

(ICAM-1) appears to be an especially good target. It is constitutively expressed on the vascular endothelium at a high level that is unaltered by inflammatory cytokines. Furthermore, anti-ICAM conjugates greater than 1 μm in diameter are not readily internalized but remain exposed on the endothelial surface for some time. Such conjugates are thus well positioned to function as molecular therapeutic bioreactors working at the blood–vessel wall interface. As a proof of concept, Murciano et al describe the efficacious lysis of pulmonary fibrin microemboli using an anti-ICAM/tPA conjugate.

While the results of the work described by Murciano et al are exciting in their own right, the work also offers a glimpse of the future promise of endothelial-targeted therapeutics. Given the large surface area of the (pulmonary) endothelium, enzyme bioreactors positioned at the endothelial surface may represent an exciting new approach to the removal or inactivation of noxious metabolites or toxins. By exploiting more specific vascular addressins as immunotargets, selected vascular beds may be targeted. Perhaps by targeting tumor vasculature with an enzyme to facilitate the conversion of a prodrug to an active antitumor agent, or conversely targeting the pulmonary or hepatic vascular spaces with an enzyme to inactivate chemotherapeutic agents, tumors may be exposed to higher and more effective doses of chemotherapeutic agents while minimizing systemic toxicity. Although the work described by Murciano et al is still in an early stage and there is much work to be done, the future is exciting; the promise is great.

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Therapeutic remodeling of myeloma chromatin

Multiple myeloma cells dysregulate critical oncogenes and tumor suppressor genes by a number of mechanisms. In addition to genetic changes, there are less well-studied epigenetic changes that can result in the

silencing of tumor suppressor genes and contribute to disease progression. These heritable changes are associated with 3 distinct modifications to the DNA and associated chromatin: methylation of cytosines, deacetylation of histones, and methylation of histones. Epigenetic changes represent powerful mechanisms for cancer progression because unlike mutations, they are able to silence not just a single gene but multiple genes in multiple pathways. At the same time, this makes them a very attractive target for anticancer drug development. By inhibiting a single target, one can expect to reactivate the expression of a number of genes whose silencing was critical to the tumor formation and at the same time expect relatively modest effects in non-transformed cells.

The relationship between these 3 epigenetic mechanisms are beginning to be elucidated. In an elegant study using a colon cancer cell line, Vogelstein and colleagues (*Cancer Cell*. 2003;3:89-95) have demonstrated that the primary event causing gene silencing appears to be aberrant histone methylation, which is followed subsequently by histone deacetylation and cytosine methylation. Agents targeting these processes are being actively developed and investigated in clinical trials.

The first agent to be developed is the cytosine nucleoside analog, 5-aza-2'-deoxycytidine, a potent inhibitor of DNA methylation and an active antileukemic agent. Several agents that inhibit histone deacetylation, including butyrate, valproic acid, SAHA, pyroxamide, depsipeptide, MS-275, and CCI-994, are in clinical trials. In this issue, Nicholas and Constantine Mitsiades and their colleagues (page 4055) provide the first glimpse of these powerful new agents in myeloma. They show that, as with other tumors, in myeloma SAHA is a powerful inducer of p21, growth arrest, and apoptosis. So far we have not seen the development of any histone methyltransferase inhibitors; however, it has recently been discovered that proteins containing a SET domain can act as histone lysine methyltransferases. Given the flurry of papers describing the

structural biology of these domains, it appears likely that specific inhibitors will not be far behind. These agents offer particular promise because they may target a primary event in epigenetic regulation, and in the case of t(4;14) MM with dysregulation of MMSET, a primary genetic event in the pathogenesis of myeloma.

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Xenogeneic studies of human stem cell plasticity

Differentiation of bone marrow–derived stem cells (BMSC) into mature hepatocytes occurs in mice and humans (reviewed in Theise and Krause, *Leukemia*. 2002;16:542-548). Murine studies show that the same BM subpopulations that are capable of engraftment of the hematopoietic system are capable of differentiation into mature hepatocytes *in vivo*. Because analogous studies using limiting numbers of specific cell subpopulations cannot be performed in humans, xenogeneic and *in vitro* systems are needed in order to determine which human cell subpopulations can differentiate into hepatocytes. More importantly, these models can then be used to determine the mechanism by which this occurs.

In this issue of *Blood*, the article by Wang and colleagues (page 4201) represents a significant contribution to the developing story regarding the plasticity of BMSC because it shows not only that human CD34⁺ cord blood (CB) and BM cells are capable of differentiating into hepatocytes, but also that specific forms of hepatic damage enhance the levels of engraftment.

The data presented corroborate those of Danet et al (*Proc Natl Acad Sci U S A*. 2002;99:10441-10445), which showed that human CB and BM cells expressing the complement receptor C1qR_p, the human homologue of murine AA4.1, differentiate into mature hepatocytes in the livers of immunodeficient mice. Although NOD/SCID mice

were sublethally irradiated prior to transplantation of human cells in both studies, the in vivo conditions required to detect human hepatocytes in the mice differed. Danet et al detected fewer than 0.1% human hepatocytes after mice were irradiated with 375 cGy and received as few as 5000 $\text{lin}^- \text{CD38}^- \text{C1qR}_p^+$ cells. In contrast, Wang et al detected no human hepatocytes after transplantation of either 2000 $\text{CD34}^+ \text{CD38}^- \text{CD7}^-$ or 1×10^5 CD34^+ cells into mice irradiated with 300 cGy,

which could be due to differences in the cell populations, the amount of irradiation, or the detection methods used. In Wang et al, specific liver damage was critical for induction of hepatocyte engraftment. Engraftment occurred after administration of the hepatotoxic agent CCl_4 and was further enhanced by administration of hepatocyte growth factor. Neither irradiation alone nor irradiation plus allyl alcohol treatment induced human hepatocyte formation.

Development of this xenogeneic model of human hepatocyte differentiation from human CB and BM paves the way for further advances in our understanding of plasticity. In addition to developing methods for obtaining physiologically relevant levels of human hepatocyte engraftment, this xenogeneic model will be useful for studies of human hepatocyte function and dysfunction in inherited diseases as well as viral hepatitis.

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