Preclinical Considerations for Imaging Technology for Cell Therapy Products

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CIRM Webinar
May 26, 2011
Overview

- Regulatory Review Principles
- CBER/OCTGT-Regulated Products
- Assessing *in vivo* Cell Fate
- Considerations for Imaging Technologies
- Working with FDA/CBER/OCTGT
“FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety…”

IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission]
What Regulations Govern Preclinical Testing?

Pharmacologic & Toxicologic Studies

“...adequate information about the pharmacological & toxicological studies...on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations.”

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]
Expectations from Preclinical Data

• To establish a rationale for the first-in-human clinical trial
  – For cell and gene therapy products the trial is conducted in the disease population, not in healthy volunteers

• To make recommendations to clinical trial design
  – Initial safe starting dose, dose escalation scheme, dosing schedule, target organ/tissue toxicity, eligibility criteria, clinical monitoring

• To meet regulatory requirements
  – 21 CFR 312.23 (a)(8)
  – 21 CFR 58 (GLP compliance)
Examples of OCTGT-Regulated Cell Therapy Products

- Stem/Progenitor cell-derived
  - Adult (mesenchymal, cardiac, neuronal, adipose)
  - Perinatal (placental, umbilical cord)
  - Fetal (neuronal, amniotic fluid)
  - Pluripotent stem cell-derived (embryonic, iPS cells)
- Functionally mature/differentiated (chondrocytes, hepatocytes, islet cells)

- Combination Products (e.g. tissue-engineered product)
  - Device* + Cells
  *In conjunction with CDRH
Inherent biological properties

- Self-renewal
- Differentiation potential
- Heterogeneous mixture (often unclear mechanism of action)

Safety concerns

- Inappropriate differentiation (e.g., ectopic tissue formation)
- Inappropriate growth (e.g., tumorigenicity)
- Migration to non-target site & persistence
- Interactions between device and biologic (combination product),
- Immunogenicity
- Risk of delivery procedure
Assessing *in vivo* Cell Fate

- Post-administration *in vivo*:
  - Where do they go (*migration*)?
  - How long do they persist (*survival*)?
  - What happens to them (*phenotype*)?

*Cell “FATE” defined here as migration, survival and phenotype*
Migration

Where do the cells go?

– Route of administration
  • Systemic versus localized biodistribution
  • Proximity to sensitive tissues (e.g., neurological or reproductive toxicity)
  • Anatomic considerations (e.g., proliferation in enclosed spaces)

– Donor cell migration
  • Targeted vs. non-targeted tissue
  • Potential for ectopic tissue formation
How long do the cells persist?

- Translation for dose level and dosing regimen
- Establish appropriate long-term monitoring
  - Tumorigenicity
  - Other toxicities
Phenotype

What happens to the cells?

– Differentiation
– De-differentiation
– Transdifferentiation
– Integration (anatomical ± functional)
– Tumorigenicity & ectopic tissue formation
## Current Methodologies for Cell Distribution

- Immunohistochemistry (IHC) and PCR
  - Terminal procedure
  - Snapshot in time

<table>
<thead>
<tr>
<th>Methods</th>
<th>Data Obtained</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>Survival &amp; Migration</td>
<td>qPCR • IHC</td>
<td>• Cell migration • Proliferation</td>
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<tr>
<td></td>
<td></td>
<td>• Requires multiple groups and multiple sacrifice time points</td>
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<td></td>
<td></td>
<td>• Sampling by tissue section</td>
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<tr>
<td>Phenotype IHC</td>
<td>Protein expression</td>
<td>• Antibody availability and specificity</td>
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<td>• Semi-quantitative</td>
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Potential “Value Added” Information from *in vivo* Imaging

- Safety
- Real-time serial data in the same animal
- Reduce animal use
- Optimal dose
- Optimal timing of (repeat) administration
- Provide information on potential mechanism of action
- Application to cells + scaffold (combination product)
  - Scaffold degradation, mechanical properties (if possible?)
  - Host response (i.e., inflammation)
- Bridge to clinical: trial design and monitoring
Ideal Imaging Technology

- Real-time
- Serial imaging over months
- Quantification of viable cells
- High sensitivity and specificity
- Good signal to noise ratio
- Non-toxic to cells and recipients
- Minimal effect on cell function and characteristics
- No leakage
- Functional integration
Imaging Technologies

• Direct cell labeling: MRI
  – Superparamagnetic iron oxide (SPIO)
  – Fluorine based MRI contrast agent

• Indirect labeling: PET
  – Genetic modification with Thymidine Kinase (TK)
Issues to Consider

• Imaging may require manipulation (e.g., genetic labeling or cell loading with contrast agent)
  – Understanding the effect of the manipulation on cell viability, phenotype (i.e., identity) and activity (differentiation capacity, potency, and *in vivo* ‘efficacy’)

• Sensitivity
  – Dividing cells dilute signals

• Quantification

• How does imaging data correlate with histology and qPCR results?
Effect of Contrast Agent Loading on Cell Biological Activity

- **Reduced proliferation:** NSC-Gadolinium

- **Reduced GAG production:** MSC-Resovist (Ferucarbotran)

- **Inhibited chondrogenesis:** MSC-Feridex or Resovist

*Depends on contrast agent, dose, loading condition, cell type*
Heterogeneous Contrast Agent Loading

- Signal/cell varies
- *In vivo* quantification of cell number is challenging

Cannot Differentiate Viable and Non-viable Cells

- NSC loaded with Feridex
- Right (R, white bar)- Live cells
- Left (L, black bar)- Dead cells

Contrast Taken up by Macrophages

- MSC-ferumoxides; intracardiac injection
- At 4 weeks post-implant, most of the contrast agents were found in cardiac macrophages

Immunogenicity of Reporter Gene

- Subjects developed cytotoxic T lymphocytes (CTLs) against cells expressing Thymidine Kinase
- Repeat administration enhanced CTLs
- Fourth dose: half-life < 1 day


Use of Imaging Technologies

• May assist in safety evaluation and translation to the clinic
  – Appropriate validation?
  – Required sensitivity?
  – Is standardization possible?
  – How to ensure appropriate interpretation?

• Encouraged but not required
Early Communication with OCTGT

• Pre-preIND interactions
  – Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (P/T & CMC) and the sponsor
  – Initial targeted discussion of specific issues
  – Primary contact: Mercedes Serabian
    mercedes.serabian@fda.hhs.gov

• PreIND meetings
  – Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  – Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population
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Regulatory Questions: Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or Patrick.Riggins@fda.hhs.gov or by calling (301) 827-6536

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