Preclinical Safety Evaluation of Lentivirus Vectors: FDA Regulatory Expectations

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Goals of Today's Presentation

- familiarize audience with FDA/CBER's role in development of gene therapeutic agents for entry into clinical trials
- familiarize audience with preclinical guidance for demonstrating safety of gene therapeutic agents
- discuss safety issues in which lentiviral gene therapeutic agents may differ from other viral-based, gene therapies

FDA's Objectives in Development of Gene Therapies

- assure safety and rights of subjects in all phases of drug development
- assure that scientific quality of phase 2, 3 investigations will support licensure
- safeguard public health while promoting development of novel products

Phases of Drug Development

- **Pre-entry**
  - discovery, evaluation, refinement
- **Phase 1**
  - safety, side effects, bioactivity
- **Phase 2**
  - safety, activity, hypothesis generation
- **Phase 3**
  - safety, efficacy, hypothesis testing

Initial Steps in the Development of a New Gene Therapy Agent

- **Product characterization**
  - manufacturing and quality control issues
- **Biologic activity**
  - *in vitro* and/or *in vivo* “proof of concept”
- **Safety**
  - toxicology testing in animals
    - safety
    - biodistribution

Goals of Preclinical Safety Evaluation

For All Therapeutic Products:

- Recommend initial safe starting dose and safe dose-escalation scheme in humans
- Identify potential target organ(s) of toxicity
- Identify appropriate parameters for clinical monitoring
- Identify "at risk" patient populations (inclusion/exclusion)

Relevant Concerns in the Safety of Viral Vectors for Gene Therapy

- level and persistence of gene expression
- aberrant localization or trafficking
- inappropriate expression of gene product
- germ-line transfer of viral/therapeutic gene(s)
- generation of replication-competent virus
- insertional mutagenesis

General Concepts in the Design of Safety Evaluation of Gene Therapeutic Agents

- demonstration of biologic/pharmacologic activity
  - efficiency/feasibility of gene transfer
  - done as “proof of concept” in animal model
- animal species/model selection for safety
  - most appropriate species
  - disease/alternative models
  - number/gender/age of animals
- route of administration
- dose selection

Some limitations of preclinical studies for gene therapies

- **Reversibility of the toxicity may be missed in *in vitro* models**
- **Adverse events in animals:**
  - may not be relevant to clinical trials
  - may be acceptable in seriously ill populations
- **Long-term toxicities or events:**
  - may not be determined in preclinical animal studies
  - may be missed in phase 1 trials
  - may require long-term follow-up

Questions to be Answered by Preclinical Studies

1. What is the relationship of the dose to the biologic activity?
2. What is the relationship of the dose to the toxicity?
3. Does the route and/or schedule affect activity/toxicity?
4. What risks can be identified for the clinical trial?

The requirements for demonstration of product characterization, biologic activity, and safety of lentiviral vectors for gene therapy will be no different than for those of other, virus-based vector systems

HOWEVER, the level of concern for specific issues, as well as the approach taken to demonstrate safety will be different, based on the relevant biology of the product.

Potential Concerns in the Safety of Lentiviral Vectors for Gene Therapy

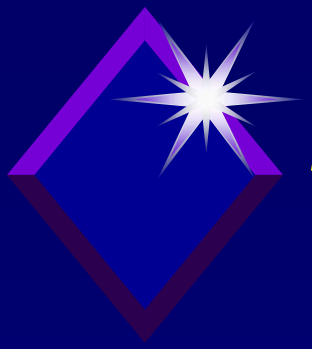
- generation of replication-competent virus
  - ability to recombine/pseudotype with retroviruses
- aberrant localization or trafficking
  - inappropriate expression of gene product
  - latent infection of non-target cells
  - germ-line transfer of viral/therapeutic gene(s)
- level and persistence of gene expression
- insertional mutagenesis

Expectations for Demonstration of Safety of Lentiviral Vectors

- lentiviruses are new molecular entities
  - pharmacologic profiles, dose/response relationship, proof of concept
  - full toxicology profiles, vector distribution
  - demonstration of recombination/rescue potential by other human, pathogenic viruses
  - focus is on SAFETY; rationale is secondary, but still important

Approaches to Preclinical Safety Studies for Gene Therapies

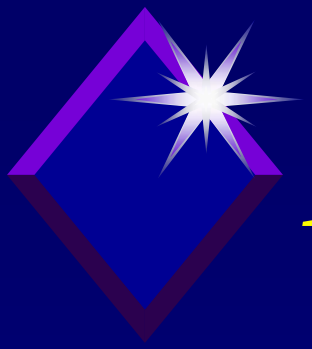
- creative, problem-solving
- data-driven
- no one “right” way to conduct studies
- should be based on best available science, technology to date
- careful design and judicious use of animals
  - should allow for early initiation of clinical studies
  - should allow for uninterrupted clinical development



Thought for the Day:

"....It must be remembered that there is nothing more difficult to plan, more doubtful of success, nor more dangerous to manage, than the creation of a new system. For the initiator has the enmity of all who would profit by the preservation of the old institutions and merely lukewarm defenders in those who would gain by the new one....."

MACHIAVELLI - THE PRINCE



Further questions? Contact us!

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