How can we explain the difficulties in finding the best way to use GO? Calicheamicin is a very toxic intercalating agent that is 1000-fold more potent in vitro than doxorubicin. Its conjugation with a monoclonal antibody allows the drug to be delivered directly to leukemic cells and explains its efficacy, but the favorable risk–benefit ratio of the conjugate may be only within a narrow dose range. The use of repetitive low doses is likely a way to enhance the drug’s efficacy without increasing toxicity.6,8 The ongoing study AML18, from the drug repetitive low doses is likely a way to enhance within a narrow dose range. The use of vs 2 doses of 3 mg/m2 of GO in addition to studies will be of major interest.

molecular AML subsets within the MRC regard, future results from the ongoing study in NPM1-positive AML.6 In this promyelocytic leukemia and in the ALFA AML, as in AML with high CD33 unsurprisingly, observed in chemosensitive and L¨owenberg, the ef

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Comment on Boyerinas et al, page 4821

Osteopontin: an unhealthy sleep remedy for ALL

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In this issue of Blood, Boyerinas and colleagues report about a novel mechanism of leukemia cell evasion from chemotherapy.1 A cute lymphoblastic leukemia (ALL) cells hijack endosteal bone marrow niches by adherence to osteopontin (OPN), a highly acidic extracellular matrix protein. Normally, OPN is secreted by osteoblasts and functions as a bridge between bone and blood, ie, between the endosteal marrow niche and hematopoietic progenitor cells (HPCs). In these niches, HPCs remain quiescent because of OPN-suppressed proliferation, presumably to maintain and limit the size of the HPC pool.2,3 The authors hypothesized that ALL cells may use a similar OPN-dependent mechanism to occupy endosteal niches, where quiescent ALL cells can replace HPCs and survive conventional cytotoxic chemotherapy. The authors demonstrate that ALL cells adhere to OPN via integrins (α4β1, α5β1, α9β1) and, in addition, actively secrete OPN, thereby participating in the remodeling of the niche. In a xenograft mouse model, highest levels of OPN were seen around dormant ALL cells. Through this OPN-mediated mechanism, ALL cells survive in endosteal niches and can become the seed for minimal residual disease and relapses. Consequently, the authors demonstrate that OPN neutralization with antibodies awakens ALL cells in the ALL mouse model, causing an increase in dividing/cycling ALL cells, which in turn sensitized ALL cells to cytarabine (Ara-C) therapy.
During the last 2 decades, there has been substantial progress in identifying key cellular and molecular players in crosstalk between normal and malignant hematopoietic cells and the marrow microenvironment. At least 2 hematopoietic stem cell (HSC) bone marrow niches have been described: one endosteal and one perivascular (see figure). Specialized osteoblasts lining the bone surface form endosteal niches. On the other hand, sinusoidal endothelial cells and a small population of perivascular reticular cells with sinusoidal endothelial cells and a small endosteal niches. On the other hand, sinusoidal endothelial cells and a small population of perivascular reticular cells with long processes, expressing high amounts of CXCL12 (called CXCL12-abundant reticular or CAR cells), create vascular niches, which are scattered throughout the marrow cavity. Earlier groundbreaking in vivo studies from the same group revealed that malignant B cells not only interact with stromal cells and molecules that are described within HSC niches but specifically invade, exploit, and disrupt HSC niches during malignant progression, thereby negatively affecting benign hematopoiesis.

How can we stop leukemia cells from parasitizing in these niches and give them a taste of their own medicine? CXCR4, a chemokine receptor that tethers hematopoietic cells to CXCL12-secreting stromal cells, is the first therapeutic target for disrupting crosstalk between leukemia cells and the marrow microenvironment. Many clinical trials use CXCR4 antagonists (eg, plerixafor/AMD3100) for "chemosensitization" when given in combination with cytotoxic agents. These studies are either ongoing or are recently finished, and a first trial in acute myeloid leukemia has reported encouraging results. Targeting OPN in ALL, as introduced in this study, follows a similar concept: OPN neutralization releases ALL cells from their dormant state in the endosteal niches and makes them better accessible and receptive toward cytotoxic drugs that target cycling cells. As such, this study is in line with an ongoing important paradigm shift in cancer therapy, moving from cancer cells as the primary target of therapy toward new treatments that also interfere with protective tumor-microenvironment interactions. It is also tempting to think about analogies between OPN and "The Sleeping Beauty": ALL cells are doomed to sleep in endosteal niches by OPN, but once this curse is lifted, life in the marrow awakens. The encouraging data about OPN neutralization in ALL in this study stir hope that, unlike in "The Sleeping Beauty", it will take a much shorter time than 100 years until the reversion of leukemia cell dormancy in ALL can be clinically tested.

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

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Comment on Gandre-Babbe et al, page 4925

**JMML patient-derived iPSCs induce new hypotheses**

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In this issue of Blood, Gandre-Babbe et al have, in part, overcome the obstacle of validating the molecular underpinnings of juvenile myelomonocytic leukemia (JMML) with the generation of induced pluripotent stem cells (iPSCs) from individuals with JMML. Validation of the molecular underpinnings of JMML derived from mouse models, has been limited in humans due to a scarcity of primary clinical samples. JMML is a rare childhood leukemia that has nonetheless played a central and highly informative role in clarifying the consequences of RAS hyperactivation in human malignancies as well as in human congenital disorders. JMML also continues to be the recipient of intense investigation because its only curative therapy is allogeneic hematopoietic stem cell (HSC) transplantation, and yet 50% of children will succumb to leukemia relapse following this arduous therapy. JMML is renowned for displaying features of a disease based on well-defined and unambiguous genetic mutations, since most children diagnosed with JMML bear nonoverlapping loss-of-function mutations in NF1 or CBL or gain-of-function mutations in NRAS, KRAS, or PTPN11. Each of these mutations yields RAS hyperactivation with a net output of excessive signaling through RAS effector pathways, including the canonical RAF-MEK-ERK and PI3K-AKT pathways. Functionally, the hallmark of hematopoietic progenitors from individuals with JMML is cytokine-independent growth in vitro and exquisite sensitivity to the growth factor granulocyte macrophage colony-stimulating factor (GM-CSF).

The advent of iPSC technology has provided an opportunity to generate a renewable source of patient-derived reagents that may potentially produce authentic models of JMML in vitro and in vivo for deeper molecular analysis, straightforward and efficient screening of novel pharmacologic
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