

RAC Meeting, March 14, 2007

**Regulatory Perspective:
Use of Retroviral Vectors for
Treatment of X-SCID**

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Acknowledged Risks Associated with Use of Retroviral Vectors

- Risk of replication competent retrovirus (RCR)
 - Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors, 11/28/06
- Risk of insertional mutagenesis from vector
 - Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events, 11/28/06

More than theoretical risks

Current FDA Perspective: X-SCID Clinical Trials

- Gammaretroviral vectors can be used in clinical trials to treat 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 existing infections.

Based on Advice Received from CTGTAC, March 4, 2005

Other Clinical Indications?

- 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 other clinical trial, the FDA should reconvene the CTGTAC to reassess the risks.

Based on Advice Received from CTGTAC, March 4, 2005

Guidance for Industry:
Gene Therapy Clinical Trials –
Observing Subjects for Delayed
Adverse Events

Recommendations Relevant
to Risks of Retroviral Vector-
Mediated Malignancy

Use of Integrating Vectors: Special Considerations May Apply

- *When*
 - Used to Transduce Target Cells with High Replicative Capacity and Long Survival
- *If*
 - Surrogate is accessible for assay
- Test for vector sequences every 6 months first 5 years; yearly next ten years; or until no vector is detected.
- Recommended Points to Include in Informed Consent: accurately reflect risk of cancer

Integrating Vectors, Continued

- When at least 1% of surrogate cells have detectable vector (by PCR, or other sensitive method)
 - assess the pattern of vector integration sites using a method based upon data with appropriate positive and negative controls, and supporting studies to assess assay sensitivity, specificity, and reproducibility.

Integrating Vectors, Continued

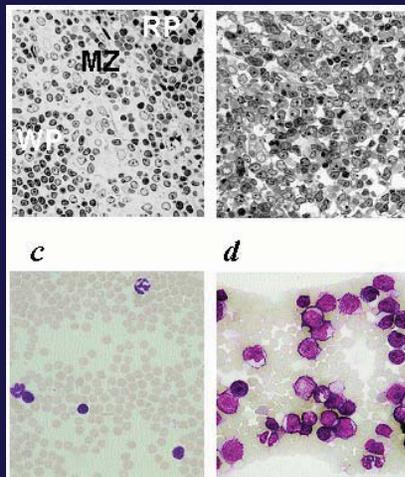
- While oligo or monoclonality does not *a priori* result in malignancy, we recognize that these observations increase the risk, and therefore recommend additional monitoring when
 - **Persistent monoclonality**
 - **Clonal expansion**
 - **Evidence of vector integration near or within locus known to have oncogenic activity**

Other FDA Initiatives: Addressing Risks of Retroviral Vector- Mediated Malignancy

- Gene Therapy Database
 - All Serious Adverse Events in gene therapy clinical trials are entered into database
- Large-scale toxicity study
 - National Toxicology Program

National Toxicology Program: Safety assessment of retroviral vectors

- Determine the sensitivity of a preclinical model for detecting retroviral vector-mediated insertional tumorigenesis



Myeloid Leukemia



Evi-1

Control

Li, et al, Science, 2002

- Impact of vector dose and enhancer deletion on tumor frequency

Summary

- Current report from France does not change FDA perspective on risks associated with retroviral vectors
- Two guidance documents provide recommendations to sponsors to address risks to subjects participating in retroviral vector-mediated clinical trials
- Gene Therapy Database
- NTP study: assessment of preclinical model to study risks associated with retroviral vectors

Guidance for Industry: Gene Therapy Clinical Trials
- Observing Subjects for Delayed Adverse Events

Posted: 11/28/2006

<http://www.fda.gov/cber/gdlns/gtclin.htm>

Guidance for Industry: Supplemental Guidance on
Testing for Replication Competent Retrovirus in
Retroviral Vector Based Gene Therapy Products
and During Follow-up of Patients in Clinical Trials
Using Retroviral Vectors

Posted: 11/28/2006

<http://www.fda.gov/cber/gdlns/retrogt1000.htm>

For Additional FDA Information and Guidance on Gene Therapy

<http://www.fda.gov/cber/gene.htm>

<http://www.fda.gov/cber/genadmin/octgtprocess.htm>