AML (12%-33%), MDS (23%), and in most AML French-American-British (FAB) 

Although point mutations of 
tions and rearrangements in human leukemia. 

In a novel mouse model of MDS/AML, retroviral transduction is hypothesized to 
create two hits (expression of the mutant AML1D171N allele and activation of Evi1 
via insertional mutagenesis) that converge on AML1 function. 

T 
he molecular pathogenesis of MDS and 
the mechanism of its transformation to 
AML are not well understood. Although sev-
eral mouse models of MDS have been de-
veloped recently, most fail to recapitulate key 
features of the human disease. In one of the 
best genetically defined systems, transplanta-
tion of bone marrow cells retrovirally trans-
duced with Evi1 results in bone marrow fail-
ure, erythroid dysplasia, and evidence of 
increased apoptosis.1 

Despite reproducing these hallmarks of MDS, the mice do not de-
velop AML, suggesting that additional genetic 
events are required for full transformation. 

The AML1 gene is a frequent target of muta-
tions and rearrangements in human leukemia. 
Although point mutations of AML1 are rare in 
most AML. French-American-British (FAB) 
subtypes, they are relatively common in M0 
AML (12%-33%), MDS (23%), and in 
therapy-related and radiation-associated MDS/ 
AML (38%-46%).2 In this issue of Blood, 
Watanabe-Okochi and colleagues use a murine 
retroviral transduction/bone marrow transplan-
tation model to characterize 2 mutant 
AML1 alleles previously identified by their group: a 
frame shift after S291 that results in truncation of 
the C-terminal transactivation domain, and a 
dominant-negative allele that reduces DNA binding and tran-
scriptional activity.6 

This leads to the prediction, not tested in the 
current study, that Evi1 and the AML1D171N 
allele cooperate in vivo because they conspire 
to reduce AML1 activity. If further studies 
support this model, there would be a rational 
basis for developing therapies that target this 
protein–protein interaction. 

Conflict-of-interest disclosure: The author 
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OSTEOPEOGENIC STEM CELLS: TRANSPORTABLE, 
BUT REGENERATIVELY LIMITED

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Questions about the transplantability 
of mesenchymal stem cells, their 
ability to engraft within the bone 
marrow of recipients, and hence 
their clinical usefulness have been 
hotly debated for several decades. 
In this issue of Blood, Dominici 
and colleagues demonstrate robust 
serial osteopoietic engraftment, 
but highlight that 

Due to the presence of hemopoietic stem 
cells in the bone marrow, bone marrow 
transplantation has been successfully used to 
treat hematological diseases for many decades. 
Based on the concept that bone marrow also 
contains microenvironmental or mesenchymal stem 
cells (MSCs) with osteopoietic potential, the 
clinical use of bone marrow transplantation to 
treat bone disorders is also very appealing. 
Although initial studies suggested that MSCs 
cannot be transplanted intravenously, more recently 
documented animal models and preclinical stud-
ies have demonstrated that donor MSCs engraft 
in the bone marrow and give rise to bone and 
muscle.1-4 Furthermore, a series of clinical trials 
performed by this group,5,6 involving children 
with severe osteogenesis imperfecta, 
demonstrated that transplanting 
unmanipulated bone marrow 
resulted in a marked improvement in 
total body mineral content, accelerated linear 
growth, and decreased fracture rates. Similar 
results were evident following transplantation of 
unpurified MSCs. In all of these studies, however, 
the observed accelerated growth diminished over
time. In this issue of Blood, Dominici and colleagues use a murine model for conducting a comprehensive set of serial transplantations to determine whether this outcome is related to the transplantability of cells with limited osteopoietic potential, or rather due to the engraftment of cells with robust potential that are nevertheless subject to regulatory influences, which prevent sustained therapeutic levels of donor osteopoiesis. This elegant study demonstrates that normal bone marrow donor stem cells with osteopoietic potential home and engraft after transplantation, but that these cells offer only limited regenerative contribution to host osteopoiesis. Although the precise mechanism for this lack of sustained contribution remains unclear, the authors use serial transplantation to suggest that it is not due to a limited cell potential, but rather results from either intrinsic cell or extrinsic microenvironmental regulation. Together with other recent studies, this work demonstrates that MSCs are transplantable intravenously, do engraft within the bone marrow, and do contribute to osteopoiesis. However, this work highlights the lack of sustained contribution in any therapeutic use of these cells as a critical issue for the future long-term treatment of bone disorders. Further studies will be required to determine what causes the lack of durable donor-derived osteopoiesis, and will hopefully lead to treatments that will allow the widespread use of marrow transplantation to treat bone disorders.

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The journey from laboratory bench to this clinical study began half a century ago with 2 independent observations. In 1958, the Hungarian physiologist Gyorgy Gárdos described calcium-dependent potassium loss from red cells. The “Gardos pathway” is now known to be mediated by a calcium-activated K channel. D. C. Tosteson’s seminal studies of abnormal cation content and permeability in sickle cells led to the characterization of dehydrated cells with high hemoglobin concentration. The importance of these dehydrated cells was reinforced by subsequent discoveries that polymerization is exquisitely sensitive to Hb S concentration, and that dehydrated sickle cells are very short-lived, selectively trapped in the microcirculation, and removed during vaso-occlusive episodes.

Sickle cell dehydration is thought to result from a complex interplay of Hb S polymerization and several cation transport systems in sickle cells. A transport pathway that normally regulates volume in reticulocytes, the potassium-chloride cotransporter (KCC) appears to function pathologically in sickle cells, overshooting its target hemoglobin concentration and priming the reticulocyte to sickle. Hb S polymerization activates a nonselective cation leak pathway in a fraction of sickle cells upon deoxygenation. Calcium entry via this sickling-induced pathway triggers activation of the Gardos channel, which mediates rapid KCl and water loss. Abnormal KCC activity in the sickle reticulocyte may thus facilitate a vicious spiral in which sickling and Gardos channel activation reinforce each other to dehydrate the cell. In vitro and animal studies have been insufficient, however, to elucidate how these pathways interact in vivo. Brugnara’s pioneering clinical investigation of another Gardos channel blocker, clotrimazole, laid the foundation for the development of senicapoc. The demonstration in the current study that senicapoc reduces the number of dense sickle cells establishes conclusively that the Gardos pathway is active in vivo and contributes to sickle cell dehydration.

Ataga and colleagues show that senicapoc treatment was well-tolerated, resulted in increased hemoglobin, and reduced markers of hemolysis—reticulocyte count, bilirubin, LDH levels—strongly suggesting that sickle cell survival was improved. Thus, the study demonstrates that prevention of dehydration in a clinical setting is feasible and decreases in vivo hemolysis in sickle disease.

Recently, a phase 3 trial of senicapoc was terminated early because of low probability of achieving a reduction in crisis rate, the primary...
Osteopoietic stem cells: transplantable, but regeneratively limited

Susie Nilsson