recommendation that “only well-designed clinical trials that have the greatest possibility of improving survival and quality of life for cancer patients are undertaken.” Native American tribal wisdom says that when you discover you are riding a dead horse, the best strategy is to dismount. Based on a large amount of animal work, and an initial positive clinical trial, P-gp inhibition held significant promise to improve survival in AML, especially in the elderly. However, based on the findings of this study, combined with the previous trials, further clinical trials in this area should be viewed with skepticism, and effort redirected to other, more novel, strategies.

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

REFERENCES

Comment on Wölfler et al, page 4116

**Tracing C/EBPα+ cells and their progeny**

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In this issue of Blood, Wölfler and colleagues describe a mouse model that allows tracking of hematopoietic cells that express C/EBPα and the progeny thereof. Their data indicate that expression of C/EBPα drives commitment of multipotent progenitors toward a myeloid cell fate, but lymphoid potential is retained as well.

Multiple hematopoietic stem cells (HSCs) that reside in the bone marrow can give rise to all myeloid and lymphoid lineages of the blood, but the process of lineage specification is complex. Cytokines and growth factors are critically important, although there is still lively debate about the “instructive” versus “permissive” nature of their actions (see comment in Enver and Jacobsen). Cytokines are able to instruct progenitor cells to develop into a certain lineage, but stem cell–intrinsic programs that predetermine lineage fate appear to exist as well (reviewed in Schroeder). Both these extrinsic and intrinsic cues will ultimately lead to changes in gene expression programs that will guide the differentiation of progenitors into mature cell types, and the activation of transcription factors is key to these processes.

One such transcription factor is the CCAAT/enhancer-binding protein α (C/EBPα). It has been demonstrated that C/EBPα is essential for the formation of granulocytes and in particular for the transition from the common myeloid progenitor (CMP) toward the granulocyte/macrophage progenitor (GMP). Initial studies suggested that C/EBPα is expressed at low levels in HSCs, is up-regulated upon maturation toward CMPs and GMPs, and is not expressed...
in erythroid/megakaryocyte progenitors (MEPs) or lymphoid cells. However, little was known about the precise cell type in which C/EBPα is first expressed within the hematopoietic hierarchy, and what the ultimate fate of the progeny of these C/EBPα-expressing cells would be.

Wolff and colleagues make use of a model in which Cre recombinase is knocked-in in the Cebpα locus and Cre is therefore expressed under the control of the endogenous Cebpα promoter. These mice lack one Cebpα allele but this does not impair myeloid development or steady-state hematopoiesis. Next, these Cebpα+/Cre mice were crossed with ROSA26 EYFP reporter mice, in which EYFP is only expressed after Cre-mediated recombination ofloxP sites within the locus. Thus, as soon as the Cebpα promoter becomes activated, expression of Cre will allow the expression of EYFP. Not only will cells in which the Cebpα promoter is activated become EYFP+, but also all progeny of these cells will be positive for EYFP since theloxP sites are irreversibly deleted, regardless of whether C/EBPα remains expressed (see figure).

Based on this mouse model several conclusions can be drawn: (1) only 4% of the most immature stem cells express C/EBPα, and the number of cells that express (or have expressed) C/EBPα increases to approximately 15% in multipotent progenitors; (2) upon differentiation along the myeloid lineage from CMP to GMPs an increasing number of cells express (or have expressed) C/EBPα, and practically all mature monocytes and granulocytes have expressed C/EBPα at least at some point during their development; and (3) despite the notion that erythroid and lymphoid cells do not express C/EBPα, it is clear from these tracing studies that at least some of these cells did express C/EBPα early in their development. In particular, this last point raises some important issues because it argues against a lineage-restrictive role for C/EBPα. Apparently, the expression of C/EBPα in immature progenitors does not prevent the differentiation toward a lymphoid or erythroid cell fate, even though the majority of C/EBPα-EYFP+ progenitor cells become myeloid cells. These findings are in line with the notion that the promiscuous expression of myeloid, erythroid, and lymphoid genes precedes the actual lineage commitment.

The Cebpα+/CreR26EYFP mouse model allows the identification of C/EBPα-expressing cells and particularly their progeny in an in vivo setting, but does not allow the quantification of C/EBPα expression at the protein level, which would for instance be possible in a transgenic mouse in which EYFP would be directly fused to C/EBPα. In addition, this C/EBPα-EYFP model would provide more insight into the kinetics of C/EBPα expression, and would allow the analysis of exact down-modulation of C/EBPα upon commitment along the lymphoid or erythroid lineage. Since the dosage and timing most likely matter, it will be interesting to develop those models as well.

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**REFERENCES**


**Comment on Peffault de Latour et al, page 4175**

**Abnormalities in Th17 T cells in aplastic anemia**

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In this issue of Blood, Peffault de Latour et al demonstrate that interleukin-17 (IL-17)–producing Th17 T cells are increased in the peripheral blood and bone marrow of patients with aplastic anemia, compared with healthy controls. They also provide evidence that IL-17 contributes to the severity of marrow failure at an early stage. This work advances our overall understanding of the mechanisms of immune-mediated hematopoietic suppression and may ultimately have important clinical implications for the treatment of aplastic anemia.

Idiopathic aplastic anemia is characterized by pancytopenia and bone marrow hypoplasia, resulting from immune-mediated suppression of hematopoiesis. Although the management of aplastic anemia is challenging and the outcome frequently fatal,
Tracing C/EBPα+ cells and their progeny

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