infection rates) of lenalidomide-Dex treatment with lower versus higher Dex dose\(^6\), and the high rates and durability of responses to lenalidomide-bortezomib in a study where most patients did not receive Dex.\(^7\)

This study by Hsu et al triggers captivating new questions. What is the impact of Dex on patients’ NK-cell activity against autologous MM cells and does it correlate with clinical outcome after lenalidomide-Dex treatment? Does the impact of Dex on lenalidomide-induced immunostimulation depend on disease stage, underlying degree of MM-associated immunoparesis, status of prior treatment(s), or concomitant use of other therapeutics (eg, proteasome inhibitors)? Will this study’s results differ quantitatively or qualitatively in MM patients who are younger or without renal impairment (ie, in patient populations different from those of the current study) or with thalidomide or pomalidomide treatment? Do the in vivo interactions of the tumor cells with their microenvironment alter the balance between the opposing immunologic effects of lenalidomide versus Dex? Can doses or schedules of lenalidomide and/or Dex be adjusted to preserve their synergistic direct proapoptotic activity against MM cells, while minimizing Dex-induced immunosuppressive effects? Which clinically applicable marker(s) can identify such potential optimal settings to help individualize the use of these agents?

Until these questions are answered, a key message from this stimulating study is that, in clinical settings where lenalidomide use aims to augment the anti-MM activity of immunotherapeutics, caution should be exercised with concurrent use of potent glucocorticoids.

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**Comment on Hosking et al, page 1633**

**When the negative is positive**

**Susan L. Slager**  
**MAYO CLINIC**

In this issue of *Blood*, Hosking and colleagues report the lack of correlation between genetic variants within the MHC and the risk of ALL.\(^1\)

A cute lymphoblastic leukemia (ALL) is the most common pediatric cancer. It is a biologically heterogeneous disease with B-cell precursor ALL as the most common subtype accounting for ~ 70% of childhood ALL. There is now conclusive evidence that the risk
Comment on Haling et al, page 1719

Talin’s second act-ivation: retraction

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In this issue of Blood, Haling and colleagues demonstrate that in addition to talin-dependent integrin activation, talin is required for platelet fibrin clot retraction by physically linking integrins to the actin cytoskeleton.

Integrins are ubiquitous transmembrane α/β heterodimers that provide an essential link between the extracellular and intracellular environments, which is vital for both normal and pathophysiologic processes. The well-characterized platelet-specific integrin αIIbβ3 (like several other integrin receptors) is constitutively expressed on the cell surface in a low-affinity state. Agonist stimulation or exposure of platelets to extracellular matrix proteins generates intracellular signals that enhance integrin-binding affinity for ligands. Ligand binding to αIIbβ3, in turn, transduces signals from the extracellular environment into the cell leading to platelet adhesion and aggregation. Finally, integrin αIIbβ3-dependent clot retraction is necessary for normal thrombus stabilization and wound healing. In platelets, these bidirectional signaling events are tightly regulated processes; perturbation of this regulation can lead to pathologic conditions such as hemorrhage or occlusive platelet thrombi.

The integrin cytoplasmic domains are key regulatory sites for integrin bidirectional signaling. Multiple proteins have been identified that bind to integrin cytoplasmic domains and, as such, are likely to play a role in regulating integrin function.1 One of these proteins, talin, binds to β-integrin cytoplasmic tails and is an important regulator of integrin activation (reviewed in Shattil et al2). Talin is an abundant (~3%-8% of total platelet protein)3 cytoskeletal protein composed of a 220-kDa C-terminal rod domain and a 50-kDa N-terminal FERM (4-point-one/ezrin/radixin/moesin) head domain. This N-terminal FERM domain binds to β-integrin cytoplasmic domains and the C-terminal rod domain interacts with F-actin, thus providing a physical link between the actin cytoskeleton, integrins, and the extracellular matrix. Several elegant biochemical, mutational, and structural studies identified sites in both talin and the β-integrin cytoplasmic domains that mediate the interaction between these 2 binding partners.3,4 Talin binds to a conserved membrane distal NpxY motif, which is hypothesized to be important for talin recruitment to β-integrin tails.4,5 Key studies, however, revealed a second critical site of interaction between the β-integrin membrane proximal region and the talin head FERM domain that is necessary for talin-dependent integrin activation.2 Of particular relevance to the study by

REFERENCES
When the negative is positive

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