GATA-1 is a key element for lineage commitment of progenitors downstream of the CMP. Furthermore, the level of GATA-1 expression in these progenitor-cell compartments appears to play an essential role in determining what progenies are generated.

Precise regulation of GATA-1 activity is essential for normal hematopoiesis, as mutations that interfere with its normal function contribute to megakaryocytic leukemia in children with Down syndrome (DS-AMKL). Likewise, in several animal models reduced expression of GATA-1 has been linked to increased progenitor-cell proliferation and hematologic abnormalities. Of great interest, mice engineered to express the mutant form of GATA-1 associated with DS-AMKL show a transient expansion of a unique yolk sac and fetal liver progenitor.[5] As Tober and colleagues suggest, it is tempting to speculate that the target cell of the *GATA1* mutation in this malignancy is the yolk sac megakaryocyte progenitor described in their report. Future studies focused on human fetal progenitor cells and DS-AMKL patient samples will likely provide the next wave of important new insights into the development of this disease.

The author declares no competing financial interests.

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Comment on Tiedt et al, page 1503

Happy to have the megakaryocyte blues

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While brief in length, the report of a *Pf4-Cre* transgenic mouse by Tiedt and colleagues describes a long-sought-after tool that should advance the study of megakaryocyte biology and platelet function.

Genetically modified mouse models have been a rich resource for understanding normal development and disease pathogenesis, and nowhere has this been truer than in the field of hematology. Tissue-specific and conditional Cre recombinase expression combined with strategically placed *loxP* sites allow one to control gene deletion or mutant allele expression, thereby bypassing problems often encountered with organism-wide gene modification.[1] The *Pf4-Cre* mouse is the first reported murine model that provides megakaryocyte lineage-restricted Cre recombinase expression.

Tiedt and colleagues used platelet factor 4 (PF4) regulatory elements for their studies. To overcome expression infidelity often encountered when using small promoter elements, they introduced the Cre cDNA into the first exon of the PF4 gene within a murine bacterial artificial chromosome. To detect functional expression of the introduced Cre cDNA, the mice were crossed with the often-used *ROSA26-lacZ* reporter mouse that expresses LacZ only in cells that express Cre. As hoped, the beautiful blue LacZ stain was detectable only in megakaryocytes in the bone marrow and spleen. However, in an observation that has frustrated investigators in the past, not all megakaryocytes stained positive for LacZ, and staining intensity was quite variable.

The inconsistent LacZ staining in the megakaryocytes could reflect peculiarities of gene expression from the ROSA locus in megakaryocytes. Alternatively, it could reflect a gene dose effect secondary to incomplete Cre-mediated DNA excision if the onset of Cre expression occurs in polyploidy megakaryocytes, cells that will have many copies of the ROSA26-LacZ locus. If the latter were true, it would not make for a very useful mouse model. Fortunately, these investigators crossed the *Pf4-Cre* mouse to a background in which the integrin β1 gene has the first coding exon flanked by LoxP sites.[2] In this case, cells expressing Cre should not express integrin β1. Megakaryocyte DNA from *Pf4-Cre integrin* $\beta1^{lox/lox}$ mice showed complete excision. Moreover, the platelets lack integrin β1 surface expression, while lymphocyte, monocyte, and granulocyte integrin β1 expressions are unaffected, supporting the idea that Cre-mediated excision is megakaryocyte lineage specific.

Tiedt and colleagues have succeeded where others have failed, and their findings underscore the fact that expression reporters and deletion reporters do not always yield congruent findings. The *Pf4-Cre* mouse provides a new addition to the toolbox for those who study megakaryocytes and platelets, but it remains to be seen exactly where it will be useful. The integrin β1 data suggest that the mice will be informative in studies of platelet function, and likely in studies of platelet biogenesis. Its usefulness for understanding earlier aspects of megakaryocytopoiesis is unclear and depends on when Cre expression begins developmentally. It is now up to the rest of the field to put the *Pf4-Cre* mouse to good use to better understand the mysteries of the marrow's most enigmatic cell, the megakaryocyte, and the function of its platelet offspring.

The author declares no competing financial interests.

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