Preclinical Considerations for Imaging Technology for Cell Therapy Products

Patrick Au, PhD
FDA/CBER/OCTGT/DCEPT/PTB

CIRM Webinar
May 26, 2011


U.S. Department of Health and Human Services
Food and Drug Administration

Overview

- Regulatory Review Principles
- CBER/OCTGT-Regulated Products
- Assessing *in vivo* Cell Fate
- Considerations for Imaging Technologies
- Working with FDA/CBER/OCTGT

Safety is Always Primary…

"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

Cell Therapies: Considerations during Evaluation

Inherent biological properties

- Self-renewal
- Differentiation potential

} Stem/Progenitor

- 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

Survival

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

	Methods	Data Obtained	Limitations
Survival & Migration	•qPCR •IHC	•Cell migration •Proliferation	•Requires multiple groups and multiple sacrifice time points •Sampling by tissue section
Phenotype	IHC	Protein expression	•Antibody availability and specificity •Semi-quantitative

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

  Brekke C et al., *NMR Biomed*. 2007;20(2):77-89

- Reduced GAG production: MSC-Resovist (Ferucarbotran)

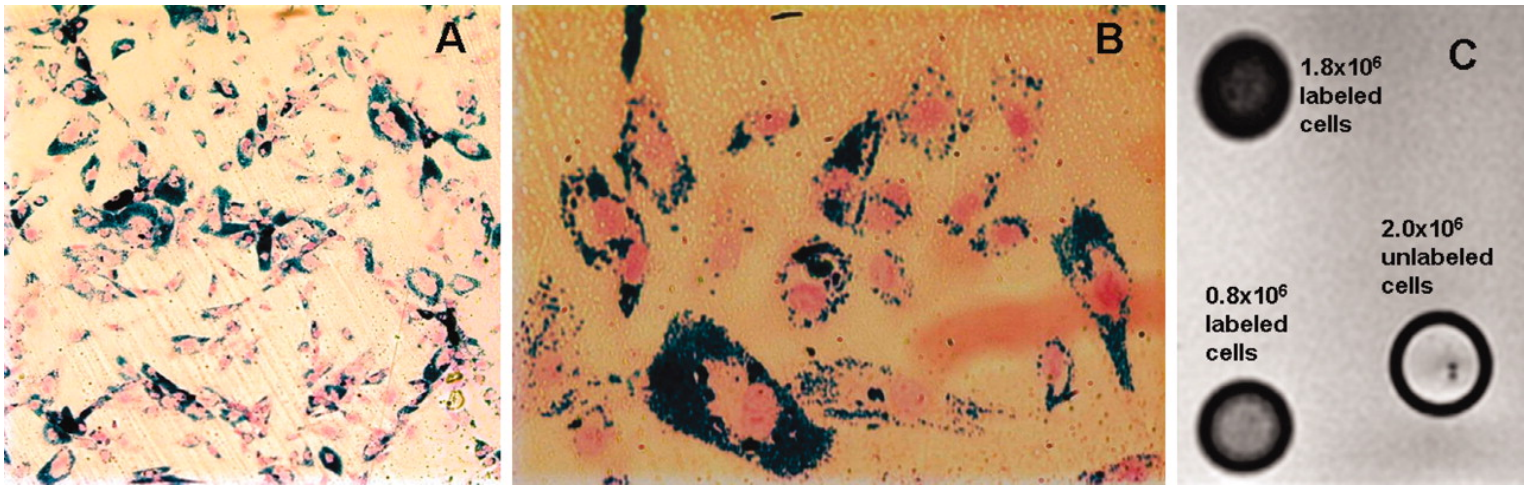
  Boddington SE et al., *Mol Imaging Biol*. 2011;13(1):3-9.

- Inhibited chondrogenesis: MSC-Feridex or Resovist

  Kostura L et al., *NMR Biomed*. 2004;17(7):513-7.
  Henning TD et al., *Contrast Media Mol Imaging*. 2009;4(4):165-73.

