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 in-
cluded. Addition of rapamycin could make these
cells more effective. In principle, the
problem of GVHD has been solved!

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Monosomy 7 and the
myeloid malignancies

Cytogenetics has made an enormous contri-
bution to our understanding of the path-
ophysiology and prognosis of childhood leu-
kemia. 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 enor-
mous prognostic significance. The tel–acute
myeloid leukemia 1 (AML1) fusion associ-
ated with a (12:21) translocation has a stan-
dard chemotherapy-induced cure rate of
between 90% and 100%. In contrast, ALL
with the Philadelphia chromosome is only
effectively treated with massive chemoradia-
tion therapy and stem cell transplantation.

In this issue of Blood, Kardos and col-
leagues (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

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 en-
coding B-domain–deleted factor VIII
(FVIIIΔB). This phase 1 trial was based on
encouraging preclinical studies, mostly in rab-
bits, and essentially confirms the safety of this
approach in patients. The vectors could be de-
tected in the peripheral blood mononuclear
cells for at least a year. Although some partici-
ants had detectable circulating FVIII levels
(>1%) on repeated occasions, experienced
fewer bleeding episodes, and required fewer
FVIII protein infusions compared with historic
levels (2%-4%) in 2 dogs with hemophilia A follow-
ing liver-directed gene therapy using an AAV-based
vector encoding FVIIIΔB. Although AAV
has successfully been used for gene therapy
in hemophilia B dogs6 and results from clin-
cial 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 rela-
tively large size of the B-domain-deleted
FVIIIΔB cDNA. Scallan and colleagues
showed that this limitation could be over-
come 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 col-
leagues is an important step forward since it
is the first demonstration that long-term
phenotypic correction of the bleeding dia-
thesis 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.
levels, potentially allowing the use of lower, clinically acceptable vector doses. The simultaneous development of different gene therapy approaches is justified to bring a cure for hemophilia A one step closer to reality.

—Thierry VandenDriessche
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Fanconi anemia stem cells: going round and round

Fanconi anemia (FA) is a congenital form of aplastic anemia and is transmitted through an autosomal recessive mode. Inactivation of any of the 7 FA genes leads to progressive bone marrow (BM) failure, congenital abnormalities, and a predisposition to malignancy. Since a defect in any of the FA genes leads to a similar clinical phenotype, FA proteins appear to act together physically and functionally in a common pathway. However, the question remains: What role does each FA protein or the FA complex play in hematopoiesis?

Studies using the FA group C mouse model have shown that Fancc−/− hematopoietic stem cells have impaired function shown by reduced repopulating ability and are found at lower numbers in Fancc−/− BM. These results and the fact that BM aplasia in patients with FA is progressive suggest that the FA gene products are required for the maintenance of normal numbers of stem cells and/or for normal stem cell development.

In this issue, Li and colleagues (page 2081) have defined a new phenotype associated with Fancc−/− stem cells. Using 2 simple assays, these authors have evaluated the cycling state of the hematopoietic stem/progenitor cell fraction from Fancc−/− mice. They show that the stem/progenitor-enriched fraction is less quiescent than wild-type (WT) controls showing more bromodeoxyuridine (BrDu) incorporation and fewer cells in G0. They go on to show that the altered cell cycle kinetics in Fancc−/− cells are, at least in part, cell autonomous and do not result from unscheduled DNA synthesis or increased damage and repair. In addition, the increased cycling activity found in Fancc−/− hematopoietic cells does not seem to be a compensatory response related to their proapoptotic phenotype but may indeed contribute to the increased apoptotic response of these cells to cytokines. On the other hand, the defect in cytokine signaling in Fancc−/− hematopoietic cells may contribute to the increased cycling activity. In any case, Li and colleagues clearly demonstrate that an accelerated cycling rate in Fancc−/− cells, whether a direct or indirect consequence of absence of the Fancc gene, is a contributing factor to stem cell exhaustion in FA leading to BM failure.

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CD38: what is it there for?

CD38 is very much a molecule of the moment. Since it has been mentioned in well over 1000 articles in the past 5 years, we are entitled to ask, “What is it there for?” It is a type II transmembrane glycoprotein, the extracellular domain acting as an ectoenzyme, catalyzing the conversion of nicotinamide adenine dinucleotide (NAD+) into nicotinamide, adenine diphosphate–ribose (ADPR), and cyclic ADPR. CD38 is expressed on many types of cells, but recent interest focuses on its role on B lymphocytes. Its expression during B-cell ontogeny is tightly regulated: it appears on bone marrow precursor cells but is lost on mature lymphocytes; on germinal center cells it protects against apoptosis, but on leaving the germinal center, memory cells lack the antigen; on terminally differentiated plasma cells it is one of the few surface antigens present. In chronic lymphocytic leukemia (CLL), expression of CD38 signifies a poor prognosis, though it does not correlate precisely with the presence of unmutated immunoglobulin variable region (IgV) genes and may vary during the course of the disease.

Is it more than a prognostic marker? Deaglio and colleagues (page 2146) suggest that CD38 is involved in signaling through the B-cell receptor (BCR). Unfortunately, even CD38+ CLL cells express the molecule at such low density that few cells show detectable signals on ligation by antibody. However, when the expression of CD38 was upregulated by exposing the cells to interleukin 2 (IL-2), incubation with anti-CD38 antibodies mediated a signal that could be detected by Ca++ flux. Because CD38 patches on the