A new phase for human gene transfer studies - a well-defined risk inherent in techniques that produce real clinical benefit

A leukemia-like SAE in an X-SCID study

- **Retrovirus-mediated transfer into CD34+ cells**
- **Successful and prolonged immune reconstitution of 11 children with X-SCID - clinical correction**
- **Leukemia-like disease in one patient - lymphocytosis, splenomegaly; good response to chemotherapy**
- **Detailed understanding of mechanism - integration and retroviral enhancer activation of proto-oncogene LMO2**

Summary

- Sustained correction of the T and B cell immunodeficiency
- Efficient protection against infections
- Evidence for the transduction of pluripotent hematopoietic progenitors likely with self renewal capacity
- Oligoclonal transduction leads to a fully polyclonal T lymphocyte pool

SCID-XI gene therapy trial

Follow-up (October 1st, 2002)

Patient	F.U. (year)	γc expression	T Immunity	B Immunity	Clinical status
1	3.6	+++	++	++	A.W.
2	3.5	+++	++	++	A.W.
3	(.7)	+	-	-	A. (BMT)
→ 4	3.0	+++	++	++	A. Lymphoprol. syndrome
5	2.8	+++	++	++	A.W.
6	1.4	+++	++	+	A.W.
7	1.3	+++	++	++	A.W.
8	.9	+++	++	+	A.W.
9	.7	+++	++	+	A.W.
10	.5	++	++	+	A.W.
11	1.3	+	-	-	A.

Regulatory responses

- **France - clinical hold until event is better understood; hold still in effect**
- **U.S. - SCID studies on clinical hold; Biological Response Modifiers Advisory Committee (BRMAC) recommends resumption, benefits >> risks; FDA letter to investigators indicating study still on hold, but requesting revised consent form, modifcation of protocol to include description of monitoring for clonal expansion, integration events; case-by-case decision to proceed**

Regulatory responses (cont'd)

- **Italy - no clinical hold, but request for description of monitoring and informed consent changes**
- **England - no clinical hold, benefits >> risks.**
- **Japan - no active SCID studies. 2 planned studies on hold**
- **Germany - all clinical retrovirus gene transfer studies on hold, no defined end point**

Questions for RAC 0CT 29 planning meeting

- **What happened in X-SCID SAE?**
- **Was adverse event expected or predictable? Was it preventable with existing technology?**
- **Would new technology prevent similar events (prevent insertional mutagenesis, more effective early detection)?**
- **Changes to current policy (NIH guidelines, etc.)?**
- **Changes to informed consent process?**

Issues identified at October 29 RAC planning meeting

- **Technical - choice of vectors and regulatory elements, mechanisms for site-specific integration, use of non-integrating vectors, etc.**
- **Monitoring - what, how frequently, how long, ?tissue archiving**
- **?Modification of informed consent process**

Molecular and technical issues?

- **Screen transduced cells for dangerous integration events before grafting? Graft only innocuous transduced cells?**
- **Systematic post-grafting cellular and molecular monitoring to detect adverse events?**
- **Different design of integrating vectors to reduce chances of insertional mutagenesis? SIN vectors, insulator elements, suicide or ablative mechanisms?**
- **More emphasis on non-integrating vectors?**

Possible modifications