Depends on contrast agent, dose, loading condition, cell type

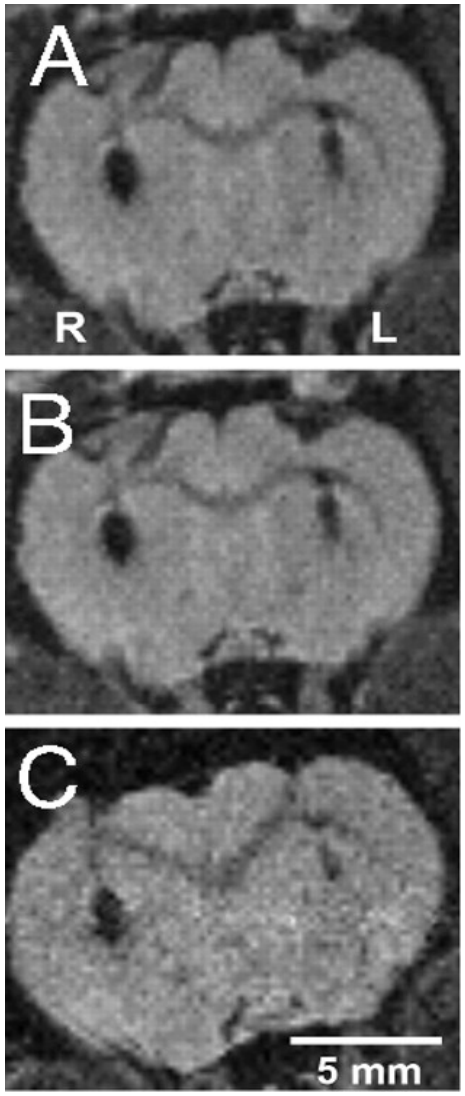
Heterogeneous Contrast Agent Loading



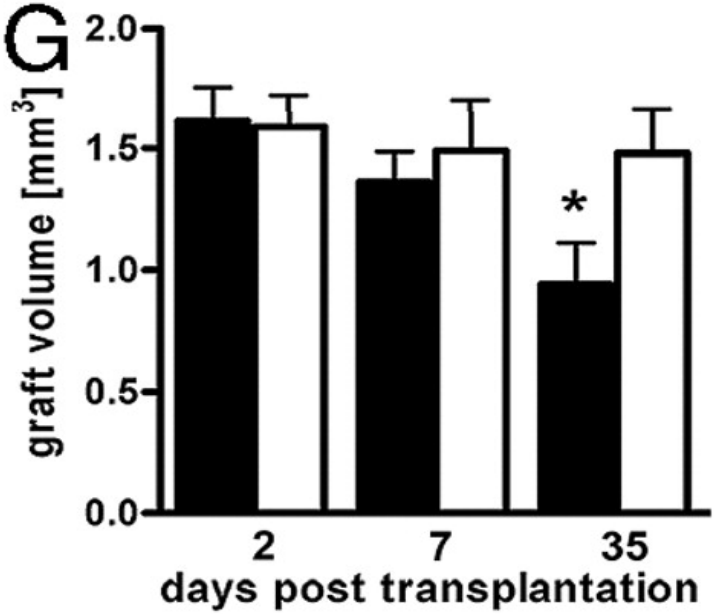
- Signal/cell varies
- *In vivo* quantification of cell number is challenging

Amsalem Y et al., *Circulation*. 2007;116(11 Suppl):I38-45.

Cannot Differentiate Viable and Non-viable Cells

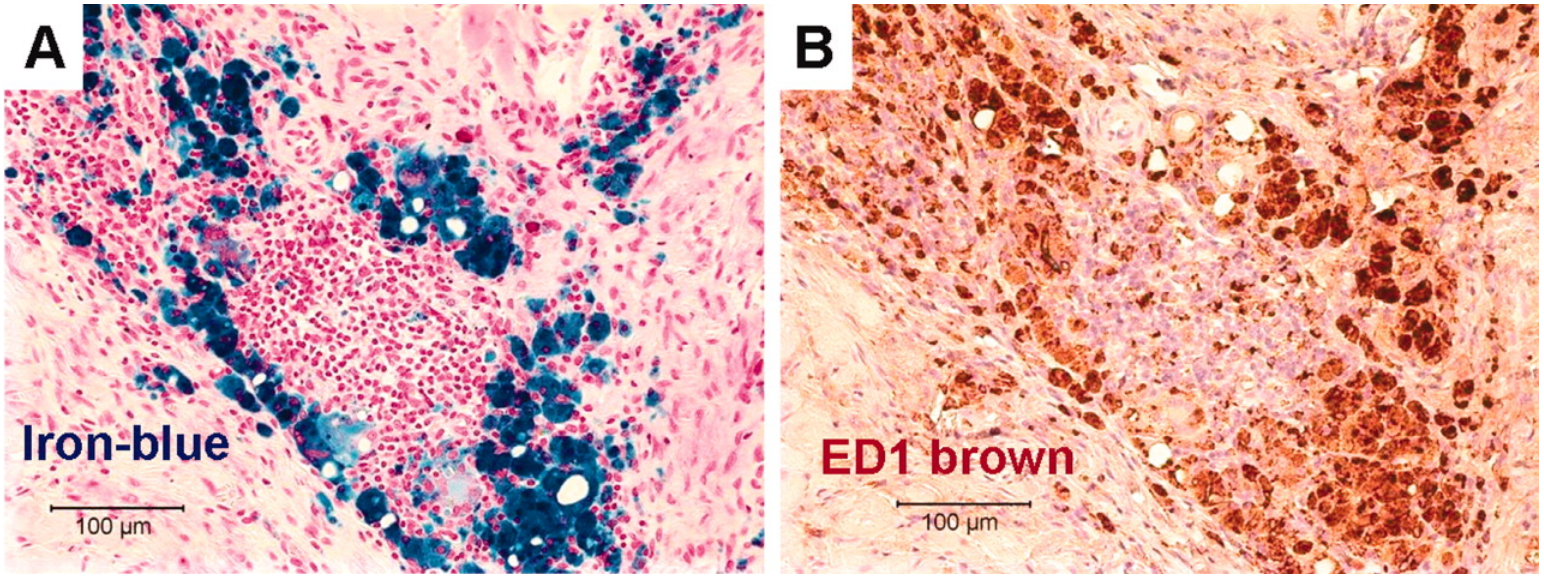


- NSC loaded with Feridex
- Right (R, white bar)- Live cells
- Left (L, black bar)- Dead cells



Guzman R. et al. *Proc Natl Acad Sci U S A*. 2007;104(24):10211-6.

