The Not-So-Odd Couple—Regenerative Medicine and Regulatory Science

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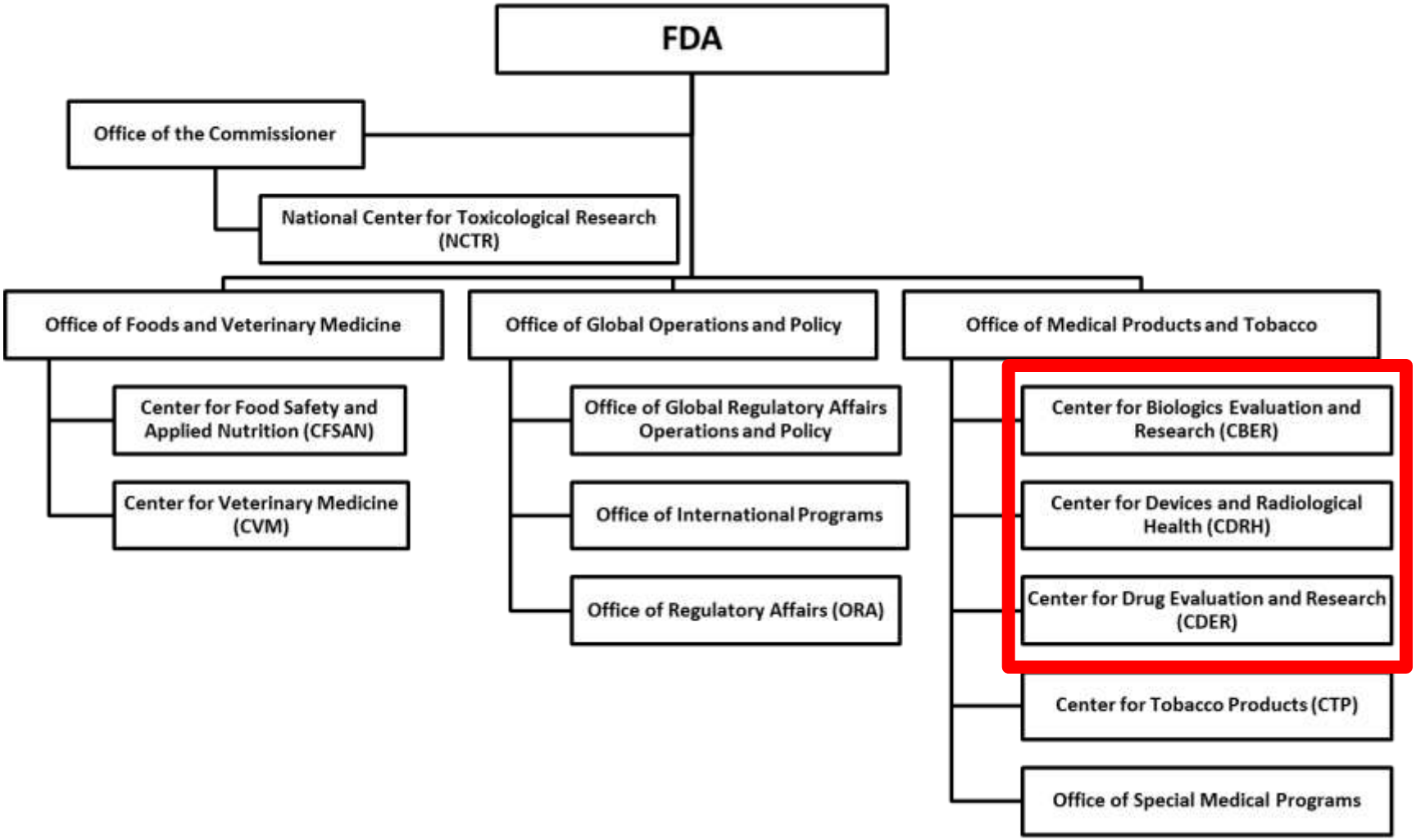
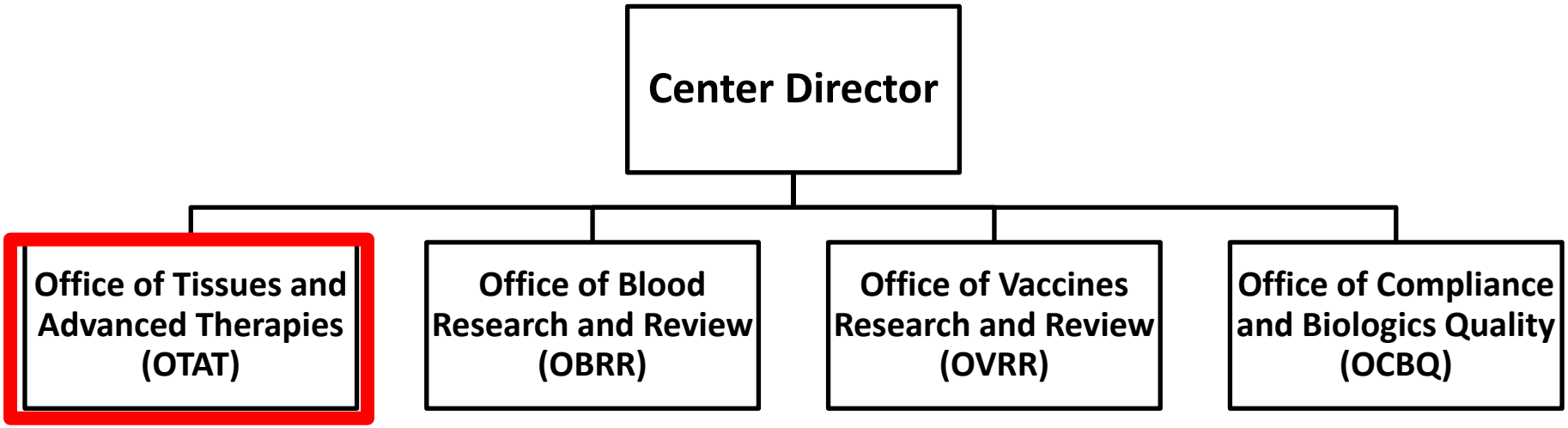
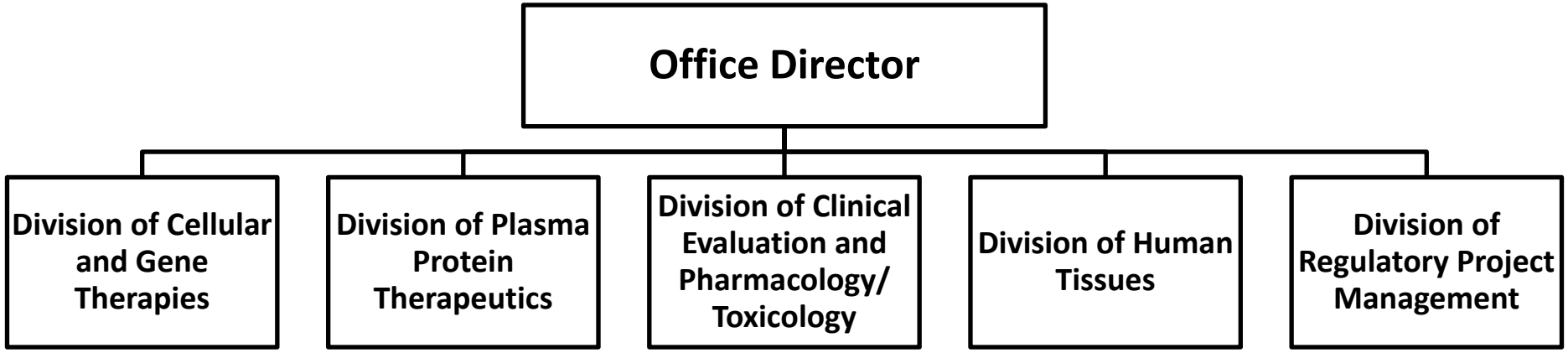
FDA Organization



