

Potential Symposium Regarding Insertional Mutagenesis

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Background

The recent safety modifications to retro- and lentiviral vectors (e.g., SIN, insulators) were designed to decrease the frequency of enhancer mediated activation of cellular genes. However, the lentiviral vector insertion in the French β -thalassemia trial disregulated gene expression by an alternate mechanism (i.e., aberrant splicing resulting in expression of a truncated protein missing mRNA binding sequences involved in down-regulation).

RAC Safety Symposium?

- **Advances in the understanding of retroviral/lentiviral vectors**
- **New protocols using modified lenti and retroviral vectors in hematopoietic cells**
 - **Would the RAC review of such protocols be enhanced by a discussion of the current data through a safety symposium?**

Possible Symposium Questions

- While there have been numerous studies of the integration patterns of retroviruses and lentiviruses, what data exists regarding clonal expansion, and/or oncogenesis with lentiviral vectors?
- How useful are the available *in vitro* and animal preclinical models in predicting events in human gene transfer?

Possible Symposium Questions

- **What alternative mechanisms of insertional oncogenesis should be considered?**
- **How might the different integration patterns for retro vs. lentiviral vectors affect the risks of insertional mutagenesis by different mechanisms (e.g., is there higher risk of gene disruption/truncation by lenti inserting more frequently into transcription units)?**
- **What types of preclinical models should be used to detect such events?**

Possible Symposium Questions

- **How could retro/lentiviral vectors be designed with additional safety modifications to address the alternative mechanisms of insertional mutagenesis?**
- **What can be learned from the retroviral vectors designed to induce insertional mutagenesis to screen for genes involved in cancer (i.e., how not to design a gene transfer vector)?**

Question for RAC Discussion

- Are there sufficient issues and new data to warrant the organization of a safety symposium regarding insertional mutagenesis by retro- or lentiviral vectors for human gene transfer ?
- If so, what topics should be proposed for discussion?