young than 65 years of age), with no co-
morbidities such as history of DVT or arterial
thromboembolic events, recent orthopedic
surgery or vertebroplasty, immobilization,
inherited thrombophilic abnormalities, his-
tory of coronary ischemic disease, atrial fibril-
lation. Nevertheless, the dose of dexametha-
sone is also a major risk factor and should be
considered when deciding on the type of VTE
prophylaxis. Thus, based on this study by
Larocca et al, in newly diagnosed MM patients
treated with lenalidomide and low–dose dexam-
thasone who are at low risk for VTE, aspir-
in reduces the risk of VTE to < 3% and may
be considered an appropriate form of
thromboprophylaxis.

According to the design of the study, the
expected incidence of VTE in the aspirin
group will be 12% to 67%. However, we must
acknowledge that we do not know the real inci-
dence of VTE in young MM patients with no
risk factors for VTE who receive lenalidomide
with low–dose dexamethasone without any
type of prophylaxis. If one had to provide an
estimate, one could anticipate that this risk
would be well below 10%.

While this study by Larocca et al addresses
the issue of prophylaxis in low–risk patients,
we still need data from prospective studies to
define the optimal thromboprophylaxis regi-
men for patients treated with lenalidomide-
based induction regimens at intermediate or
high risk for VTEs or those treated with lena-
idomide and high–dose dexamethasone.

Based on currently available data, it seems that
aspirin may not be adequate for patients at
intermediate or high risk and these patients
should receive LMWH for at least the initial
phase of induction. New antithrombotic
agents (thrombin and factor Xa inhibitors)
may also be evaluated in this context. Finally,
genetic polymorphisms that have been shown
to play a role in the development of VTE in
patients treated with thalidomide–based regi-
mens5 may also prove to be of value.

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tech.

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Comment on Ubukawa et al, page 1036

Exit strategy: one that works

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Enucleation is the culmination of terminal erythroid differentiation. It results in
the release of 2 million new enucleate reticulocytes into your circulation and mine
each second. In this issue of Blood, Ubukawa and colleagues shed new light on the
mechanism, showing that non-muscle myosin IIb is intimately involved.1

Photomicrographs illustrating the different steps during the enucleation process. The nucleus is first displaced
to one side of the erythroblast (left panel). A contractile actin ring is then formed to pinch off the
nascent reticulocyte from the nucleus (middle panel). Subsequent redistribution of membrane between the
2 lobes of the dividing cell by vesicle shuttling further restricts the area of contact between the 2 emerging cells
(right panel). Images courtesy of Dr Marcel Bessis.

Mammalian red cells and their immediate
precursors, reticulocytes, are, unlike
their counterparts in some other vertebrates,
without of nuclei as a result of an “asymmetric”
cell division at the final step of terminal ery-
throid differentiation. Fission of the erythro-
blast generates the enucleate reticulocyte and a
larger moiety in which an extruded nucleus is
encased in a plasma membrane (pyrenocyte).2

There has over many years been keen interest
in defining the molecular machinery respon-
sible for enucleation and in the similarities and
differences between this process and classic
cytokinesis, which produces 2 identical daugh-
ter cells. By studying and comparing both pro-
cesses, Ubukawa and colleagues offer new
insights into the roles of various cytoskeletal proteins in the 2 cases.

Inhibition of non-muscle myosin II ATPase
by blebbistatin blocked both cell division and
enucleation, implying its participation in both
processes and establishing a previously
undefined role for myosin in enucleation.
Non-muscle myosin IIa and myosin IIb are both
expressed during terminal erythroid differentiation and while both seem to be involved in cell division, a specific requirement for myosin IIb in enucleation was documented. Moreover, because inhibition of actin polymerization by cytochalasin D blocks both cell division and enucleation, an actomyosin-driven step in enucleation of erythroblasts during terminal erythroid differentiation may be inferred.

Enucleation is a multistep process (see figure) that requires displacement of the nucleus in the erythroblast to one side during the preparatory stage. This is followed by formation of a contractile actin ring, pinching off the nascent reticulocyte from the nucleus, and subsequent redistribution of membrane between the 2 lobes of the dividing cell by vesicle shuttling to restrict the area of contact between the 2 emerging cells. The coordinated execution of these diverse events during a period of 8 to 10 minutes requires complex machinery embracing a number of distinct cytoskeletal components, and we hope that future work using specific inhibitors, Ubukawa et al added myosin to the other elements, notably tubulin and specific inhibitors, Ubukawa et al added myo-proteins and signaling interventions. Using embracing a number of distinct cytoskeletal

... disposing of its nucleus. This is a problem that cal stability, the nucleated precursor must evolve to meet. To fulfill the requirements of mammalian fetus. The allure of this topic is due, at least in part, to the special physiologic demands that the mature mammalian red cell has expressed during terminal erythroid differentiation. In response to vascular damage, shear stress, or other prothrombotic factors, the coordinated activation of intracellular signaling proteins by primary adhesion/activation and G protein–coupled receptors, as well as bidirectional signaling by unligated or ligand-bound integrin, exquisitely controls complex platelet functional responses and ultimately, prothrombotic and procoagulant activity. Pleines et al used megakaryocyte–platelet family member RhoA in murine megakaryocytes/platelets induces macrothrombocytopenia but also protects against occlusive thrombosis or cerebral infarction, providing new insights into both RhoA function as well as platelet-related diseases. This multifaceted study of RhoA function in mouse platelets—by conditional gene knockout in megakaryocytes—is pertinent to the production of platelets in the marrow, their survival in the circulation, the hemostatic quality of the platelets in response to prothrombotic stimuli, and their effectiveness in thrombus formation in vivo. These experiments are topical in clinical hematology, because in certain congenital disorders, immune thrombocytopenia,

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Comment on Pleines et al, page 1054

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In this issue of Blood, Pleines and colleagues show how deletion of the GTPase family member RhoA in murine megakaryocytes/platelets induces macrothrombocytopenia but also protects against occlusive thrombosis or cerebral infarction, providing new insights into both RhoA function as well as platelet-related diseases. This multifaceted study of RhoA function in mouse platelets—by conditional gene knockout in megakaryocytes—is pertinent to the production of platelets in the marrow, their survival in the circulation, the hemostatic quality of the platelets in response to prothrombotic stimuli, and their effectiveness in thrombus formation in vivo. These experiments are topical in clinical hematology, because in certain congenital disorders, immune thrombocytopenia,
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