This study demonstrates the feasibility of ALT-803 use was associated with activa-
tion proliferation and expansion of the ALT-803 is a high-molecular-
weight IL-15 superagonist molecule consisting of an IL-15 mutein (N72D) bound to IL-15Rx fused to IgG1Fc (see figure). This unique molecule aims to mimic the physiologic trans-presentation of IL-15 and significantly increase its half-life. In the current study, the drug was well tolerated, and none of the patients had any flare-up of GVHD needing systemic treatment. The subcutaneous (SC) form of the drug was associated with more favorable pharma-
cokinetic profile with lower peak but more sustained serum concentrations. Patients who received ALT-803 via the SC route also had a lower elevation in the inflam-
matory cytokines like IL-6 and interferon γ, which is probably the reason why it was better tolerated in these patients. Inter-
estingly, most of the SC cohort patients developed self-limited injection site rash with predominantly γγδ T-cell infiltration. ALT-803 use was associated with activation, proliferation, and expansion of the NK cell numbers in the peripheral blood; however, more modest effects were seen in the CD8 T cells. Encouragingly, clinical responses were observed with 1 prolonged complete remission lasting several months in a myelodysplastic syndrome patient.

Furthermore, ALT-803 is one of the several agents currently at various stages of clinical development incorporating novel modifications in the key cytokine molecules aimed at enhancing their ability to stimulate cytotoxic T and NK cells. Immunoengineering of molecules like rhIL-2 is leading to a whole new class of agents that can target specific T-cell sub-
sets differentially, leading to selective ac-
tivation of cytotoxic T cells or regulatory cells in order to promote antitumor or anti-
-inflammatory activity, respectively. Most recently, Sockolosky and colleagues have reported on the construction of IL-2 cytokine-receptor orthogonal pairs that interact with each other to deliver native signals but do not interact with their natural counterparts, limiting off-target effects and providing an avenue to stimulate natural or engineered immune effectors in vivo. The current study by Romey and colleagues is another promising step in the development of approaches that safely leverage the potential of cytokine-mediated immune stimulation in the clinical setting.

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

REFERENCES
3. Ruggeri L, Capanni M, Urbani E, et al. Effectiveness of donor natural killer cell allo-
reactivity in mismatched hematopoietic trans-


RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Liao et al, page 2568

Stress erythropoiesis: selenium to the rescue!

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Studies investigating how micronutrients regulate erythropoiesis within the erythroblastnic niche have primarily focused on iron homeostasis. In this issue of Blood, Liao et al highlight an additional regulator of the erythroblastnic niche, selenium (Se). Se acts to promote stress erythroid cell expansion and differentiation as well as directly acting on monocytes, inducing their differ-
entiation to erythroblastic island macrophages.

Inadequate micronutrient intake causes anemia in ~30% of the world population, and micronutrient deficiencies commonly associated with anemia include vitamin B12, folate, and iron. An overlooked cause of anemia is low levels of Se.
Se deficiency causes anemia in humans and has eluded investigators because Se deficiency often occurs in the setting of multiple micronutrient abnormalities, such as patients with chronic inflammation/disease or patients on total parenteral nutrition.3,4 Therefore, Se studies have relied heavily on controlled experimental systems, such as mice and in vitro differentiation cultures.

Se engages in oxidation-reduction reactions through its incorporation into the selenocysteine-containing family of selenoproteins.5 Almost all selenoproteins possess antioxidant activities, which likely guided previous research to focus on the relationship between Se and oxidative stress during erythropoiesis. Indeed, genetic approaches and dietary deprivation of Se in mice were shown to lead to an increase in red cell reactive oxygen species and subsequent hemolysis, thereby confirming its antioxidant activity.6,7 Of note, Paulson and Prabhu made an observation that diverged from prevailing notions regarding selenoproteins. Se-deficient mice possessed elevated erythroid progenitors and lacked compensatory reticulocytosis, suggesting that Se exerts a broader effect, much earlier in erythropoiesis than at the macrophage differentiation level.

Fig. 1. Schematic representation of Se function during stress erythropoiesis. Mouse stress erythroid progenitors (SEP) migrate from the bone marrow to the spleen, where Se acts to increase SEP numbers and differentiation to erythroid precursors. Optimal precursor maturation relies on the formation of functional EBIs. Se promotes the differentiation of island macrophages by upregulating Spic expression in monocytes. Professional illustration by Patrick Lane, SciEyeStudios.

An unexpected discovery from this work is that Se influences erythroid niche development in the spleen, where stress erythropoiesis predominantly occurs in the mouse. EBIs are characterized by terminally differentiating erythroid precursors invested by a single central macrophage.9 Selenoprotein deficiency affects macrophage differentiation from monocytes due to altered Spic expression and heme homeostasis, and the resultant decrease in red pulp macrophages correlates with quantitative and qualitative diminution of stress EBIs. This exciting work answers long-standing mechanistic questions regarding the role of Se in stress erythropoiesis, which may carry clinical implications, particularly, for anemia of inflammation/chronic disease. In this context, where micronutrient handling by the body, including iron, is perturbed, Se supplementation could be considered. Nevertheless, before translating these findings more broadly to humans, many questions remain. For example, anatomic differences exist between murine and human stress erythropoiesis. In humans, stress responses mainly occur in the bone marrow, whereas stress erythropoiesis occurs in the spleen of mice. Do these anatomic differences reflect differences in the composition and function of stress EBIs? Adding to this complexity, the identity of the central macrophage during steady-state erythropoiesis remains unclear. As we witness a dramatic increase in the interest of EBIs in the field of erythropoiesis, we are certain that the differences between steady state and stress EBIs, highlighted by their differing reliance on Se, will ignite further exploration into understanding these niches.

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REFERENCES

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