Mitochondrial Manipulation Technologies: Preclinical Considerations

Wei Liang, Ph.D.
FDA / CBER / OCTGT
Wei.liang@fda.hhs.gov

Ethical and Social Policy Considerations of Novel Techniques for Prevention of Maternal Transmission of Mitochondrial DNA Disease: Workshop
Institute of Medicine
March 31 - April 1, 2015
Washington, DC
Objectives of Preclinical Testing

- Support the safety and provide the scientific basis of the administration of an investigational product in the target patient population
- Provide evidence of an acceptable benefit : risk profile
- Inform the design of the proposed clinical study
  - Enrollment of appropriate patient population
  - Safe starting dose and dosing regimen
  - Adequate monitoring plan and stopping rules
What Regulations Govern Preclinical Testing?

Pharmacologic & Toxicologic Studies

“...adequate information about the pharmacological and 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, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.”

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]
Preclinical Testing Strategy: FDA / CBER Guidance

Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-853-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013
Preclinical Testing Program: Step-Wise and Science-Based

- **Proof-of-concept (POC)** studies to support the feasibility and activity of the product and associated study procedures for a specific indication

- **Pilot** studies to explore key parameters to guide definitive preclinical study design

- **Definitive** safety studies to support the proposed clinical trial
Preclinical Study Design Considerations

- Use of relevant animal species / models
- Application of the 3 R’s (Reduce, Refine, Replace)
- Nonbiased designs (randomization, blinded assessment)
- Adequate numbers of animals / group
- Mimic the proposed clinical trial design as closely as possible
- Adequate safety and / or activity endpoints
- Sufficient study duration
To discuss available animal models and/or in vitro methods to address the safety and prospect of benefit of mitochondrial manipulation technologies.
Preclinical issues raised by FDA / CBER:

- The possibility of inadvertent damage to the manipulated oocyte or embryo
- The long-term risks associated with the carryover of abnormal mtDNA to the offspring
- The potential for abnormal embryo / fetal growth, resulting in offspring with significant defects
Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting

- General considerations cited by the Committee members:
  - There is not sufficient animal data to support the use of mitochondrial manipulation technologies in first-in-human clinical trials
  - Multiple animal species / models will probably be necessary to assess overall safety concerns
  - Sufficient numbers of animals (mothers and offspring) are needed to adequately evaluate the safety concerns
  - Long-term follow-up of offspring through all developmental stages will be necessary, with possible multi-generational evaluation
What Regulations Govern Preclinical Testing?

Pharmacologic & Toxicologic Studies

“…adequate information about the pharmacological and 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, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations.”

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]
When to Engage CBER / OCTGT

- **Pre-pre-IND interactions**
  - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (Pharmacology / Toxicology and product / CMC) and the sponsor
  - Initial targeted discussion of specific issues

- **Pre-IND meetings**
  - Non-binding, formal scientific discussions with clinical and nonclinical review disciplines (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 for CBER / OCTGT

- Wei Liang, PhD
  Wei.liang@fda.hhs.gov
  240-402-8323

- Regulatory Questions:
  Contact the Regulatory Management Staff in OCTGT at
  CBEROCTGTRMS@fda.hhs.gov
  or Lori.Tull@fda.hhs.gov
  or by calling 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
Phone: 1-800-835-4709 or 240-402-8010

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 240-402-7800

Manufacturers Assistance and Technical Training Branch (MATTB)
Email: industry.biologics@fda.gov
Phone: 240-402-8020

Follow us on Twitter:
https://www.twitter.com/fdacber
Thank you!