Preclinical Assessment of Investigational Cellular and Gene Therapy Projects

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Objectives

• Review Draft FDA Guidance: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

• Relate experiences with pre-clinical assessments of cells and tissue engineered products

• Review benefits and pitfalls of mouse models to elucidate mechanisms of action.
Disclaimers

• “This draft guidance, when finalized, will represent the Food and Drug Administration’s (FDA’s) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations...”
Refers to or summarizes guidance
Preclinical Assessment of Investigational CGT Products

• Introduction
• Background
• Preclinical Study Considerations
• Recommendations for CT Products
• Recommendations for GT Products
• Recommendations for Therapeutic Vaccines
Introduction

• To provide recommendations on the type of pre-clinical information needed to support clinical trials of cell and gene therapy (CGT) products
  • Cell therapies
  • Gene therapies
  • Therapeutic vaccines
  • Xenotransplantation
  • Certain device-biologic combos

• Doesn’t apply to:
  • 361 HCTP/s
  • Devices, CDER and OBRR reviewed products, preventive vaccines
Introduction

• Traditional approaches for typical drugs are often not appropriate.

• OCTGT uses flexible, science driven review to address safety.
  • Considers biology of product and clinical indication.
  • Incorporates the basic principles of toxicology studies.
Preclinical Program Should:

• Establish biological plausibility
• Identify active dose levels, escalation and overall regimen
• Provide support for chosen route of administration
• Support trial eligibility criteria
• Identify physiologic parameters to guide monitoring
• Identify public health risks
Recommendations: Product

• The clinical product should be used for preclinical studies
  • Not always possible
  • Rationale and differences should be explained in IND submission

• Lot release testing in preclinical studies should be as close as possible to clinical products
Cell-Coated Platinum Coils for the Treatment of Intracranial Aneurysms

• Platinum coils are a standard treatment
  • Known aneurysm recurrence rate

• Coating coils with cells before delivery could facilitate repair of vessel wall

• Preliminary animal study
  • Human cell coated coil for experimental aneurysm in rabbits
Cell-Coated Platinum Coils for the Treatment of Intracranial Aneurysms

- Human cells appeared to properly localize
- Extravascular inflammation
- Rabbits were not immunosuppressed
- IND strategy:
  - Next studies - autologous rabbit cells in the same model
  - Same culture procedures as for human manufacturing
Recommendations: Animal Species Selection

- Biological response should be similar to humans
- Consider anatomy, viral replication, immune tolerance, compatibility with patient delivery system
- More than one species might be required
- In-Vivo tests to help identify ideal animal species
- Rationale and summary part of IND submission
Selection of Animal Models of disease/injury

• Same models from basic research may benefit preclinical studies
• Might be preferable to healthy animals to assess mechanism and safety
• Possible identification of biomarkers to monitor clinical trials
Limitations of Animal Models of Disease/injury

- Inherent variability of the model.
- Limited historical/baseline data for the model.
- Technical limitations with the physiological and anatomical constraints of the model.
- Animal care issues
- Limited fidelity in modeling human pathophysiology of the disease/injury of interest.
Recommendations: Animal Model of Disease

• In the IND submission describe:
  • Similarities and differences between animal model and human disease
  • Effect of animal disease on the pharm/tox of the product
  • Effect of animal disease on the efficacy of the product

• Tiered approach
  • Pilot studies with CGT product
  • Help select animal model for later studies
Mesenchymal Stem Cells for ALS

- Commonly studied animal model is SOD-1 knockout mouse
- Only the hereditary form of ALS in humans is associated with SOD-mutation
  - 5-10% of ALS cases
- Animal model may not be applicable for 90% of clinical patients
MSC for ALS

- Animal models not predictive for human trials
- IND strategy
  - Safety of cells
  - Safety of route of administration
  - Reference published human studies
  - Risk/benefit equation
**Risk Benefit Assessment**

**Benefit**
- Good pre-clinical data
- MOA and dose defined
- Biomarkers of efficacy
- Prior clinical experience
- Poor prognosis without Rx
- Limited other Rx

**Risk**
- Less clinical experience
- Known toxicity
- Undefined MOA
- Pediatric population
Proof of Concept Studies

• Benefit side of the Risk/Benefit relationship

• Establish the rationale and feasibility of the proposed clinical trial
  • Help define the dose range and timing
  • Optimize the Route of Administration
  • Help characterize the mechanism of action

• Can be combination of *in vitro* and *in vivo* studies
Toxicology Studies

- Adequate numbers and randomization
- Appropriate controls
- Bracketed dosing
- Dosing schedule modeled on clinical protocol
- Clinical route of administration
  - Including delivery device where applicable
- Assessments for standard acute and chronic effects
- Assessments for product specific expected toxicities
Good Laboratory Practices

• GLP required for toxicity studies per 21 CFR part 58
  • Recognition that isn’t always possible
  • Rationale needs to be included in IND submission
Data in Support of Clinical Trials- Mayo Solution

• Not GLP or GMP, but a defined and established system for data supporting IND and IDE submissions.

