NIH/OBA
Gene Transfer Safety Symposium
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US **Regulatory Update**

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Regulatory Update

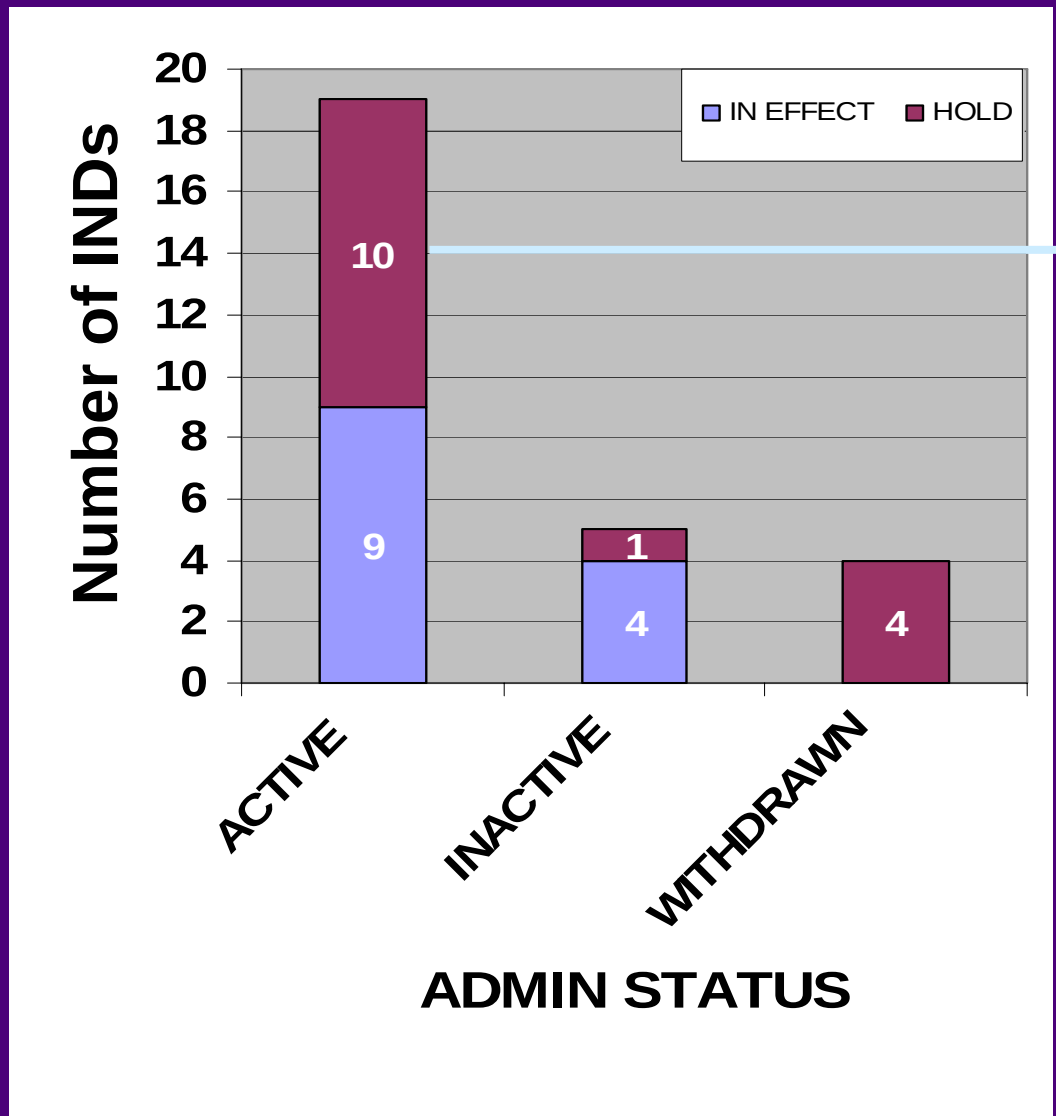
- Review of FDA Actions in **January 2003**
  - Administrative and IND status of 28 INDs on hold, January, 2003
- FDA Actions in **January, 2005**
- March 4, 2005, Meeting of the Cellular, Tissues, and Gene Therapies Advisory Committee
  - Topics
  - Speakers
  - Questions
  - Recommendations

January 13, 2003 Letter to Retroviral Vector Sponsors

Category	Revise Informed Consent	Monitor Clonality	Clinical Hold
SCID, All Active Hematopoietic Stem Cells	Yes	Yes	Yes
Inactive HSC	Yes	Yes	Require to resume trial
All other retroviral vector clinical trials	Yes	Yes	No, Recommend

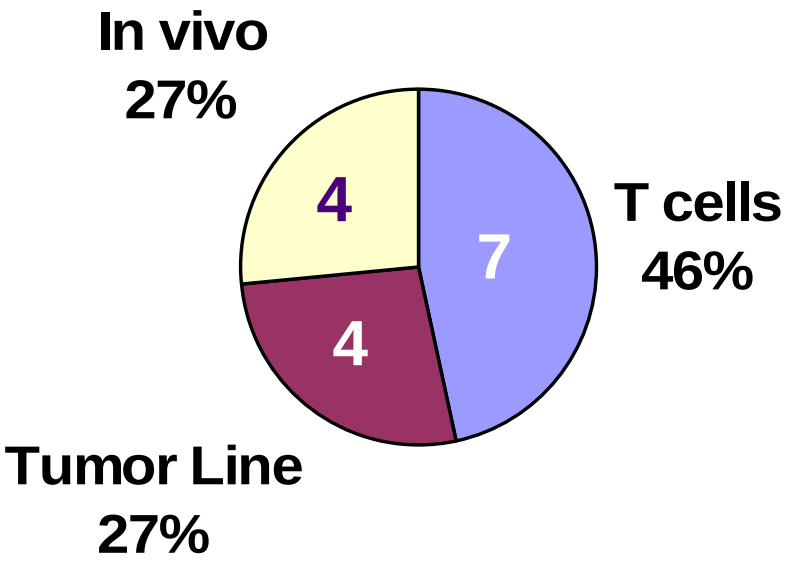
All sponsors were asked to provide risk/benefit analy
CBER evaluated each response.

