 000 000 per year for a child. Although patients with inhibitors are treated effectively with bypass agents such as recombinant factor VIIa, one dose of fVIIa for a 53-kg patient costs \$10 464 at our hospital. Total costs for 7 to 10 days of treatment after major surgery or a serious bleed can exceed \$500 000. Prevention

of inhibitor development would be a major advance.

The paper by Gangadharan and colleagues demonstrates that hematopoietic stem cell (HSC)–directed gene therapy with a retroviral vector expressing porcine fVIII cured hemophilia A mice without inhibitor development (see figure). This result is consistent with that of Moayeri et al² who performed HSC transplantation in hemo-

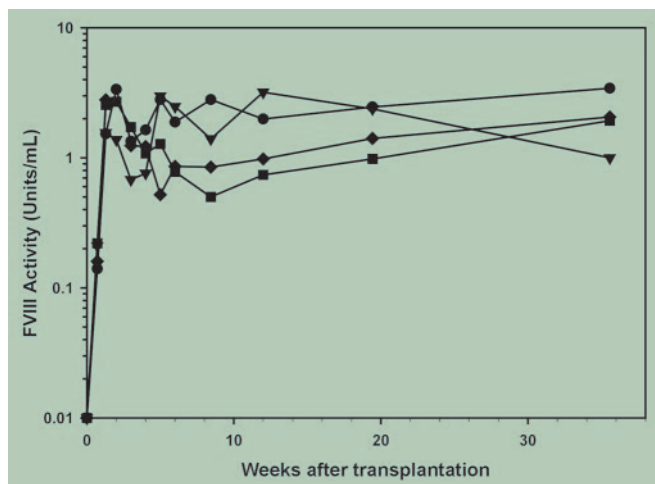
philia A mice using a retroviral vector expressing the human *fVIII* gene.

There are 2 major advantages to using the porcine gene. First, the porcine *fVIII* gene resulted in greater activity in vivo than the human *fVIII* gene, which is probably due to a higher specific activity of the pig protein. Second, most inhibitors to human fVIII do not cross-react with porcine fVIII, making it possible that a vector with the porcine gene might be used in the large subset of patients that already has inhibitors to human fVIII. Although plasma–derived porcine fVIII is not currently available, recombinant porcine fVIII is being tested.³

There are also caveats. First, use of this gene required at least partial bone marrow ablation, which has toxicities, and would be difficult to justify for patients with hemophilia. However, an in vivo delivery of retroviral vector to HSCs could have a similar effect. Indeed, neonatal intravenous injection of a retroviral vector expressing canine fVIII cured hemophilia A dogs without inhibitor formation.⁴ Since this procedure⁵ transduces HSCs in addition to liver cells, it is possible that the tolerance to canine fVIII was due to the transduction of blood cells. An in vivo delivery without selection should be clinically acceptable if it were safe. However, the second caveat of using HSC–directed gene therapy in patients is that an integrating retroviral vector might result in leukemia due to insertional mutagenesis. It will be important to demonstrate that this risk is very low. Nevertheless, the paper by Gangadharan et al suggests that a cure may be on the horizon for hemophilia A. ■

REFERENCES

1. Lusher JM. Inhibitor antibodies to factor VIII and factor IX: management. *Semin Thromb Hemost*. 2000;26:179-188.
2. Moayeri M, Hawley TS, Hawley RG. Correction of murine hemophilia A by hematopoietic stem cell gene therapy. *Mol Ther*. 2005;12:1034-1042.
3. Parker ET, Craddock HN, Barrow RT, Lollar P. Comparative immunogenicity of recombinant B domain–deleted porcine factor VIII and Hyate:C in hemophilia A mice pre-sensitized to human factor VIII. *J Thromb Haemost*. 2004;2:605-611.
4. Xu L, Nichols TC, Sarkar R, McCorquodale S, Bellinger DA, Ponder KP. Absence of a DDAVP response after therapeutic expression of Factor VIII in hemophilia A dogs with liver-directed neonatal gene therapy. *Proc Natl Acad Sci U S A*. 2005;102:6080-6085.
5. Wang B, O'Malley TM, Xu L, et al. Expression in blood cells may contribute to biochemical and pathological improvements after neonatal intravenous gene therapy for mucopolysaccharidosis VII in dogs. *Mol Genet Metab*. 2006;87:8-21.



In vivo expression of BDD porcine fVIII under reduced-intensity transplantation conditioning. See the complete figure in the article beginning on page 3859.