doi:10.1038/sj.mt.6300263

Molecular Therapy

What Are the Consequences of the Fourth Case?

In a recent board meeting of the European Society of Cell and Gene Therapy (ESGCT), potential consequences of a new severe adverse event in gene therapy have been discussed, leading to a statement available on the ESGCT Web site (http://www.esgct.org/announcements.cfm). This concerned a report given by Alain Fischer at the 33rd Annual Meeting of the European Group for Blood and Marrow Transplantation (EBMT) that described a fourth case of a malignant cell expansion in the clinical phase 1 trial conducted since 1999 at the Necker Hospital in Paris to treat newborns and young infants suffering from a rare form of X-linked severe combined immunodeficiency disease (SCID-X1).

Because a similar trial conducted in London with an equal number of patients has so far not been affected by such complications, it seems likely that the adverse events accumulating in Paris arose as a result of protocol-specific cofactors. Given the more than 6 years' latency of leukemia development in the last case, the prognosis of the remaining patients enrolled in both trials remains somewhat uncertain. Nevertheless, the current discrepancy between the two trials may no longer be explained by chance but rather by attendant circumstance.

Before considering potential cofactors, it must be stressed that none of these could have been anticipated and prevented by the principal investigators when the trials were designed. In addition, there continues to be more good news than bad news from both SCID-X1 trials. First, every day of persistent autologous immune function in SCID patients enrolled in a phase 1 trial primarily designed to evaluate safety is a success. Second, three of the patients that developed leukemic complications have responded well to treatment and the immune system appears to be able to recover from nonmalignant gene-corrected clones. The gene therapy approach for SCID-X1 patients who lack a matched donor thus compares favorably to other experimental forms of bone marrow transplantation, in terms of efficiency, morbidity, and mortality. Third, the principal investigators of both trials have established great paradigms for highly responsible communication of molecular and clinical adverse events with patient families, regulatory agencies, the scientific community, and the public. Fourth, the immediate reaction of the responsible clinician-scientists and the research community since the first case of leukemia in 2002 has resulted in a wave of studies exploring underlying mechanisms potentially allowing targeted prevention.

One conclusion is certain: insertional mutagenesis is required for malignant complications to occur in gene therapy for SCID-X1. The vectors were inserted next to known cellular proto-oncogenes or other "suspect genes" in all malignant cell clones recovered from the patients, and also in a newly developed "high-risk" mouse model of SCID-X1 gene therapy. Redesigning gene vectors is thus mandatory to improve the outcome of gene therapy in this disease. Compared with the vector technology used in the first trials, novel self-inactivating (SIN) vectors based on either lentivirus, spumavirus, or γ-retrovirus have demonstrated increased efficiency and reduced risk of insertional transformation in recent and continuing platform studies. More controversial than the role of insertional mutagenesis is the potential additive factor of unregulated expression of the therapeutic complementary DNA, encoding the common γ-chain of the interleukin 2 receptor. Although indirect genetic evidence has suggested that this gene is not neutral, clinical evidence and a recent mechanistic study could not support this hypothesis. Further studies addressing this important question are expected in the near future.

Because expression of the therapeutic receptor is probably similar in the trials conducted in London and Paris, other protocol-specific cofactors must contribute to the development of transformed cell clones. Parameters to be considered include the cytokines and other components of the medium used to cultivate the cells during exposure to the gene vector, and the vector envelope. These variables may influence the target cell population, the risk of the retroviral integration close to actively transcribed proto-oncogenes, and post-transduction survival of insertional mutants.

In light of the above, the consequences of the fourth case include not only an even more intense investigation of improved vector design but also an increased awareness of and search for cofactors that may contribute to secondary cancer after proto-oncogene activation by transgene insertion. As long as the nature of the decisive cofactors remains unknown, a reasonable way to revise clinical protocols for gene therapy of SCID-X1 is to maintain the transduction protocol-related cofactors similar to those used in London and change the only factor that is known to cause trouble: the vector backbone. If minor differences of protocol design for one and the same disease already have a major impact on the manifestation of genotoxic side effects, more profound changes such as revised vector design will hopefully result in a substantial improvement of biosafety.

Christopher Baum
Associate Editor