Administrative and IND Status of 28 INDs Placed on Hold January, 2003



3 SCID (new hold)
6 no response
1 continue hold

15 INDs Received Since January, 2003 Using Retroviral Vector



FDA Response to Recent Developments January 2005

- Three INDs placed on Clinical Hold
  - X-SCID (2); ADA-SCID (1)
  - Revise Informed Consent
  - Notify IRB
- All sponsors that use retroviral vector:
  - Informed of new events
- Notified IRBs
- Convened Meeting of the Cellular, Tissues, and Gene Therapies Advisory Committee (CTGTAC), March 4, 2005

CTGTAC
March 4, 2005

Update: Retrovirus Vector-Mediated Insertional Tumorigenesis

Transcripts, Briefing Materials, Slides:
www.fda.gov/oc/advisory/acbiologics.html

Topics Presented by FDA

- Review, Retroviral Insertional Mutagenesis
- Review and Brief Update: X-SCID Gene Therapy Clinical Trial in France
  - FDA Responses (then and now)
- BRMAC, February, 2003
  - Recommendations and Actions
- Detailed Update: X-SCID Gene Therapy Clinical Trial in France, with permission:
  - Prof. Jean-Hughes Trouvin, Afssaps
  - Drs. Alain Fischer and Marina Cavazzano-Calvo, Necker-Enfants Malades Hospital, Paris, France

CTGTAC Meeting, Speakers

Relevant Data from Animal Models:

- Dr. Cynthia Dunbar
- Dr. Utpal Dave
- Dr. Christopher Baum

Update from Human Experience, ADA-SCID

- Dr. Donald Kohn

Questions for the Committee
Recommendations from the Committee

CTGTAC March 4, 2005

Question 1

CFR 312.42 defines the bases for FDA to place a study on clinical hold. CFR 312.42(b)(iv) ("insufficient information") was cited previously as a basis for placing INDs on clinical hold in response to the development of leukemia in subjects of X-SCID clinical trials. However, we note CFR 312.42(b)(i) that states FDA may place a study on hold if it finds that "Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury."

Question 1, continued

With this requirement in mind, please discuss the current incidence of leukemia (3/12) and death of one subject from leukemia reported in the clinical trial in France relative to the potential benefit of retroviral vector-mediated gene transfer in X-SCID. Consider in your discussion:

a. **The risk/benefit issues for gene therapy vs. haploidentical bone marrow transplantation.**
b. **The incidence of leukemia associated with retroviral vector administration that would make clinical trials of this therapy unacceptable in X-SCID. Would this advice differ if a subject in another clinical trial develops leukemia? Would another subject death due to leukemia influence your recommendations.**

Question 1, Recommendation

- Until data accumulate to change the risk-benefit assessment in a more favorable manner, retroviral vector-mediated gene transfer should only be used in children with X-SCID under the following conditions:
  - Failed previous hematopoietic stem cell/bone marrow transplantation
  - Have no reasonable alternative therapies
    - e.g., patients precluded from transplantation because of unacceptably high risk from previous infections.

Question 2

Please comment on what changes, if any, would reduce the risk to subjects in clinical trials using retroviral vector-mediated gene transfer in X-SCID.

Please consider the following:

a. Limit the dose based on total vector copy number in the transduced cells.
b. Limit the dose based on total number of transduced cells.
c. Alteration of retroviral vector design.

Question 2, Recommendation

- Advised against use of vector copy number or number of transduced cells to address the risks in gene therapy for X-SCID.
- Strongly encouraged investigating alternative approaches, including new retroviral vector products to lessen risk.
  - Suicide vector systems were suggested as most feasible.
  - Adequate testing in relevant animal models of any novel approach.

Question 3

Please discuss the impact, if any, of the SAEs in X-SCID, combined with the development of myeloid sarcoma in the single monkey administered hematopoietic stem cells after ex vivo transduction with a retroviral vector, on the use of retroviral vectors in other clinical indications.

Please comment specifically on the risk/benefit considerations:

a. In ADA-SCID relative to X-SCID.

b. In other clinical indications.

Question 3a (ADA-SCID) Recommendation

Allow clinical trials to proceed.

- Risks are still present.
  - Investigators and patients should be informed with strong and clear communication of risks.
- If a retroviral vector-related malignancy were to develop in any ADA-SCID clinical trial, the FDA should reconvene the CTGTAC to reassess the risks.

Question 3b (Other, Non-SCID) Recommendation

Allow clinical trials to proceed

- Risks are still present.
  - Investigators and patients should be informed with strong and clear communication of risks.

Question 4

Given the increased efficiency of lentiviral vectors to transduce cells, often resulting in multiple vector copies per cell (up to ten have been reported), please discuss whether restrictions on vector copy number per cell are warranted for the use of lentiviral vectors in ex vivo transduction clinical protocols, and, if so, what limit would you advise?

Question 4, Recommendation

- The committee did not recommend a specific number but acknowledged it's an important issue.
- FDA should assess each IND based on available data.
- Animal models should be used to assess the relative risk of leukemia induction with increased copy number.

Challenge to Gene Therapy Community