CBER Organization for Pre- and Post-market Regulation



Office of Tissues and Advanced Therapies (OTAT)



Diversity of OTAT-Regulated Products

- Stem cells/stem cell-derived
  - Hematopoietic, neural, mesenchymal
  - Placental, umbilical cord blood
  - Fetal, embryonic
  - Induced pluripotent stem cells (iPSCs)
- Somatic cells
  - Retinal pigment epithelial cells
  - Pancreatic islet cells
  - Chondrocytes
- Gene therapies
  - Genetically-modified cells
  - Replication-competent vectors
  - Non-viral vectors
  - Viral vectors
  - Genetically modified organisms
- Blood products
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Snake venom antisera
- Combination products
  - Engineered tissues/organs
- Devices
- Tissues

Regenerative Medicine (RM) Products

- For repair, replacement, or regeneration
- Usually a combination of biologic product with a medical device
  - 3D, cell-scaffold product (tissue-engineered)
- Innovative and complex nature necessitate modification, or customization, during their clinical development

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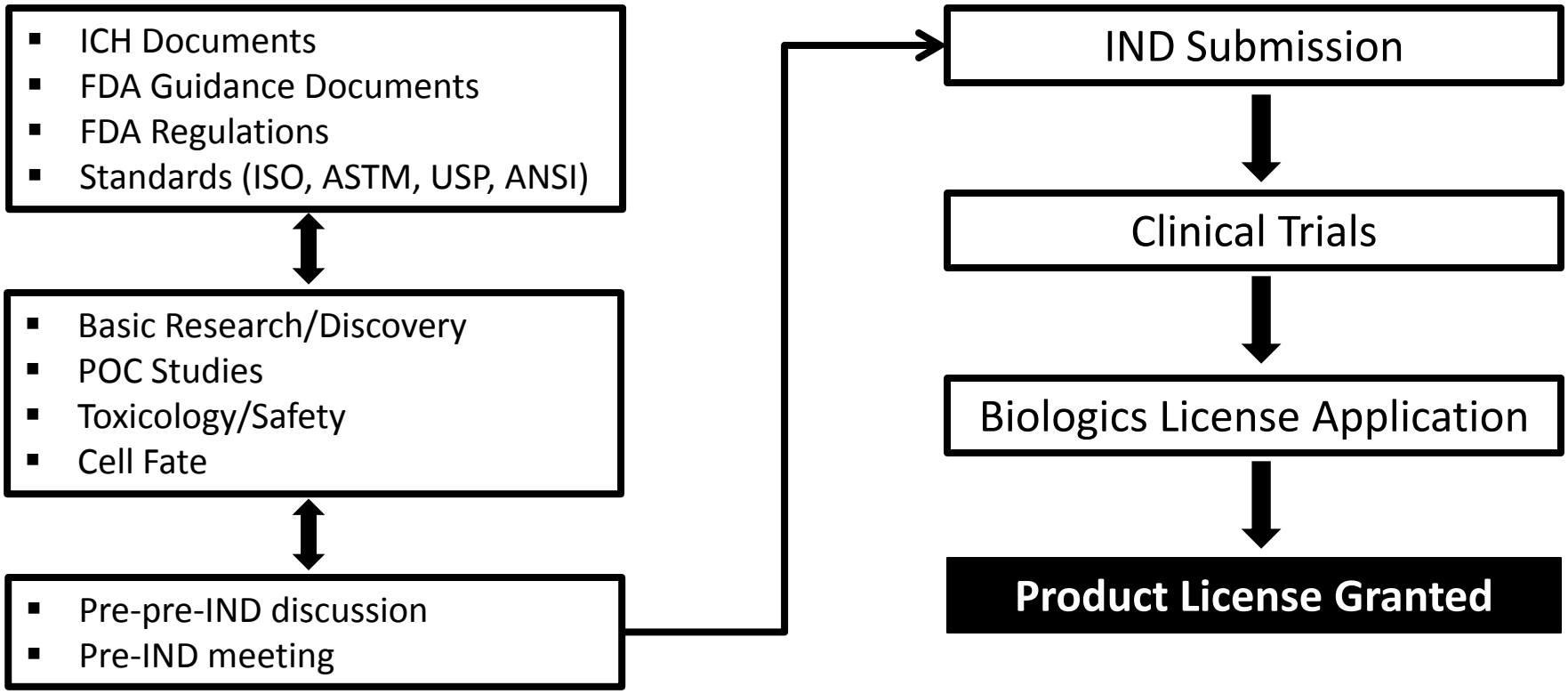
Translational Development



How do I determine preclinical safety of my RM product?

Are there standard *in vitro* or *in vivo* tests I need to conduct?

