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Myeloma: targeted therapies march on

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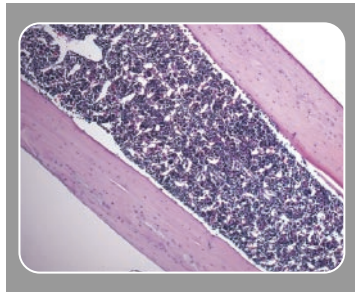
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PLENARY PAPER

Osteoblasts make for good neighbors

Over 25 years ago, Schofield¹ hypothesized the existence of a niche, or dedicated space, within bone marrow where hematopoietic stem cells (HSCs) could establish residence and proliferate. The concept of a stem cell niche is now recognized as a central component of stem cell physiology. Niches for intestinal epithelium and certain skin stem cells have been exposed, but pinpointing and characterizing the HSC niche has



proven to be a difficult task. However, mounting evidence suggests that HSC survival and differentiation hinge upon intimate contact with bone surrounding the marrow space. During fetal development, chondrogenesis and endochondral bone formation precede the local onset of hematopoiesis, and after sublethal irradiation, hematopoietic precursors are first observed along the endosteal surfaces of bone.

In this issue of *Blood*, Visnjic and colleagues (page 3258) present data suggesting a role for osteoblasts in HSC regulation. This group employed a genetic strategy to selectively, and reversibly, eliminate osteoblasts from bone. They then examined what impact osteoblast depletion would have on hematopoiesis. Essentially, they found that osteoblast ablation was accompanied by a dramatic loss of bone marrow cellularity and a reduced number of early hematopoietic progenitors. Upon reversal of the

genetic block in osteoblast lineage, osteoblasts reappeared with pockets of hematopoiesis in direct proximity to the sites of new bone formation.

The work of Visnjic and colleagues nicely complements recent reports from 2 other labs^{2,3} demonstrating that genetic manipulations to increase the number of osteoblasts trigger parallel increases in the HSC population. Taken together, there is now strong evidence that neighboring osteoblasts play a crucial role in the HSC niche and thus contribute to the formation and maintenance of all blood cell types. However, much remains to be learned about the cellular and molecular makeup of the HSC niche. As Dr Visnjic and colleagues suggest, in vivo osteoblast ablation should be a useful tool in dissecting the complex systems at play in the bone microenvironment that regulate HSC behavior. Once better understood, the reciprocal relationship between these 2 neighboring cell types—HSCs and osteoblasts—may lead to the design of more effective methods to restore the synthetic ability of marrow after cytotoxic drug treatment or in the setting of genetic deficiencies.

—Robert F. Klein

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CLINICAL OBSERVATIONS, INTERVENTIONS, AND THERAPEUTIC TRIALS / NEOPLASIA

Myeloma: targeted therapies march on

Over the past decade, considerable progress in the treatment of multiple myeloma (MM)

has improved patient outcomes and expanded options in up-front and salvage therapy. Currently, myeloma treatment advances along 2 lines. One direction is building on the proven superiority of high-dose melphalan with autologous hematopoietic stem cell support and pursuing treatment intensification such as tandem autotransplants or a sequential approach of auto- and “mini-allo” transplantation. The second area of treatment innovation comprises a novel generation of therapeutic agents more specifically targeting the myeloma cell and its interactions with the bone marrow microenvironment. These agents not only have marked antimyeloma activity, but they also appear suited to overcome classical drug resistance. Active prototypes of these drugs include thalidomide, its immunomodulatory derivative CC-5013, and the proteasome inhibitor bortezomib (Velcade, formerly PS-341). In this issue of *Blood*, 2 papers address current progress in the expanding field of biologically targeted myeloma therapy.

Alsina and colleagues (page 3271) report the results of a phase 2 trial evaluating the activity and tolerability of the farnesyltransferase (FTase) inhibitor Zarnestra (tipifarnib, formerly R115777) at a dose of 300 mg orally twice a day in 43 patients with advanced MM. Although no complete or partial remissions were observed at this dose level, 23 of 36 evaluable patients (64%) had disease stabilization lasting between 2 and 26 months. The efficacy of this single-agent therapy is remarkable considering the favorable toxicity profile and the fact that more than half of the patients enrolled were refractory to prior therapy, had undergone stem cell transplantation, and/or had thalidomide pretreatment. If additional preclinical data can provide a rationale, further clinical evaluation of Zarnestra in combination with established antimyeloma agents would seem promising.

