Gene Therapy INDs: Deficiencies and Recommendations

American Society of Gene & Cell Therapy (ASGCT)
Liaison Meeting

November 18, 2019

FDA / CBER
Office of Tissues and Advanced Therapies (OTAT)

CMC Notes:

Common CMC IND deficiencies

- Incomplete information regarding:
  - Quality of the materials used to make the product
  - Manufacturing process development (e.g., no process development runs)
  - Safety, quality and stability testing (e.g., inappropriate testing, sampling)
  - Cross referenced information (e.g., wrong cross ref, cross ref is deficient)
  - Manufacturing facility, QA/QC, shipping
- Poorly organized submissions
- Lack of alignment of CMC development with clinical timeline
- Inadequate comparability plans

Recommendations for Improvement

- Plan ahead, communicate with FDA, follow FDA guidance
- Organize submissions according to eCTD
- Resolve CMC issues early in product development
- Identify CQAs and validate assays early - crucial for establishing comparability

Pharm/Tox Notes:

Common Pharm/Tox deficiencies

- Preclinical testing program not comprehensive enough
- Differences between the preclinical and clinical product
- Inadequate preclinical study designs
- Study conduct issues
- Safety concerns based on toxicity profile
- Insufficient data to establish prospect of direct benefit for pediatric subjects

Recommendations

- Early communication with FDA
- Read the guidance - *Preclinical Assessment of Investigational Cellular and Gene Therapy Products* (Nov 2013)
- Use biologically relevant test systems
- Use available tools (e.g., *in silico*, *in vitro*, *in vivo*, etc.) to thoroughly assess safety
- Conduct toxicology studies in accordance with Good Laboratory Practice (GLP)
- Submit complete study reports

Clinical Notes: Efficient Development

- In the setting of rare diseases, have as robust natural history data as early as possible – collaborate pre-competitively
- Even the first-in-human study:
  - Design as randomized, concurrent controlled trial, blinded if possible; otherwise blinded evaluators to reduce bias
  - Evaluate effects on clinically meaningful endpoints (in addition to safety and biomarkers)
- Get early buy-in from patient groups, FDA and other regulatory agencies

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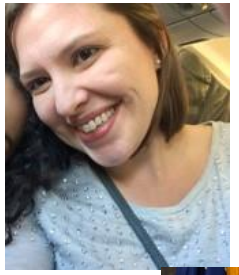

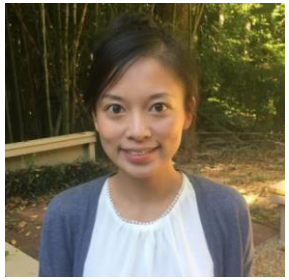

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FDA Headquarters

- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

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