Preclinical Review of RM Products is Product-Based

- No ‘one-size-fits-all’ regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support use of a specific product for a specific clinical indication
- Review approach is based on balancing benefit and risk

Preclinical Program Objectives

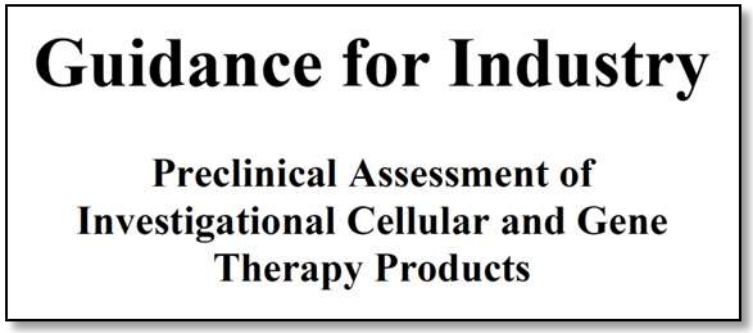
- To support a rationale for the clinical trial
  - For cell therapy products, the trial is conducted in the study population, not in healthy volunteers
- To make recommendations regarding clinical trial design
  - Dose (e.g., initial safe starting dose level, dose-escalation scheme, dosing schedule)
  - Eligibility criteria
  - Clinical monitoring (e.g., safety, activity, duration of follow-up)
- Ensure there is a reasonable benefit-risk profile for subjects

Elements that Drive the Preclinical Testing Program

- Product characteristics
- Putative mechanism of action
- Target disease indication
- Pediatric vs. adult population
- Route of administration
- Anatomic site of delivery

General Considerations for Preclinical Testing Programs

- Published November 2013
- Preclinical study considerations
  - Objectives
  - General program design
- Recommendations for assessment of cell therapy, gene therapy, and therapeutic vaccines
- Explicitly incorporates the 3Rs of animal testing
  - Reduce, refine, replace



Step 1:
Proof-of-Concept (POC) Studies

- Establish feasibility and scientific rationale
- Establish an effective dose range for cells
- Obtain early data on cell fate
- Usually conducted in a disease or injury model, if feasible
  - Support species/model selection for further preclinical testing

Step 2:
Safety Studies

- General Considerations
  - Commonly conducted in healthy animals
  - Determine the minimally effective dose (MED) and the 'No Observed Adverse Effect Level' (NOAEL)
  - Method of dose extrapolation
- Cell Fate Assessment
  - Cell distribution in target and non-target tissues
  - Persistence of cells
  - Stability of cell phenotype

Alternative Preclinical Study Design: Hybrid Study

- Incorporates activity and safety endpoints in animal models of disease/injury
  - Can also include cell fate studies
- Practicing the 3Rs (reduction of animal use)
- Can supplement, or possibly be used in lieu of, safety studies