Zarnestra belongs to a class of drugs

developed as inhibitors of the Ras oncoprotein. Their mechanism of action is considered to reside in the inhibition of Ras farnesylation that is required for its membrane association and signaling activity. Indeed, selective inhibition of FTase enzymatic activity and protein farnesylation by Zarnestra was shown in this study using patient peripheral blood and bone marrow samples. However, neither inhibition of FTase nor N-Ras and K-Ras mutation status of the myeloma cells correlated with response to treatment. These findings suggest that, even in Ras-mutated MM, deregulation of the Ras signaling cascade may be either a dominant transforming pathway or just one among redundant oncogenic events ensuring tumor growth and survival. Another likely explanation is that the biologic activity of FTase inhibitors is in fact more complex and involves proteins unrelated to Ras.^{1,2}

Podar and colleagues (page 3474) provide the preclinical rationale for evaluation of the small molecule tyrosine kinase inhibitor GW654652 as novel antimyeloma agent. This indazolylpyrimidine inhibits vascular endothelial growth factor (VEGF) receptors 1 through 3. VEGF is known to be produced by both MM and bone marrow stroma cells and has been shown to optimize the microenvironment for MM tumors via autocrine and paracrine stimulatory loops. As a potent angiogenic cytokine, VEGF may also contribute to myeloma-associated marrow neoangiogenesis. The results of the in vitro studies reported demonstrate that GW654652 blocks VEGF-induced tyrosine phosphorylation of VEGF receptor-1 (Flt-1) and related downstream signaling in MM cells and inhibits MM cell migration, proliferation, and survival. It also acts on myeloma-stroma interactions, as shown by inhibition of VEGF and interleukin-6 production in a coculture model. Secondary to the interference with the production of the MM survival factor interleukin-6, GW654652 may also offer the potential to overcome drug resistance in MM. These findings are in line with and extend previous reports on in vitro activities of other

VEGF receptor tyrosine kinase inhibitors.^{3,4} Based on the promising preclinical data, first results of clinical evaluation of this novel class of drugs are eagerly awaited.

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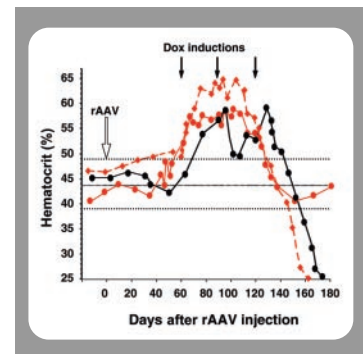
GENE THERAPY

Inadvertent autoimmunity in EPO gene transfer

Several congenital deficiencies such as hemophilia B and anemia are currently treated by administration of recombinant proteins. However, repeated clinical administration of therapeutic proteins is cumbersome, and such genetic disorders could be cured via gene transfer vectors, allowing sustained and/or controlled expression of these proteins. In this respect, the intramuscular inoculation of adeno-associated viral (AAV) vectors expressing human blood coagulation factor IX seems extremely promising for treatment of patients with hemophilia B, and clinical trials have now progressed into phase 1/2.¹ Likewise, biologically active erythropoietin (EPO) can be secreted from skeletal muscle and was shown to improve erythropoiesis in beta-thalassemic mice.² So far, protein replacement therapy with recombinant human EPO (rhuEPO) produced from mammalian cells, biologically equivalent to the natural hormone, has been extremely effective to remedy several forms of

anemia. Although approximately 3 million people throughout the world have now been treated, very few patients have developed pure red cell aplasia following rhuEPO therapy.³ It is only in the last few years that a significant increase in the # of cases of absolute resistance to rhuEPO therapy due to anti-EPO antibodies was reported, most likely as a result of slight modifications in the production and formulation of the clinical grade rhuEPO. As for gene therapy, there is clear evidence for humoral and cellular immune responses against transgenic proteins—as well as absence of such responses, depending on vector design, gene dosage, or the underlying mutation in the dysfunctional gene.

In this issue of *Blood*, 2 independent studies from Chenuaud and colleagues (page 3303) and Gao and colleagues (page 3300) describe for the first time an inadvertent autoimmune response in nonhuman primates resulting from transfer of a gene encoding a self-antigen. Their approach was to deliver the homologous EPO cDNA driven by ubiquitous and/or regulatable promoters via AAV vectors injected in muscle or aerosolized in lung, resulting in supra-physiologic serum levels of EPO, from 10- to 100 000-fold over the baseline. However, this genetic



intervention broke the immune tolerance, and, within a few weeks, some macaques suffered from severe autoimmune anemia, possibly induced by T/B lymphocytes and monocyte infiltrates in inoculated muscles as well as by neutralizing antibodies against both the transgenic and endogenous EPO. The reasons for the autoimmunity induced by homologous EPO gene transfer are not