Current Perspectives on Gene Transfer for X-SCID

Recombinant DNA Advisory Committee Safety Symposium March 15, 2005

Discussion Questions

Current SCID Gene Transfer Experience

1. **What data is available regarding the research participant who developed the third leukemia?**
   - **Is this participant the third participant described at the February 2003 RAC meeting as having two integrations in the LMO-s gene?**
     - **Was the LMO-2 integration finding reproducible?**
   - **Clonal Expansion:**
     - **Cell type**
     - **Method for early detection of clonality**
     - **Time course of expansion**
     - **Time from vector administration to malignant transformation in comparison to events in two previous participants with leukemia**

Current SCID Gene Transfer Experience

- Vector Integration
  - Sites of integration
  - Detected expression from cellular gene(s) due to integration
  - Function of cellular gene(s) (e.g., oncogene)
  - Nature of cellular gene activation
  - Other insertions observed in participant cells prior to clonal expansion
  - Any further information about the role of the γc transgene
- Vector Dose
  - Number of transduced cells administered and % transduction efficiency
  - Vector copy number

Current SCID Gene Transfer Experience

2. How does the data from the third participant compare to that from the two previous participants who developed leukemia?
3. From the lessons learned after the first two leukemia cases, it was assumed that SAEs could be minimized by limiting enrollment to research participants older than 3 months of age, and lowering the number of transduced CD34+ cells administered to participants. Does the development of a third case of leukemia call for change in these safety precautions?
4. What data is available from the other current clinical or preclinical studies?
   - Maintenance of polyclonality
   - Range of integration sites

Retrovirus Integration and Insertional Mutatgenesis

1. **What factors may contribute to the potential for insertional mutagenesis and what modifications may lower that risk?**
   - **Dosage (e.g., vector insertions/cell, percentage of transduced cells, amount of transduced cells administered, etc.)**
   - **Vector design (e.g., SIN vectors, *cis* elements such as insulators, suicide vectors, lentiviral vectors, stable episomal vectors, projected availability of targeted integrating vectors, etc.)**
   - **Target cells (e.g., stem cells, transcriptional profile, etc.)**
   - **Transgene expression (e.g., confers selective advantage, nonphysiologic expression, etc.)**
   - **Host Factors (e.g., participant age, disease indication, etc.)**

Retrovirus Integration and Insertional Mutatgenesis

2. **Should modifications be considered to the current safety monitoring schema for research participants?**
   - **What are the current methodologies?**
   - **Are there any methods for prospective rather than retrospective monitoring?**
   - **Should the timing of sample analysis be altered?**
3. **Is it possible to intervene therapeutically prior to the progression to leukemia and if so, what criteria might indicate that participants are candidates for such intervention?**

Bone Marrow Transplantation for SCID

1. **What have been the outcomes for BMT/SCT therapy in SCID and similar or related disorders? How have the outcomes changed over time?**

2. **What have been the mortality and morbidity of other major adverse events of HLA identical, haploidentical, matched unrelated donor, and cord blood SCT?**

   - **What is the incidence and severity of graft vs. host disease following haploidentical BMT or SCT?**
   - **How do pre-existing infections affect outcomes?**

3. **What are the major techniques that have been employed to improve outcomes of BMT/SCT, and what has been their comparative effectiveness?**

Bone Marrow Transplantation for SCID

4. What have been the results of BMT/SCT with respect to immune reconstitution?
5. Under what circumstances, if any, may pre-transplant chemotherapy or “conditioning” be beneficial?
6. What are the respective risks and benefits of BMT/SCT and gene transfer for immunodeficiency disorders, particularly SCID?

Questions for Consideration

1. **Should the assessment of the balance of potential benefits and risks in X-SCID protocols be modified in light of new information and data? If so, how?**

2. **In 2003, the NIH RAC recommended that:**

   "…retroviral gene transfer … 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."

   - **Does remain a prudent and medically defensible recommendation, or are changes warranted?**
   - **How would the recommendation change if additional participants develop leukemia?**

Questions for Consideration

3. Should the assessment of the balance of potential benefits and risks in other SCID protocols e.g., ADA-SCID protocols, be modified in light of our new understanding? If so, how?

4. Should the assessment of the balance of potential benefits and risks in protocols for other disease indications using retroviral vectors, be modified in light of our new understanding? If so, how?

   - Should the target population be considered in the assessment (e.g., protocols involving conditioning regimens that result in an immuno-incompetent state)?

4. What new information needs to be communicated to participants in ongoing protocols, prospective participants in new protocols, and participants from retroviral vector trials closed to further enrollment or past the protocol defined follow-up period?

Questions for Consideration

6. **Should Appendix M of the *NIH Guidelines* be modified to include additional questions about preclinical research?**
   - **Have studies been conducted to characterize the minimum number of integrants, transduced cells, and transduction efficiency required for the intended effect?**
   - **Have reversion or ablation methods to remove transduced cells or reverse their effect been considered?**
   - **Is there a plan to archive and analyze samples during the study and if so, what assay will be used?**
   - **Have studies been conducted to determine the tumorigenic potential of the transgene?**

Questions for Consideration

7. How might the risk of leukemia be reduced in gene transfer studies using retroviral vectors? This is an open research challenge in the future of gene transfer research.

8. What is the ethical status of a research intervention that provides effective therapy but that carries such a severe risk? Should the intervention be considered therapy if some or all of the participants develop serious adverse events but after years of "normalized life?"