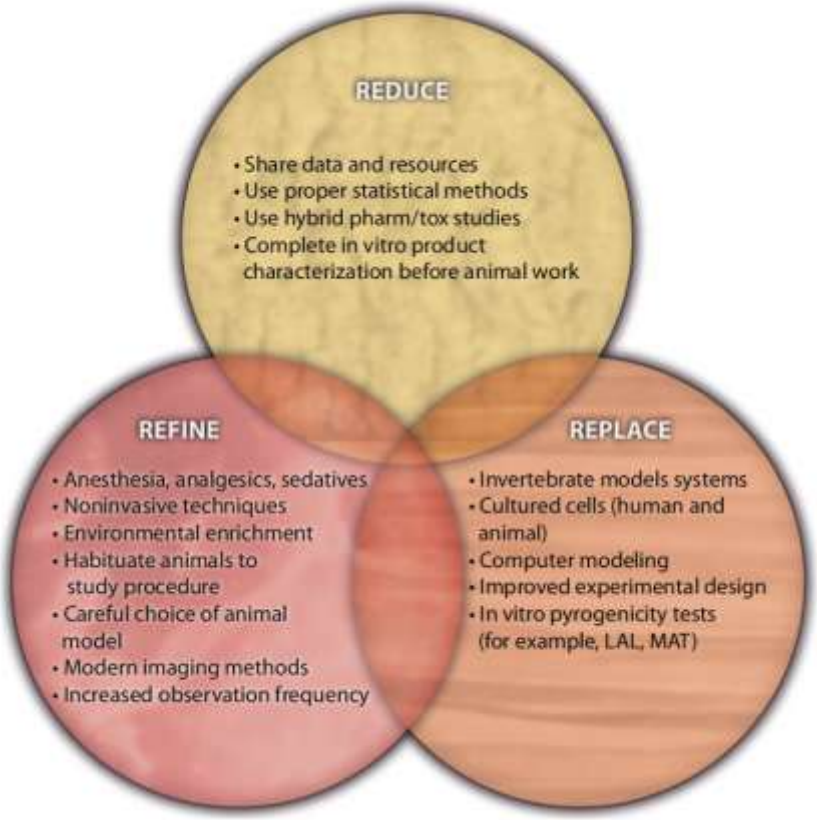
Additional Preclinical Assessments

- Tumorigenicity/Carcinogenicity
  - Concern depends on product type
  - Assessment may be embedded in the definitive safety study
- Developmental and Reproductive Toxicity (DART)
  - Concern depends on product type, target patient population, route of administration, and cell fate
  - Exclusion should be scientifically justified
- Other
  - Immune response issues
  - Issues that arise during clinical development
  - Changes in product manufacturing

Application of the 3Rs Reduce, Refine, Replace

- Consider *in vitro* or *in silico* testing to complement or possibly replace animal studies

- Submit proposals for any potential alternative approaches



Robinson Sci Transl Med 2011

Timing of Preclinical Testing

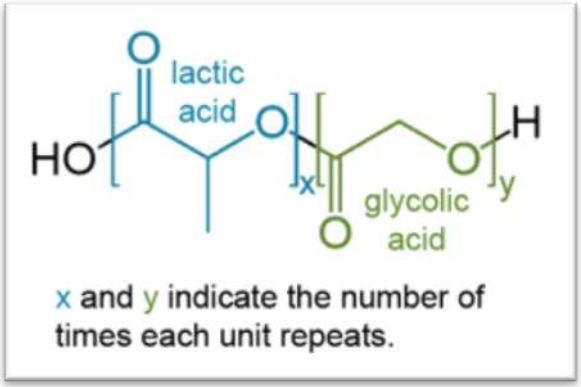
Studies	When to Conduct
POC	Prior to Phase 1
Definitive Safety	Prior to Phase 1
Tumorigenicity/Carcinogenicity	Prior to Phase 1
DART	Generally in the later phases of the clinical development program

CASE STUDY

Influence of Product Characteristics on Preclinical Study Design

Cells on Degradable Polymer Scaffold

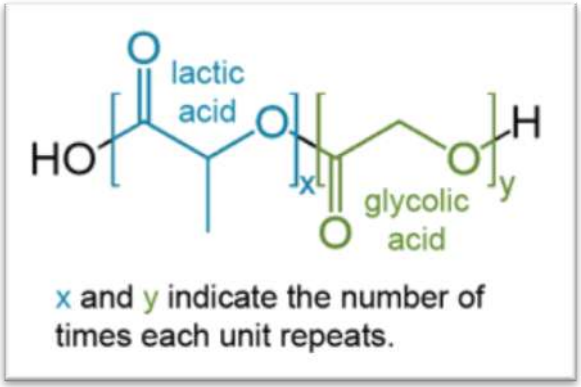
- Degradation properties of scaffold will affect preclinical study design
  - Sacrifice time points should consider degradation rate
  - Degradation products may influence choice of endpoints
- Degradation properties may affect cell viability
  - Degradation products could be toxic to cells on the scaffold
  - Degradation products may induce chronic inflammation in surrounding tissue



x and y indicate the number of times each unit repeats.

