

not affect the response because the A anti-C-activated CTL precursors cannot recognize them. Bachar-Lustig et al have effectively done the same series of experiments in vivo. Lethally irradiated strain-B mice received strain-A BM transplants containing large numbers of strain-A T cells. Rapid death ensued unless cells from a B anti-D CTL line were also included. Addition of rapamycin could make these cells more effective. In principle, the problem of GVHD has been solved!

—Richard G. Miller

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1. Miller RG. How a specific anti-self deletion mechanism can affect the generation of the specificity repertoire. In: Sercarz E, Cunningham AJ, eds. *Strategies of Immune Regulation*. New York, NY: Academic Press; 1980: 507-512.
2. Claesson MH, Miller RG. Functional heterogeneity in allo-specific cytotoxic T lymphocyte clones. I: CTL clones express strong anti-self suppressive activity. *J Exp Med*. 1984;160:1702-1716.

Monosomy 7 and the myeloid malignancies

Cytogenetics has made an enormous contribution to our understanding of the pathophysiology and prognosis of childhood leukemia. In most cases of acute lymphocytic leukemia (ALL) various translocations within a pre-B cell that probably occurred in utero set the stage for another event or events that trigger unbridled growth. The individual translocations, though not solely responsible for the leukemia, have enormous prognostic significance. The tel-acute myeloid leukemia 1 (AML1) fusion associated with a (12:21) translocation has a standard chemotherapy-induced cure rate of between 90% and 100%. In contrast, ALL with the Philadelphia chromosome is only effectively treated with massive chemoradiation therapy and stem cell transplantation.

In this issue of *Blood*, Kardos and colleagues (page 1997) review a large European experience of refractory anemia in childhood. This heterogeneous collection of premyeloid and virtual myeloid leukemias is characterized by several different cytogenetic abnormalities, the most glaring of which is monosomy 7, a

disorder characterized by an extremely poor prognosis. It must be treated with stem cell transplantation. Even a matched unrelated donor transplant offers a better chance for survival than watchful waiting or chemotherapy. Adults with monosomy 7 usually have multiple cytogenetic abnormalities, whereas the disorder is usually unadulterated in children. The haploinsufficiency associated with loss of the short arm of the chromosome is probably responsible for the development of malignancy that occurs at a variable rate even in patients with familial loss of the chromosome. The collection of monosomy 7 cells established by Kardos et al provides an important opportunity to learn much more about this disorder. It is vital to study gene expression in monosomy 7 to learn how the chromosome disorder leads to malignancy. It is believed that loss of a key suppressor is responsible, but does this permit the unbridled expression of a tyrosine kinase that finally drives the leukemia? This is the next step of inquiry in this instructive disease. For now, Kardos and her colleagues have given us important information on the best treatment approaches.

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Challenges and progress in gene therapy for hemophilia A

In this issue, Powell and colleagues (page 2038) report the results of a phase 1 gene therapy clinical trial for hemophilia A, based on intravenous injection of a retroviral vector encoding B-domain-deleted factor VIII (FVIIIΔB). This phase 1 trial was based on encouraging preclinical studies, mostly in rabbits,¹ and essentially confirms the safety of this approach in patients. The vectors could be detected in the peripheral blood mononuclear cells for at least a year. Although some participants had detectable circulating FVIII levels (>1%) on repeated occasions, experienced fewer bleeding episodes, and required fewer FVIII protein infusions compared with historic rates, the clinical benefits were overall rather limited and a dose response was lacking. It

appears therefore that the preclinical studies that constituted the basis of this trial may not have accurately predicted the vector doses required to achieve therapeutic FVIII levels. However, the limited efficacy of this particular gene therapy approach in adult patients was not entirely unexpected, due to the inability of retroviral vectors to transduce nondividing cells.

Previous studies had shown that stable therapeutic levels of FVIII or FIX could only be obtained in neonatal hemophilic mouse and dog models or in adult mice that received hepatocyte growth factor to stimulate hepatocyte cell division.^{2,3} This inherent limitation of retroviral vectors justifies the development of vectors that can also transduce nondividing cells, such as lentiviral⁴ adeno-associated viral vectors (AAV). In this same issue, Scallan and colleagues (page 2031) report stable expression (> 14 months) of therapeutic levels of FVIII (2%-4%) in 2 dogs with hemophilia A following liver-directed gene therapy using an AAV-based vector encoding FVIIIΔB. Although AAV has successfully been used for gene therapy in hemophilia B dogs⁵ and results from clinical trials for hemophilia B are encouraging, progress in hemophilia A gene therapy has been hampered by the inherent, limited packaging capacity of AAV and the relatively large size of the B-domain-deleted FVIIIΔB cDNA. Scallan and colleagues showed that this limitation could be overcome by using small regulatory elements to drive FVIII expression, in accordance with previous reports.⁶ Although recent studies had shown that therapeutic levels of FVIII could be achieved in hemophilia A dogs with no apparent toxicity following gene therapy,⁷ the work by Scallan and colleagues is an important step forward since it is the first demonstration that long-term phenotypic correction of the bleeding diathesis could be achieved, albeit partial, in a clinically relevant, large animal model of hemophilia A. However, the reason for the lack of a dose response is not clear and warrants further studies in larger cohorts. Additional improvements in vector design and increased gene transfer efficiencies will be required to further increase FVIII expression