Conclusions and Recommendations
of the
NIH Recombinant DNA Advisory Committee
Gene Transfer Safety Symposium: Current Perspectives on Gene Transfer for X-SCID
March 15, 2005

On December 5, 2002, February 10, 2003, and March 15, 2005, the NIH Recombinant DNA Advisory Committee (RAC) reviewed the clinical and molecular data concerning three adverse events that occurred in a human gene transfer study being conducted in France to correct X-linked SCID. This study involves engraftment of an autologous bone marrow derived, $CD34^+$ hematopoietic stem cell enriched, cell population transduced with a Moloney murine leukemia retrovirus derived replication incompetent vector encoding the common gamma chain (γc) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21. Three children in this study developed T-cell acute lymphoblastic leukemia (T-ALL) almost 3 years after their gene therapy treatment. The leukemias appear to share the common causative mechanism of insertional mutagenesis at or near oncogenes. In the first two participants, the vector inserted at or near the *LMO-2* gene with aberrant production of lmo-2 protein, which contributed to the abnormal growth of the leukemic cells. The integration sites in the cells of the third participant appear to involve *LMO-2,* and three other oncogenes (Science 308: 1735-1736). The unregulated expression of the γc transgene in the vector may also have a cooperative role in the induction of oncogenesis. An analysis of the available data from this and other gene transfer clinical trials for SCID led the NIH RAC to conclude that:

- The majority of children in this X-linked SCID gene transfer study have had major clinical improvement to date.

- Of the nine children in this experimental study who had successful engraftment of their gamma-c (γc) transduced cells, three developed leukemia approximately 3 years after treatment and have required chemotherapy; one participant subsequently died. The overall frequency of this adverse event in this trial cannot be determined at this time.

- The gene transfer was a cause of the leukemias.

- The occurrence of leukemia in this protocol is not a random event and constitutes a serious inherent risk in this study.

- Some subjects in gene transfer studies for non-X-linked SCID experienced mild to moderate clinical improvement.

These findings led the NIH RAC to make the following recommendations, which will be reviewed and potentially revised as new data become available.

- Retroviral gene transfer studies for X-linked SCID should be reviewed, on a case-by-case basis, and limited, pending further data, to patients who have failed identical or haploidentical stem-cell transplantation or for whom no suitable stem cell donor can be identified. Case-by-case review would include appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.

- There are not sufficient data or reports of adverse events directly attributable to the use of retroviral vectors at this time to warrant cessation of other retroviral human gene transfer studies, including studies for non-X-linked SCID. Such studies may be justified contingent upon appropriate risk:benefit analysis accompanied by implementation of appropriate informed consent and monitoring plans.