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TO: Principal Investigators for Human Gene Transfer Trials Employing Retroviral Vectors

FROM: Amy P. Patterson, M.D.
Director
NIH Office of Biotechnology Activities

SUBJECT: Outcome of the RAC Meeting and Updated Advice to Investigators Regarding Adverse Events in the X-SCID Gene Transfer Trial

The purpose of this memorandum is to advise you of the outcome of an ad hoc meeting of the NIH Recombinant DNA Advisory Committee (RAC) convened February 10, 2003 to review newly available data on a second serious adverse event on a gene transfer clinical trial for X-linked SCID. One product of that meeting was a series of recommendations for investigators in this field. These recommendations have been adopted as NIH policy and supersede those contained in a January 14 memorandum that our office conveyed to you and your Institutional Biosafety Committee.

To inform the RAC's deliberations at the February 10 meeting, the investigators involved in the X-linked SCID study provided updates on the clinical condition of the subject and discussed new data on the molecular pathogenesis of the event. In addition, the RAC heard from experts on pediatric T-ALL, retroviruses and insertional mutagenesis, oncogenes in leukemogenesis, and defective cytokine signaling in X-linked SCID. The RAC was also briefed by officials from the FDA about the agency's regulatory action to place all retroviral studies involving hematopoietic stem cells on clinical hold. Public comments were presented and several gene transfer investigators expressed their perspectives on whether the risks of insertional mutagenesis were elevated in other retroviral studies. The RAC reviewed the conclusions it had reached in December about the first event and, after further discussion of the scientific findings about both events, came to revised conclusions about the risks of insertional mutagenesis in X-SCID studies and other retroviral studies. These conclusions are presented in the attached statement of the RAC, which was accepted by the Director, NIH on February 28, 2003.

We urge you to take these new recommendations into account, particularly as you develop and implement enrollment criteria for X-linked SCID studies using retroviral vectors, and as you obtain appropriate informed consent and conduct monitoring in other studies using retroviral vectors. Please share this document with all colleagues whom you believe would benefit from this information. Investigators should continue to comply with any FDA regulatory actions, including restrictions or clinical holds placed on their individual trials.

**Conclusions and Recommendations**
**of the**
**NIH Recombinant DNA Advisory Committee**
**Regarding Two Serious Adverse Events in a Human Gene Transfer Research Study of X-linked SCID**
**February 10, 2003**
**(Approved by the NIH Director February 28, 2003)**

On December 5, 2002 and February 10, 2003, the NIH Recombinant DNA Advisory Committee (RAC) reviewed the clinical and molecular data concerning two 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 ($\gamma c$) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21. Two children in this study developed T-cell acute lymphoblastic leukemia (T-ALL) almost 3 years after their gene therapy treatment. The leukemias in both children appear to share the common causative mechanism of insertional mutagenesis at or near the *LMO-2* gene with aberrant production of lmo-2 protein, which contributed to the abnormal growth of these leukemic cells. 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 ($\gamma c$) transduced cells, two developed leukemia approximately 3 years after treatment and have required chemotherapy; the overall frequency of this adverse event in this trial cannot be determined at this time.

- The gene transfer was a cause of both 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.

- Pending further data or extenuating circumstances, reviewed on a case-by-case basis, retroviral gene transfer studies for X-linked SCID should be limited 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.