

New Developments in X-SCID Gene Transfer

March 14, 2007



X-Linked Severe Combine Immune Deficiency (X-SCID)

- X-linked inherited disease in which there are mutations in the gene encoding the common gamma chain (γ_c), a cell surface receptor protein required for development of lymphocytes
- Patients with X-SCID do not develop normal immune systems and untreated many will die within a year from infection
- Bone marrow transplant has been the standard of care but does not always result in complete immune reconstitution and is not without risks
- Gene transfer has successfully led to immune reconstitution in patients with X-SCID
- This success has been tempered by several cases of leukemia that occurred in a French Trial for X-SCID

Previous RAC Gene Transfer Safety Symposia: Current Perspectives on Gene Transfer for X-SCID

NIH RAC has reviewed the clinical and molecular data concerning the three previous serious adverse events that occurred in a human gene transfer study conducted in France to correct X-linked SCID.

- o **December 5, 2002**
- o **February 10, 2003**
- o **March 15, 2005**

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- December 9-11, 2008, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD

2009

- March 3-5, 2009, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD
- June 16-18, 2009, RAC -- NIH Main Campus, Bldg. 31, Floor 6C, Rm. 6, Bethesda, MD
- September 15-17, 2009, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD
- December 1-3, 2009, RAC -- NIH Main Campus, Natcher, Rm. E1&E2, Bethesda, MD

***Note** : NIH/OBA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for review by the committee members.

Reports and Transcripts of the Safety Symposia

- Fifth National NIH Safety Symposium: [Current Perspectives on Gene Transfer for X-SCID](#), March 15, 2005 **NEW**
 - [Webcast](#)
- Fourth National NIH Safety Symposium: [Safety Considerations in Recombinant DNA Research with Pathogenic Viruses](#) , September 21-22, 2004
 - [Webcast](#)
- Third National NIH Gene Transfer Safety Symposium: Safety Considerations in the Use of AAV Vectors in Gene Transfer Clinical Trials, March 7, 2001
 - [Transcript](#)
- Second National NIH Gene Transfer Clinical Research Safety Symposium: Safety Considerations in Cardiovascular Gene Transfer Clinical Research, December 14, 2000
 - [Transcript](#)
- First National NIH Gene Transfer Safety Symposium: Internally Deleted, Helper-Dependent Adenoviral Vectors, March 8, 2000
 - [Transcript](#)
 - [Summary](#)

On December 5, 2002, February 10, 2003, and March 15, 2005, the RAC reviewed the clinical and molecular data concerning three adverse events that occurred in a French study involving engraftment of a CD34⁺ hematopoietic stem cell enriched, cell population transduced with a retroviral vector encoding the common gamma chain (γ_c) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21. The leukemias appear to share the common causative mechanism of insertional mutagenesis at or near oncogenes. The major goal of the symposia was to increase awareness in the scientific community and the public by providing comprehensive updates of:

- the current US and international trials using gene transfer for SCID, including recently emerging safety data
- retrovirus integration and insertional mutagenesis research
- the use of bone marrow/stem cell transplantation as treatment for SCID

The RAC developed recommendations for the use of gene transfer for X-SCID and other indications using retroviral vectors.

March 15, 2005

[Agenda](#)

[Webcast and Slides](#)

[Summary](#)

[References](#)

[Conclusions and Recommendations](#) of the RAC Gene Transfer Safety Symposium: Current Perspectives on Gene Transfer for X-SCID (March 15, 2005)

February 10, 2003

[Webcast](#)

[Conclusions and Recommendations](#) of the RAC Regarding Adverse Events in a Gene Transfer Trial Studying X-linked SCID (March 20, 2003)

December 5, 2002

[Agenda, Slides & Webcast](#)

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Goals of the Safety Symposia

- Promote scientific understanding and public awareness of the latest research findings regarding insertional mutagenesis and its etiology
- Provide comprehensive updates on:
 - Current US and international trials studying gene transfer as a possible treatment for SCID
 - Latest research into retrovirus integration and insertional mutagenesis
 - Use of bone marrow and stem cell transplantation as an alternative treatment for SCID

French Study of Human Gene Transfer for X-SCID

- Study initiated in 1999 conducted at Necker-Enfant Malades Hospital, Paris, by Alain Fischer and Marina Cavazzana-Calvo
- Twelve research participants enrolled
- Nine participants experienced immune reconstitutions with significant clinical improvement
- Study involved engraftment of autologous bone marrow derived CD34+ hematopoietic stem cells that were transduced with a Moloney murine leukemia retrovirus derived replication incompetent vector encoding the common gamma chain (γ c) transmembrane protein subunit shared by receptors for Interleukins 2, 4, 7, 9, 15 and 21.

French Study of Human Gene Transfer for X-SCID

- Three children developed T-cell acute lymphoblastic leukemia (T-ALL) almost 3 years after gene transfer.
- 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 involve *LMO-2*, and three other oncogenes.
- The unregulated expression of the γ c transgene in the vector may also have a cooperative role in the induction of oncogenesis.

Overview of Research Participants

Patient	Age at Treatment (month)	Cell dose $\gamma\text{c}+\text{CD34}+$ /kg	Occurrence of lymphoproliferation	Status
P4	1	18×10^6	30 months (Aug. 2002)	Died Oct. 2005 (5 years post gene transfer)
P5	3	20×10^6	34 months (Dec. 2002)	Alive
P10	9	11×10^6	33 months (Jan. 2005)	Alive

2005 Conclusions of the RAC

- 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 γ c 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.

2005 Conclusions of the RAC

- 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.

2005 RAC Recommendations

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.

2005 RAC Recommendations

- 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.

New case of leukemia

- Diagnosed with acute T cell proliferation 61 months post-treatment
- Subject dosed at age 11 months
- Number of cells received - 4×10^6
- Data on site of insertion of vector pending
- Subject currently undergoing treatment

Goals of Panel Discussion

- Initial public discussion of this recent case
- Review the status of X-SCID trial in US and related ADA-SCID trials