FDA Perspective on Preclinical Animal POC & Safety Studies for Stem Cell Based Therapy

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Outline

- Regulatory Review Principles
- Expectation of Preclinical Assessment
- Preclinical POC and Safety Studies
  - Animal Species/Models
  - Study Design
- Working with FDA/CBER
How are Animal Studies Integrated into the Proposed Clinical Plan?

• 21 CFR, Part 312.23(a)(8)

Pharmacologic & Toxicologic Studies

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

• Provide **scientific rationale/POC** for conducting clinical trial
• Recommend a **safe starting dose, dosing schedule** and **dose escalation schemes**
• Identify the **parameters for monitoring** in the clinical protocol (e.g., safety, activity, duration of follow-up, etc.)
• Exclude **adverse interactions** with other therapeutics to be used in conjunction with the intended product in the treatment plan of the clinical protocol
• Support patient **eligibility criteria**
• Provide preliminary **risk/benefit assessment**
• Discern **mechanism of action/toxicity**
Questions that Should be Asked

• What cells will be used clinically?
  – Autologous, or allogeneic
  – Adult-, fetal-derived tissue specific stem cells or progenitor cells
  – hESC-derived cells, or iPSC-derived cells
  – Undifferentiated cells or fully differentiated/mature/ function-specialized cells…
• Are cells genetically modified? ..vector?.. transgene (s)?
• What is their intended mechanism of action? ..tissue repair, replacement, regeneration, or restoration?....secretion of growth factors?
• What is the optimal timing for product administration relative to the onset of disease/ injury?
Questions (Cont’d)

• What is the intended delivery method/route of administration? ...implanted alone... with a scaffold... encapsulated? ... at single or multiple implantation sites? ..by single or multiple administrations?
• Is short-term or long-term cell survival desired?
• Will cells proliferate, differentiate, or migrate to non-target sites following in vivo administration?
• Can cell trafficking be monitored by non-terminal modalities?
• Will immunosuppressive agents be needed?
• What are the relevant animal model(s) for assessment of POC, toxicology/safety, cell trafficking and tumorigenicity?
• What is the risk/benefit ratio for the intended patient population?
Preclinical Studies….

- Assess pharmacology/POC/cell fate in relevant animal model(s) of disease/injury
- Assess the safety/toxicology (T)/cell fate in healthy animals
- Hybrid pharmacology-toxicology study design – POC + T + cell fate in an animal model of disease/injury
- Apply 3R’s to animal studies – Reduction, Replacement, Refinement…
Animal Species/Models (1)

• Reasons for use of a large, non-rodent species
  – Comparative physiology and disease conditions
  – Large organ/tissue size may allow product administration by the clinically intended delivery procedure to the intended anatomic site
  – Large organ/tissue size may allow for cell administration at higher dose levels

• Reasons for use of a rodent species
  – Ability to use robust numbers of animals
  – Transgenic or knockout models available
  – Immune deficient rodents available for evaluation of human cells
### Animal Species/Models (2)
#### Evaluating Human Cell product

<table>
<thead>
<tr>
<th>Immunocompromised</th>
<th>Immunosuppressed</th>
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<tbody>
<tr>
<td><strong>Pros</strong></td>
<td><strong>Pros</strong></td>
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<tr>
<td>– Consistency and ease of use</td>
<td>– Allow use of large animal species</td>
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<td>– Allows certain disease/injury modeling</td>
<td>– Wider array of disease models</td>
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<td>– Defined degree of immunodeficiency with various genetic rodent models</td>
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<tr>
<td><strong>Cons</strong></td>
<td><strong>Cons</strong></td>
</tr>
<tr>
<td>– Limited to using rodents</td>
<td>– Hard to achieve consistent immunosuppression (IS)</td>
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<td>– Not predict immunoreactivity to transplanted cells</td>
<td>– IS agent might affect transplanted cells</td>
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<tr>
<td>– Physically fragile/susceptible to disease</td>
<td>– Need to discriminate IS toxicity from cell product toxicity</td>
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<tr>
<td>– Limited pathology database</td>
<td>– Uncertain translation of immunoreactivity from animal (xenoreactivity) to patient (alloreactivity)</td>
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Animal Species/Models (3)

- Understand capabilities & limitations of species used
- Selection of appropriate animal species should be based on scientific justification
- Use existing disease/Injury animal models to ‘predict” activity & safety
- Conduct small pilot studies to determine the survival potential of the implanted cells in chose animal species/models before embarking on large, pivotal animal studies
Pharmacology/POC

• *In vivo* animal disease/injury model(s)
  – Establish feasibility/rationale
    • Cell replacement, tissues repair/regeneration, secretion of paracrine/trophic factors, etc…
    • Improvement of injury/disease conditions based on morphological changes, functional/behavioral changes, ….
  – Optimize cell dose/cell ‘formulation’
    • Implanted with other cells/agents?
    • Seeded onto a matrix/scaffold?
  – Optimize ROA/cell administration procedure
  – Optimize timing of cell implantation
  – Identify non-terminal biomarkers/activity endpoints
Toxicology/Safety

- *In vivo* biologically relevant animal species/model
  - Determine types of adverse findings (AFs) related to surgical injection/implantation procedure, and/or implanted cell product, and/or concomitant therapies ...
  - Determine where, when, and how long AFs occur
  - Establish safe dose levels and dosing regimen
Study Design – Specifics (1)

