after ablative host conditioning and provide further impetus to develop conditioning strategies that more potently suppress Treg reconstitution. Clinically, the use of fully myeloablative conditioning using TBI and hematopoietic stem cell rescue before ACT has been used to robustly deplete all host lymphocytes, including Tregs. Although such a strategy has been associated with improved response rates,2 the toxicity and complexity of this regimen can be a barrier to its widespread adoption. Recombinant immunotoxins targeting cells expressing CD25, such as denileukin diftitox and LMB-2, have been used clinically to deplete Tregs in patients with cancer, but results have been marginal. In addition, as noted above, such an approach runs the risk of depleting tumor-reactive effector T cells. Thus, reagents that disarm the suppressive capacity of Tregs without having detrimental effects on effector T cells might be the best way to effectively translate the findings reported here. For example, combining ACT with blocking antibodies against cytotoxic T-lymphocyte antigen 4 (CTLA-4) might positively impact outcomes not only by inhibiting Tregs but also augmenting the effector functions of the adoptively transferred T cells. In support of such an approach, a post hoc analysis suggests a trend toward improved survival in patients previously treated with anti–CTLA-4 before receiving lymphodepletion and ACT.2 For this reason, a prospective trial testing the addition of anti–CTLA-4 with ACT would be warranted.

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

REFERENCES

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PLATELETS & THROMBOPOIESIS

Comment on Ye et al, page 2484, and Al Hawas et al, page 2493

SNARing platelet granule secretion

Michael S. Marks  UNIVERSITY OF PENNSYLVANIA

In this issue of *Blood,* Ye et al.\(^1\) and Al Hawas et al.\(^2\) clarify the roles of 2 key fusion proteins that regulate the agonist-stimulated release of bioactive factors from platelets, and thereby explain the defective hemostasis in patients with 2 rare genetic diseases.

On stimulation at sites of blood vessel damage, platelets release an array of soluble factors that facilitate platelet adhesion and other physiologic responses required for hemostasis and thrombus formation and remodeling. These factors are released from 3 types of storage compartments (\(\alpha\) granules, dense granules, and lysosomes) after their fusion with the platelet plasma membrane or open canalicular system. Fusion requires...
Cp-jeez! Aza-natomy!

Lauren Suarez and Steven D. Gore