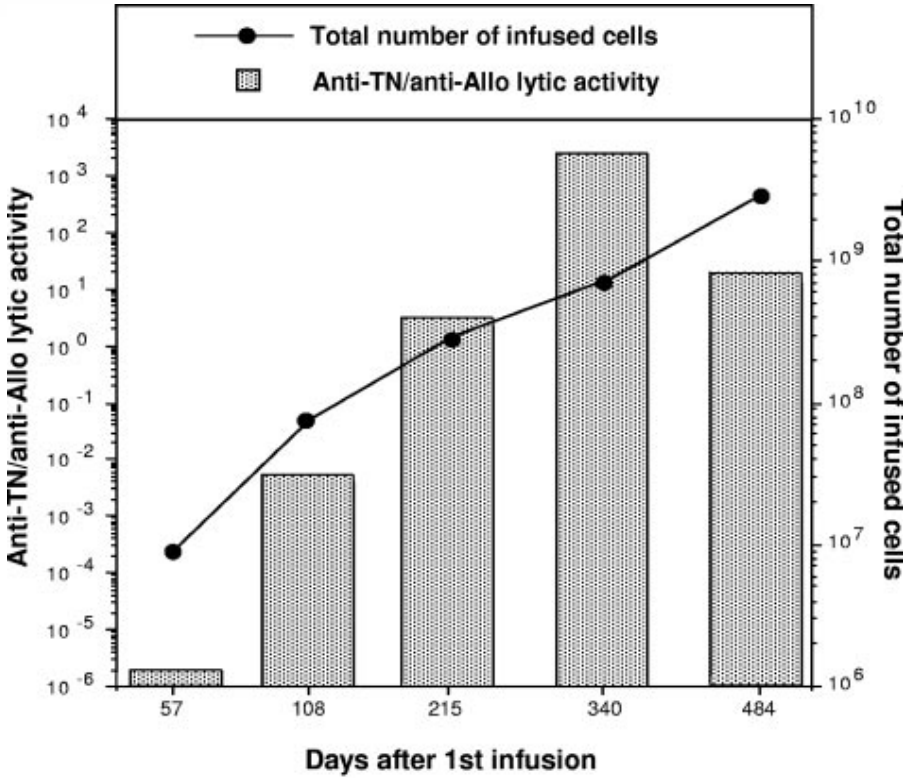
Contrast Taken up by Macrophages



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

Amsalem Y et al., *Circulation*. 2007;116(11 Suppl):I38-45.

Immunogenicity of Reporter Gene



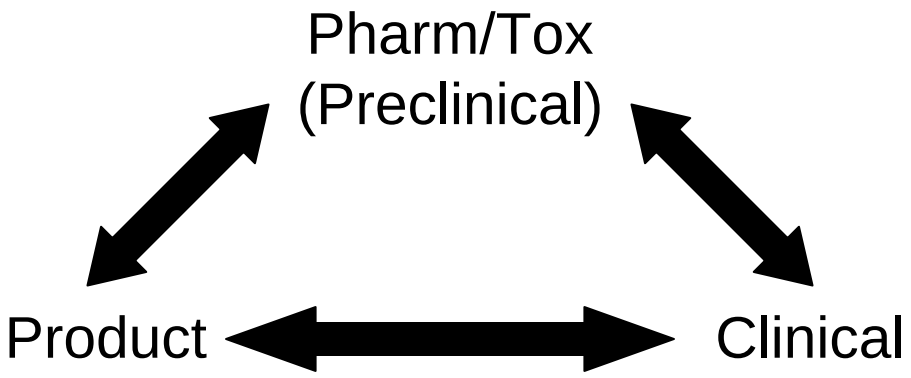
- Subjects developed cytotoxic T lymphocytes (CTLs) against cells expressing Thymidine Kinase
- Repeat administration enhanced CTLs
- Fourth dose: half-life<1 day

Riddell SR et al., *Nat Med*. 1996; 2(2):216-23.

Traversari C et al., *Blood*. 2007; 109(11):4708-15.

Use of Imaging Technologies

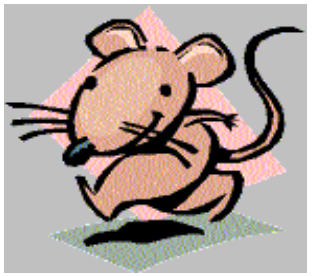
- May assist in safety evaluation and translation to the clinic
  - Appropriate validation?
  - Required sensitivity?
  - Is standardization possible?
  - How to ensure appropriate interpretation?
- Encouraged but not required



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

Contact Information



Patrick Au, PhD
pakwai.au@fda.hhs.gov
301-827-3880

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

OCTGT Learn Webinar Series:
http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm