Preclinical Assessment of Cell and Gene Therapy Products to Support an IND: A CBER/FDA Perspective

Rukmini Bhardwaj, PhD
Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

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Presentation Outline

- Organizational structure of CBER/OTAT and regulated products
- Cell and Gene Therapy (CGT) Products
- Regulatory Review Principles
- Preclinical considerations for assessing the safety and activity of CGT products
- Potential Pitfalls/Regulatory Issues
- Opportunities for early interaction with CBER/OTAT
CBER Organizational Structure and Products
Regulated by OTAT
Center for Biologics Evaluation and Research (CBER) - Product Review Offices

- Office of the Center Director
- Office of Tissues and Advanced Therapies (OTAT)
- Office of Blood Research and Review (OBRR)
- Office of Vaccines Research and Review (OVRR)
Diversity of CBER/OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)

- **Stem cells/stem cell-derived products**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)

- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)

- **Products for xenotransplantation**

- **Therapeutic vaccines and other antigen-specific active immunotherapies**

- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants, Fibrinogen, Thrombin, Plasminogen
  - Immune globulins
  - Anti-toxins
  - Snake venom antisera

- **Tissues**

- **Devices**

- **Combination products**
  - Engineered tissues/organs
CGT Products: Definition and Therapeutic Use in Human Diseases

- Cell therapy—autologous, allogeneic, or xenogeneic living cells that may or may not have been processed *ex vivo*

- Gene therapy—products that mediate their effects by transcription and/or translation of transferred genetic material, or by specifically altering host (human) genetic sequences
  - Vector based—viral/non-viral
  - *Ex vivo* genetically modified cells
  - Products incorporating genome editing

Examples

- Cell therapies: mesenchymal stem cells (MSCs), tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells

  *Alzheimer’s, graft versus host disease, solid tumors*

*Molecular Therapy, Volume 24, Issue 3, March 2016, Pages 430-446*
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- Genetically engineered cell therapies: CD34+, T cell receptor (TCR)-T, chimeric antigen receptor (CAR) T cell
  Blood disorders, hematologic malignancies, solid tumors

*Molecular Therapy, Volume 24, Issue 3, March 2016, Pages 430-446*
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- Vector-based gene therapies: viruses, plasmids
  *Monogenic diseases, cancers*
Examples of CGT-based Immunotherapy Products Regulated in OTAT

**Examples**

- Chimeric Antigen Receptor (CAR) T cells
- TCR transgenic (Tg) T cells
- Non-T cell CARs (B cell, NK cell, etc.)
- Regulatory T cells (Tregs)
- Mesenchymal Stem Cells (MSCs)
- Therapeutic Vaccines (e.g., dendritic cells, irradiated tumor cells, peptide vaccines, lipid nanoparticles carrying mRNA, etc.)

*Molecular Therapy, Volume 24, Issue 3, March 2016, Pages 430-446*
Lifecycle for Investigational Products

- Preclinical
- Clinical Trials
  - Phase 1
  - Phase 2
  - Phase 3
- Marketing Application
- Post-marketing

- Development
- Preclinical

- IND Submission
- End of Phase 1 Meeting
- End of Phase 2 Meeting
- BLA
- Safety Meetings
- Marketing Submission
Evaluating Safety and Activity of CGT Products to Support an IND

- IND Application: required to conduct a clinical trial in the US
  - Using an investigational product in a first-in-human (FIH) trial
  - Using an approved/investigational product for a new clinical indication/route of administration (ROA)/formulation
  - Has a 30-day FDA review clock

- IND review team:
  - Is interdisciplinary
    - Regulatory Project Manager (RPM)
    - Chemistry, Manufacturing, and Controls (CMC) reviewer
    - Pharmacology/Toxicology (P/T) reviewer
    - Clinical reviewer
    - Statistical reviewer
    - Consult reviewer(s) (as needed)
  - Reviews information supporting rationale and safety of the trial
  - Interacts with the sponsor, as needed, to resolve issues or concerns
  - Makes a “go” or “hold” decision by the 30-day date
### 21 CFR 312.20 Subpart B: IND Application

| ☐ | Form FDA 1571 | 21 CFR 312.23(a)(1) |
| ☐ | Table of Contents | 21 CFR 312.23(a)(2) |
| ☐ | Introductory statement and general investigational plan | 21 CFR 312.23(a)(3) |
| ☐ | Investigator's brochure | 21 CFR 312.23(a)(5) |
| ☐ | Protocols | 21 CFR 312.23(a)(6) |
| ☐ | Chemistry, manufacturing, and control data (including environmental assessment) | 21 CFR 312.23(a)(7) |
| ☑ | Pharmacology and toxicology data | 21 CFR 312.23(a)(8) |
| ☐ | Previous human experience | 21 CFR 312.23(a)(9) |
| ☐ | Additional information | 21 CFR 312.23(a)(10) |
| ☐ | Biosimilar User Fee Cover Sheet | Form FDA 3792 |
| ☐ | Clinical Trials Certification of Compliance | Form FDA 3674 |
Key Elements in Regulatory Review of CGT Products

- Science-based approach to regulation

- **Product manufacturing (CMC)**

- **Pharmacology/Toxicology (P/T)**

- **Clinical trial design**
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Considerations for Preclinical Programs for CGT Products
How Do Preclinical Data Contribute to the Proposed Clinical Plan?

- Provide **rationale** or **proof of concept (POC)** for the first-in-human (FIH) clinical trial in subjects with the target disease

- Make recommendations to inform clinical trial design
  - Eligibility criteria
  - Route of administration (ROA), initial safe starting dose level, dose escalation scheme, dosing regimen
  - Potential toxicities, clinical monitoring, risk mitigation

- Provide comprehensive **safety assessment** in a relevant animal species/model
  - Identifying any acute and chronic, local and systemic toxicities
  - Risks of the proposed ROA, delivery procedure
How does CBER/OTAT evaluate preclinical safety and activity?

...and what sponsors should consider when developing a new product?
Initial Considerations for a Preclinical Testing Program

- The diversity and biological properties of CGT products necessitate a flexible testing strategy - no “one size fits all”
  - Based on accumulated knowledge and experience
  - Based on available technology
  - Science-based
  - Data-driven
Sources of Preclinical Data to Support an IND

- Appropriately designed, well-executed POC studies
- Good Laboratory Practice (GLP)-compliant toxicology studies
- Published data in peer-reviewed journals
- Authorized cross-reference to similar products in previous US FDA submissions
General Expectations for a Preclinical Testing Program for CGT Products

- Pharmacology
  - Provide *rationale* or *POC* for CGT product administration in a specific clinical population
  - Understand mechanism of action and biological activity in a relevant animal species/disease or injury model
  - Select optimal dose levels, and dosing regimen
  - Assess vector biodistribution/cell fate *in vivo* to support activity following clinically relevant ROA

- Prospect of Direct Benefit (PDB) is required for clinical studies in children (*per 21 CFR 50.52 Subpart D*)—if the trial represents more than minimal risk
General Expectations for a Preclinical Testing Program for CGT Products

 Toxicology

- Provide comprehensive **safety assessment** of the CGT product in a relevant animal species to support clinical trials
- Determine a No-Observed-Adverse-Effect-Level (NOAEL)
- Characterize adverse findings following product administration:
  - Identify target tissue(s) of toxicity
  - Local or systemic effects
  - Acute, delayed, or prolonged findings
  - Cells/vector/transgene-related immune responses
  - Tumorigenicity risk
  - Dosing procedure or device-related toxicities

- Cell/vector/transgene presence is important in the interpretation of any findings
Potential Safety Concerns for CGT Immunotherapies

- Product-related
  - Manufacturing (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
  - Inappropriate cell proliferation (i.e., tumor formation)
  - Inappropriate cell differentiation (i.e., ectopic tissue formation)
  - Cell/vector distribution to non-target sites and potential toxicities
  - Inflammatory/immune response to the administered product
  - Toxicity to host tissues/organs (e.g., GVHD for allogeneic T cell products)
  - Toxicities due to cross-reactivity- on-target/off-tumor, off-target activity
  - Toxicities due to pharmacological action of CGT- cytokine release, tumor lysis, etc.

- Procedure and/or device-related
CGT Product Administered in Preclinical Studies

- **Product should be as similar as possible to the intended clinical product**
  - Tissue/sample source, harvesting procedure, expansion, culturing, formulation, encapsulation/scaffold seeding, storage, etc.
  - Vector production/vector construct/transgene expression/final formulation/titer

- **Adequate product characterization**
  - Cellular morphology, phenotype
  - Molecular, biochemical markers
  - Vector sequence, genomes, empty capsids

- **Animal-derived analogous product**
  - Characterize the level of analogy between the animal product and the intended human product
  - Translation of data to humans
Considerations for Appropriate Animal Species/Model(s)

- Scientific justification should be provided for each animal species/model(s) used
  - There is no ‘default’ to the use of nonhuman primates
  - There is no ‘default’ to the use of both a rodent and a non-rodent species
- Assess safety, distribution, and bioactivity using appropriate animal species/model(s)
- Understand the limitations of each species/model(s) used
Selection of Animal Species/Model(s)

- Comparability to the target patient population
  - Phenotype, pathophysiology, clinical outcomes
- Permissiveness to cell product
  - Human derived, autologous, allogeneic
- Anatomic site of product delivery
  - Comparable to clinical, if feasible
- Feasibility of using the intended clinical delivery system/procedure
Preclinical Study Design Considerations

- Nonbiased
- Mimic the planned clinical scenario as closely as possible
- Administration of appropriate control product and multiple dose levels of the investigational product
- Adequate numbers of animals/group to enable robust study interpretation
  - Incorporate the three R’s of animal testing into preclinical programs
    - Reduce
    - Refine
    - Replace
Preclinical Study Design Considerations

- Sufficient study duration to assess both acute and long-term outcomes
- Multiple time points for evaluations
- Comprehensive bioactivity, distribution, and safety assessments
- Other specific in-life/terminal assessments
Mirror the Clinical Scenario (as Feasible)

- **Mimic clinical scenario as closely as possible**
  - Test clinical product and formulation
  - Mimic clinical injection procedure, anatomical location, delivery system / device**, timing of product delivery, dosing regimen

**Conduct bench testing of the delivery device with the CGT product to determine product-device compatibility and verify the dose level administered
Study Assessments and Endpoints

Multiple in-life and post-mortem time points for activity and safety
- Biochemical, functional outcomes (e.g., neurological, cardiac, ophthalmic) which are disease dependent
- Bio Distribution—cells, vector
- Tumorigenicity—cells, vector, transgene
- Transgene—expression, activity
- Immunogenicity—cells/vector/transgene

Standard toxicology parameters
- Mortality, in-life—body weights, food consumption, etc.
- Clinical observations
- Clinical pathology
- Gross pathology and histopathology—target and non-target tissues (use of standard IHC, ISH etc., microscopic pathology)
- Nature/timing/severity/frequency of adverse findings
Vector Biodistribution /cell fate

- **Biodistribution profile in biofluids and tissues**
  - Target and nontarget tissues: Distribution, Persistence, and Clearance
    - For GT products
    - ✓ Vector presence and clearance profile in target, non-target, and germline tissues
    - ✓ Transgene expression (level and duration) in vector positive tissues
  - For CT products
    - ✓ Cell survival, engraftment, integration, proliferation, differentiation, and migration

- **Important to evaluate the POC and Safety results with vector biodistribution /cell fate data**

- **Guidance for GT-based BD assessment:**
  - Guidance for Industry: Long Term Follow-up After Administration of Human Gene Therapy Products (Jan. 2020)
Regulatory Expectations for Toxicology Studies

21 CFR 312.23 (a)(8) – Pharmacology and Toxicology

- For each toxicology study intended primarily to support safety, a full tabulation of data should be submitted.

- Each toxicology study submitted should be performed per GLP (21 CFR Part 28), or an explanation provided.

- Oversight of the conduct of all non-GLP toxicology studies and the resulting final study report by an independent QA unit/person is strongly recommended (21 CFR 58.35).
Potential Preclinical Pitfalls When Submitting an IND

- Insufficient information to assess subject risk, including:
  - Insufficient characterization of product safety
  - Lack of preclinical safety data for intended product
  - Incomplete safety study reports

- Inadequate preclinical study design
  - Differences between preclinical and clinical products
  - Irrelevant animal species/model
  - Irrelevant ROA
  - Inadequate animal numbers/dose levels/study duration
  - Inadequate evaluations (safety/activity endpoints)

- Inadequate data to support PDB in a FIH study in children (21 CFR 50 Subpart D)
Opportunities for Interaction During Preclinical Development

- Preclinical Development
- Preclinical
- Phase 1
- Phase 2
- Phase 3
- BLA
- Marketing Application
- Post-marketing

- INTERACT
- Pre-IND Meeting
- End of Ph 1 Meeting
- End of Ph 2 Meeting
- Pre-BLA Meeting
- IND submission
INTERACT Meetings

- **INITial Targeted Engagement for Regulatory Advice on CBER products**

- **Goal:** To obtain early feedback on a product development program for a novel investigational agent

- **Purpose:**
  - A mechanism for early communication with OTAT
  - Non-binding, informal scientific discussions between CBER review disciplines and the sponsor
  - Initial targeted discussion of specific issues

- **Requests** for INTERACT meetings should be sent to INTERACT-CBER@fda.hhs.gov

[Link to full document](https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm)
INTERACT Meetings (Cont’d)

- **Timing:** When you have generated preliminary preclinical data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies

- **Pharmacology/Toxicology (P/T) advice:**
  - Design of POC or other pilot safety/distribution studies
  - Adequacy of the selected animal species/models
  - Acceptability of innovative preclinical testing strategies, products and/or delivery modalities
  - Advice on modification of a preclinical program or study design, as applicable, to ensure judicious use of animals
Pre-IND Meetings

- **Goal:** To achieve a successful IND submission

- **Purpose:**
  - Non-binding, *formal* scientific discussion between all review disciplines (CMC, P/T, and Clinical) and the sponsor
  - Comprehensively communicate the product/clinical development plan
  - Discuss the format of the IND submission

- **Timing:**
  - POC and preliminary safety studies completed
  - Ready to conduct definitive safety studies
Pre-IND Meetings: Preclinical Data

- A comprehensive summary of all completed preclinical studies
  - *In vitro* and *in vivo* studies, animal species/models, study designs, resulting data and interpretation

- Complete protocols for the proposed definitive preclinical safety/toxicology, distribution studies
  - Animal species/models, dose levels, dosing regimen and procedure, study endpoints, sacrifice intervals, etc.
FDA Guidance for Human CGT Products


- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)


- Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (Jan 2020)
Guidance for Industry: Human Gene Therapy for Retinal Disorders (Jan 2020)

Guidance for Industry: Human Gene Therapy for Rare Diseases (Jan 2020)

Guidance for Industry: Human Gene Therapy for Hemophilia (Jan 2020)


Draft Guidance for Industry: S12 Nonclinical Biodistribution Considerations for Gene Therapy Products (September 2021)
Summary

- OTAT resides within CBER and regulates a wide array of products, including cell and gene-based therapies.
- The preclinical program for any CGT product is determined on a case-by-case basis.
- Preclinical data submitted in the IND should support the safety and biological activity of the CGT product in the proposed clinical indication.
- There are multiple opportunities to obtain FDA feedback on preclinical development plans prior to IND submission.
- Novel therapies mean novel testing paradigms, therefore, pre-submission interaction with FDA is encouraged.
Acknowledgements

- Colleagues in OTAT/CBER
Contact Information

- Rukmini Bhardwaj, PhD
  rukmini.bhardwaj@fda.hhs.gov

- Regulatory Questions:
  OTAT Main Line – 240 402 8190
  Email: OTATRPMS@fda.hhs.gov and Lori.Tull@fda.hhs.gov

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

- CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm

- Phone: 1-800-835-4709 or 240-402-8010

- Consumer Affairs Branch: ocod@fda.hhs.gov

- Manufacturers Assistance and Technical Training Branch: industry.biologics@fda.hhs.gov

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Thank you!