counts and the peripheral blood smear is recommended. If new morphologic abnormalities or cytopenias are noted or if there is a loss of response to treatment, a bone marrow biopsy with staining for reticulin and collagen should be performed. 

A recent Italian trial has first reported that patients with MYH9 mutations significantly benefit from 6-week eltrombopag treatment, with increase of platelet count and disappearance of bleeding tendency in most of them. 

Whereas the experiences gathered so far in ITP patients indicate that Tpo-mimetic-induced fibrosis is reversible if drug therapy is discontinued, the irreversibility of marrow fibrosis associated with MPLSer505Asn mutation provides ground for reflection. In addition, data presented here by León and colleagues cast doubt that, under prolonged Tpo stimulation, patients with thrombocytopenia sustained by ineffective megakaryocytopenia would be predisposed to this complication.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES
5. Althaus K, Greinacher A. Recent advances in the understanding of myocardial risk, splenomegaly and progression to bone marrow fibrosis. Semin Thromb Hemost. 2007;33(2):189-203.

Aβ and C(lot), but not D(egradation)

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In this issue of Blood, Zamolodchikov and Strickland examine the association of β-amyloid (Aβ) peptide with fibrinogen. These findings shed new light on the relationship between Alzheimer disease and cardiovascular disease, as well as on a novel biochemical mechanism regulating clot stability and dissolution.

Comment on Zamolodchikov and Strickland, page 3342
blood 5 APRIL 2012 | VOLUME 119, NUMBER 14 3197

Comment on Naik et al, page 3352

JAMming the signals

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In this issue of Blood, Naik and colleagues have identified a new mechanism used by platelets to inhibit the signals that drive their activation through integrin αIIbβ3, which serves to prevent inappropriate or premature thrombus formation.1

The activation of platelets at sites of injury or arterial disease is rapid because of the involvement of numerous positive feedback systems. Activated platelets release factors that activate approaching platelets, which similarly secrete activatory factors ... and the cycle continues. This chain reaction, which is mediated by platelet agonists of various shapes and sizes, requires effective regulation to limit the extent of response to injury or to prevent accidental activation, which may lead to thrombosis. This is mediated through endogenous inhibitory mechanisms that are able to “turn down the gain” on platelet reactivity or to inhibit the signaling mechanisms used by platelet-stimulating factors such as collagen, thrombin, and ADP.

In recent years the repertoire of such mechanisms has started to become apparent, and these, too, come in various shapes and sizes. The inhibitory effects of prostacyclin (PGI2) and nitric oxide (NO) that are released by the healthy endothelium are well established, accompanied by the ADP metabolizing pathway directly, this “indirect” approach may be expected to have low risk of bleeding.

These findings also have important implications for understanding the contributions of fibrinogen to hemostasis and thrombosis. Other proteins besides Aβ, including fibronectin (reviewed in Wollberg2), have been shown to both alter fibrin structure and decrease the rate of fibrinolysis. These two clot properties also co-exist in many thrombotic diseases. Until now, findings of abnormal fibrin network structure were considered sufficient to explain differences in fibrinolysis. However, the current study puts an end to this biologic handwaving because it shows that changes in fibrin network structure may not be sufficient to explain abnormal fibrinolysis in all cases. Could as-yet-unidentified molecules circulating in disease states directly alter binding of fibrinolytic enzymes to fibrin in other thrombotic diseases? Experiments to explicitly measure binding of tissue plasminogen activator and plasminogen(ogen) to the fibrin network in cases of reduced fibrinolysis may reveal such novel molecules. As such, this work establishes a new standard for future studies of mechanisms regulating clot structure and stability.

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

REFERENCES

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