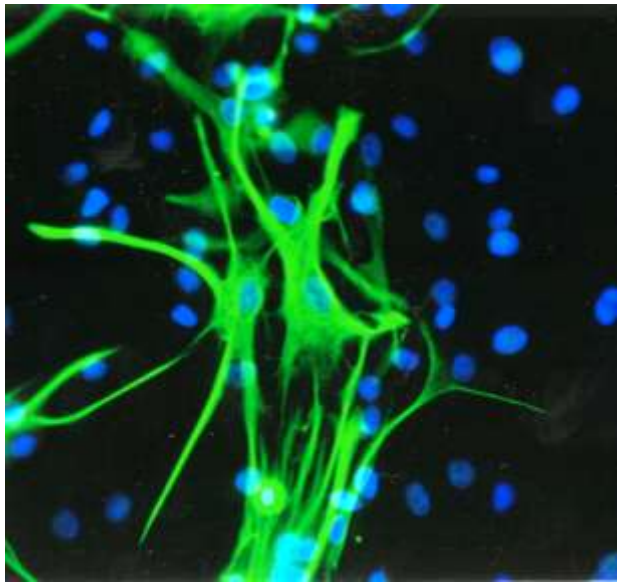
Cells on Degradable Polymer Scaffold

- Anatomic area of implantation
  - Will scaffold need to perform a certain function?
  - Degradation properties may affect the mechanical integrity over time of the final RM product *in vivo*
  - Need to make sure preclinical studies have biomechanical endpoints for RM products with load-bearing functions



Concerns Related to the Cells on the Scaffold

- *Ex vivo* manipulation
  - Expansion, encapsulation, scaffold seeding
- Potential inflammatory/immune response to the product
  - Allogeneic, xenogeneic
- Inappropriate cell proliferation
  - Tumor formation
- Inappropriate cell differentiation
  - Ectopic tissue formation
- Cell migration to non-target sites or tissues



If I make changes to my RM product do I have to repeat my animal studies?

Modifications to RM Products

Need for additional testing based on multiple factors:

- Type of modification
  - Change in scaffold material
  - Change in cells
  - Change in manufacturing
- Data from regulatory science research

Regulatory Science

The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of all FDA-regulated products.

Regulatory Science Research

- FDA has research labs in each product center
  - CBER/OTAT labs working on ways to determine the impact of modifications to a RM product
- Labs focus on basic science and translational research
  - Mechanism of action
  - New techniques for safety and activity evaluation

Regulatory Science & Regenerative Medicine

- Correlate product characteristics measured *in vitro* to preclinical and clinical performance
  - POC studies in animals
  - Scientific publications
- Use of biomarkers to predict functional performance
- Fully characterizing the cellular component to determine the origin, identity, and potential fate

OTAT Regulatory Science Research

- *Predicting the Safety and Efficacy of Cell and Tissue Products Used for Repair of Damaged Tissue and Structures through Cell Growth and Maturation Pathways* (Principal Investigator: **Malcolm Moos**)
  - Identification of signals and signal pathways critical for controlling cell fate decisions

- *Ensuring Safety and Efficacy of Stem Cell-based Products* (Principal Investigator: **Steven Bauer**)
  - Development of practical and applicable test methods to determine cell behavior during manufacturing and *in vivo*

- *Developing Ways to Measure Safety and Efficacy for Tissue-engineered Products* (Principal Investigator: **Brenton McCright**)
  - Identification of biological factors controlling the growth and development of organs and tissues to better predict safety and activity

Summary

- Complexity and uniqueness of RM products necessitate a case-by-case approach to their preclinical development
- Complete product characterization is key
- Tools and knowledge gained in regulatory science research can aid in product characterization and development

Thank You!

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OTAT Contact Information

- **Regulatory Questions**
  - Contact the Regulatory Management Staff in OTAT at CBEROCTGTRMS@fda.hhs.gov
  - Contact Lori Tull at lori.tull@fda.hhs.gov or (240) 402-8361
- **OCTGT Learn Webinar Series**
  - http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

Public Access to CBER

- **CBER Website**
  - http://www.fda.gov/BiologicsBloodVaccines/default.htm
- **CBER Toll Free Number**
  - 1-800-835-4709
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  - Phone: 240-402-7800
- **Manufacturers Assistance and Technical Training Branch (MATTB)**
  - E-mail: industry.biologics@fda.gov
- Follow us on **Twitter** at https://www.twitter.com/fdacber

Regulatory Science Resources

- **FDA: Advancing Regulatory Science**
  - http://www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience/default.htm
- **Cellular Therapy Research at CBER/OTAT**
  - http://www.fda.gov/BiologicsBloodVaccines/ScienceResearch/BiologicsResearchAreas/ucm124376.htm
- **Synopsis of the Food and Drug Administration-National Institute of Standards and Technology Co-Sponsored "*In Vitro* Analyses of Cell/Scaffold Products" Workshop**
  - Published in *Tissue Engineering Part A*, 2009 Mar 15(3):455-60 (PMID: 19215220)


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