• A voluntary opt-in system where membership requires participation in the entire process.

• DSCT is overseen by a group individuals interested in standardizing and providing the best data in support of clinical trials.
Data in Support of Clinical Trials

• The Human Cellular Therapy Laboratory performs few animal studies independently

• Partner with numerous research laboratories

• DSCT provides templates and standardization for reports from diverse investigators

• Consistent report formats
  • Can be used for multiple INDs
Reduction, Refinement and Replacement

• Refers to Animal Welfare Act of 1975
• Reduction by use of a single species and by non terminal studies when justified
• Refinements such as incorporation of pain management and non-terminal imaging
• Replacement by use of in-vitro studies when available
MSC for Multisystem Atrophy (MSA)

- Degenerative neurologic disorder of autonomic system
- Median survival ~9 yrs
- IND strategy
  - Cross reference ALS IND
    - Same cells and ROA
  - Refer to published safety study of MSC for MSA
    - Different ROA than our proposed IND
  - No additional pre-clinical studies required
Product Development for Later Phase Clinical Trials

• As the CGT product changes through early trials, consider additional preclinical studies to address any outstanding issues
  • Manufacturing
  • Dose
  • Patient population

• Consult with OCTGT to ensure seamless product development.
Preclinical Study Reports

• Separate report required for each in vitro and in vivo safety study

• Include
  • Protocol + all amendments
  • Detailed description of study design
    • Animals, doses, route of delivery, controls
  • Complete data set for all parameters measured
    • Tabular data for all animals
  • Analysis and interpretation of results
Cellular Therapy Products

- Two broad categories
  - Stem Cell Derived
    - Variable capacity for self renewal
    - Able to differentiate into variety of cell types
    - Fate is determined mainly by milieu post administration
  - Mature/Functionally Differentiated
    - No self renewing or differentiation
Animal Species/models

• Considerations
  • Ability to access the anatomic site for administration
  • Ability to deliver specific dose to target site
  • Immunodeficient animals for long term assessment
Immunologic Tolerance

• How do you test a product if the animal rejects it?
  • Immunosuppression
  • Gene modified immunodeficient animals
  • Humanized animals
  • Immune privileged site
  • Combination
  • Analogous animal product
Using an Analogous Animal Product

• Need to demonstrate comparability to product
  • Sample harvest
  • Cell identification and culture
  • Growth kinetics
  • Phenotype and function
  • Final product formulation
  • Storage and stability
Study Design: Overall

• Cell phenotype
• Cell source
• Ex vivo manipulation
• Minimal effective dose
• Limiting dose
• Cell fate
• Possibility of host immune response
• Local and systemic toxicities
Study Design: Safety

- Administration site reactions
- Inflammatory response
- Host immune response
- Migration away from administration site
- Ectopic tissue formation
- Abnormal proliferation
- Tumorigenicity
MSC delivered through injection catheter at clinical doses and proposed rate of administration.
Study Design: Product Fate

• Survival/engraftment affected by:
  • Biocompatibility
  • Route of Administration
  • Genetic relationship of the host
  • Immune status
  • Timing

• Distribution
  • Typical pharmacokinetics don’t often apply
  • Imaging, immunohistochemistry, PCR, karyotype

• Differentiation and integration

• Tumorigenicity
Study Design: Product Fate

• Differentiation and Integration
• Tumorigenicity
CT Products with Scaffolds

- Cells
- Scaffolds
- Biocompatibility
- Cell seeding
- Study groups
  - Varying cell density and loading
- Biologic responsiveness
- Dose response and durability
- Safety
Stem Cell Fistula Plug in Perianal Crohn’s Disease

- Fistula plug is standard surgical treatment
- Clinical trial using MSC coated fistula plug
- IND strategy
  - Demonstrate MSC coating of plug
  - Refer to published reports of safety of MSC for Crohn’s
  - Refer to safety record of plug, clinically available device
- Risk mitigation strategy
  - MSCs stay on plug despite trypsin
  - Plug can be surgically removed in necessary
Stem Cell Fistua Plug in Perianal Crohn’s Disease

• Submitted preclinical in vitro studies
• No animal studies required for IND to proceed
Conclusions

• Draft Guidance is a good road map to follow for successful IND submission
• FDA encourages communication
• Risk based approach
• Develop cooperative relationship with groups performing animal pre-clinical studies
  • They may need some guidance if they’re new to the IND process