• Mimic clinical scenario as closely as possible
  – Use cell product intended for clinical use…or analogous cells
    • Cell viability, concentration/formulation, composition of cell phenotypes determined by similar makers that characterize the clinical product…
  – ROA, delivery system/procedure (scaffold, capsule, injection device, injection flow rate, …)
  – Timing of cell delivery relative to disease/injury onset, dosing regimen, etc.
  – Anatomical location relative to diseased/injured area, number of implants/ injections, etc.
Study Design – Specifics (2)

• Nonbiased design
  – Randomized assignment to groups
  – Appropriate controls (sham, vehicle, etc.)
  – In-life and postmortem assessments conducted in a blinded manner

• Adequate numbers of animals/group to ensure statistically & biologically robust interpretation

• Sufficient study duration and multiple time points - to allow for adequate assessment of:
  – Functional, laboratory, and morphological outcomes
  – Local/systemic effects in target/non-target tissues
  – Time of onset and persistence profile of significant findings
Study Design – Specifics (3)

• Safety Assessment /‘Standard’ toxicology endpoints
  – Mortality
  – Clinical observations, body weights, appetite, etc
  – Clinical pathology – hematology, coagulation, serum chemistry, urinalysis
  – Pathology
    • Target & non-target tissues
    • Scheduled & unscheduled deaths
    • Comprehensive gross pathology
    • Microscopic pathology – blinded assessment
Study Design – Specifics (4)

- Microscopic pathology (cont’d)
  - Injection/implantation procedure associated risks, scar formation..
  - Implanted cells associated risks,
    - Cell survival/engraftment
    - Cell proliferation & differentiation – (i.e. hypercellularity, graft expansion, tumor/ectopic tissue formation,)
    - Effect to neighboring host tissues
  - Inflammatory/immune cell infiltrates
Study Design – Specifics (5)

• Fate of implanted cells
  – Survival/engraftment
  – Integration (anatomical/functional)
  – Proliferation
  – Differentiation/phenotype expression
  – Transdifferentiation/de-differentiation, fusion
  – Migration/trafficking (target and non-target sites)

• Terminal/non-terminal assessment
  – Various imaging modalities
  – PCR, IHC, ISH

• Product-dependent endpoints [tumorigenicity, immunogenicity, etc…]

• Disease-dependent endpoints [cardiac, neurological, metabolic, etc…]
Tumorigenic Potential

Tumorigenic potential - hyperplastic or unregulated growth is a safety concern

• Test the intended clinical product
  – Intended site of implantation
  – Maximum feasible dose
  – Controls – assurance of engraftment; spontaneous tumors, etc…
  – Sufficient study duration
  – Interpretation of data
   • Type of tumor formation
   • Incidence of tumor formation
   • Anatomical location of tumor/size of tumor
   • Origin of tumor cells (human?)
Cell Delivery System

• Is the device approved/cleared for intended use? If not:
  – Detailed device information should be submitted in the CBER submission for a CDRH consult review
  – A device Master File should be submitted to CDRH

• Conduct ‘bench testing’ of the delivery device
  – Biocompatibility of the animal & human cells to the device (i.e., cell shearing, adsorption onto the walls of the device, stability of the device to delivery pressures, etc.)

• Perform preclinical safety evaluation studies using the intended clinical device, if possible
Other Cell Delivery Systems

• Encapsulated cell product
  – Capsule material – biocompatibility testing
  – Function of encapsulated cells, cell viability, capsule size, strength and integrity of the capsule

• Cells seeded on a scaffold for tissue engineering/tissue regeneration
  – Scaffold material – biocompatibility testing
  – Cell seeding – ‘dose’, cell growth, cell function, cell-scaffold interactions

• Use the intended clinical product in the preclinical studies
Submit Complete Reports for Toxicology Studies

- **Not just summarized statements**
- Detailed description of the study performed:
  - Test system (i.e., animal species/animal model)
  - Test articles
    - Product preparation – cell source, culturing condition, formulation/scaffold seeding, storage conditions…
    - Product characterization – cell viability and phenotypic characterization…
  - Study design – ROA, dose level/dosing regimen, study groups, interim sacrifice, study endpoints…
- Results: for all parameters evaluated-
  - Submit *individual animal data* for all parameters evaluated
  - Submit summarized and tabulated results
Early Communication with OCTGT

• Pre-preIND interactions
  – Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (Pharm/Tox & CMC) and the sponsor
  – Initial dialogue - targeted discussion of specific issues

• PreIND meetings
  – Summary data and sound scientific principles to support use of a specific product in a specific patient population
Summary

• It is important to engage FDA at an early phase of the product development program, to enable identification of potential issues and the appropriate pathway to resolution.

• The preclinical study designs should be supported by scientific rationale/data

• Novel therapies mean novel testing paradigms
Resource Information…

• Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy IND Applications
• ICH Documents [link](http://www.fda.gov/cber/guidelines.htm)
• CBER/FDA Cellular, Tissue and Gene Therapies Advisory Committee Meeting: “Cellular Therapies Derived from Human Embryonic Stem Cells: Scientific Considerations for Pre-Clinical Safety Testing.” (April 10-11, 2008) Transcript Available at: [link](http://www.fda.gov/ohrms/dockets/ac/cber08.html#CellularTissueGeneTherapies)
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