Preclinical Considerations for Stem Cell-Based Products

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Overview

- Translation from Preclinical to Clinical
- [Some] Questions that Should be Asked…
- Preclinical Study Design(s)
  - Animal Species/Model Considerations
  - The Cellular Product Administered
  - Study Design Specifics
- Working with CBER/OCTGT

Translation from Preclinical to Early Phase Clinical Trials

- Proof-of-concept [POC] – *in vitro*/*in vivo*
  - Potential mechanism of action [neuroprotective, neurotrophic, neoangiogenesis, etc…]
  - Establish pharmacologically effective dose(s)
  - Optimize ROA/dosing regimen
  - Rationale for species/model selection for further testing
- Safety of conducting clinical trial – risk/benefit
  - Dosing scheme
  - Potential target tissue(s) of toxicity/activity
  - Parameters to monitor clinically
  - Eligible patient population

[Some] Questions that Should be Asked...

- What cell type(s) will be used?
  - What is their differentiation state/potential?
  - If mixed cell types – what is the composition of the final product?
- What is the source of the cell(s)?
- What is their intended mechanism of action?
  - Is cell survival/engraftment necessary to achieve the desired outcome?... For how long?
  - Are the cells intended to prevent further damage or to compensate for what has been damaged?
  - Do the administered cells replace lost/damaged cells?...do they stimulate endogenous mechanisms of repair?
  - Do the cells secrete growth factors/cytokines?

[Some] More Questions…

- How many cells are needed for a minimal/optimal biological effect?
- Are the cells implanted alone?...with a scaffold... encapsulated?
- Are the cells modified?...now a ‘gene therapy’?
- What is/are the biologically relevant animal species for your product?
- Are there potentially relevant animal models of disease/injury that can be used?

[Even Some] More Questions…

- What is the optimal method/route to deliver the product?
- What is the optimal timing for product administration relative to the onset of disease/ injury? …[back to mechanism of action]
- What happens to the cells *in vivo* following delivery?
- Will repeat administration be needed?
- What is the risk/benefit ratio for the intended patient population?

Preclinical Study Design(s)

- Pharmacology/POC studies in relevant animal model(s) of disease/injury
- Toxicology (T) studies in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T – Obtain bioactivity & toxicology endpoints in an animal model of disease/ injury

Pharmacology/POC

- *In vitro / ex vivo* activity/mechanism of action
  - Bioactivity
    - Neurotrophic activity (nerve cells)-- protection of neuron from apoptosis
    - Angiogenic activity (endothelial cells)– induction of vascular structures
- *In vivo* animal disease/injury model(s)
  - Feasibility/establishment of rationale
  - 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
  - Identification of non-terminal biomarkers/activity endpoints

Animal Species/Model Considerations

- Comparative physiology of animal to human
  - Model of disease/injury
  - Local microenvironment & pathophysiology condition may impact the safety of the product
- Route of administration – comparability to clinical
  - Systemic vs. targeted delivery
  - Delivery system/delivery procedure
- Species specificity of the product
- Species specificity of the innate immune response
- Apply the 3 R'S – Reduce, Refine, Replace – in preclinical study designs

What Cells Should be Used in the Preclinical Studies?

- Need to understand the intended mode of action of the cells
  - Is cell survival/engraftment necessary?..
  - How long do the cells need to survive to achieve the desired outcome?
  - Is desired activity a result of a paracrine effect following cell implant?
- 'Clinical' product (human cells)
  - Immune competent animals given immunosuppressive drugs
  - Genetically immunodeficient strains
  - Immune privileged implantation sites
  - 'Immune privileged' cells
- Use of analogous cell product

Regarding the Cells Administered…

- Comparability to the clinical product
  - Tissue/sample harvest, cell isolation, expansion, culturing, formulation/scaffold seeding, storage conditions, etc.. should be as similar to the intended clinical product as possible
  - Cellular morphology and phenotype should be characterized

Regarding Analogous Cells…

- Uncertainties:
  - Potentially different function(s) or regulation
  - Limited characterization of the animal cells
  - Potentially different impurities/contaminants
- Comparability between animal & human cells is an important step towards understanding the safety of the proposed cell therapy
- Conduct small pilot studies to determine the survival potential of the cells in each animal species used before embarking on large, pivotal animal studies

Cell Delivery Device System

- Is the device cleared for use in the intended anatomical location in humans?
- Conduct ‘bench testing’ using the delivery device
  - Biocompatibility of the animal & human cells to the device
- Can your product be used in multiple catheters or delivery devices... or are you limited to a proprietary device from a single manufacturer?
- Use the intended clinical device in the animal studies

Preclinical Study Design: Specifics

- Nonbiased design
  - Randomized assignment to groups
  - Appropriate controls (sham, vehicle, etc..)
  - In-life and postmortem assessments conducted in a blinded manner
- Mimic clinical scenario as closely as possible
  - Use cells intended for clinical use…or analogous cells
  - Cell viability, concentration/formulation, volume, rate of delivery, implant site, number of implants/ injections, etc…
  - ROA, delivery system, timing of cell delivery, dosing regimen, etc…
  - Anatomical location/extent of the diseased/injured area

Preclinical Study Design: Specifics

- Adequate numbers of animals/group to ensure statistically & biologically robust interpretation
- Sufficient study duration, depending on the biology of the product, to allow for adequate assessment of:
  - Functional, laboratory, and morphological outcomes...
  - …and the potential for reversion/resolution of findings
- Include several time points for measuring nonterminal/terminal parameters to evaluate early and late findings post-cell administration

Preclinical Study Design: Specifics

- ‘Standard’ toxicology endpoints
  - Mortality
  - Clinical observations, body weights, appetite
  - Clin path – serum chemistry, hematology, coagulation, urinalysis
  - Pathology-target & non-target tissues
    - Scheduled & unscheduled deaths
    - Comprehensive gross pathology
    - Microscopic pathology – blinded assessment
- Terminal/non-terminal assessment
  - Various imaging modalities
  - PCR, IHC, ISH

Preclinical Study Design: Specifics

- Product-dependent [tumorigenicity, immunogenicity, etc…]
- Disease-dependent [cardiac, neurological, etc…]
- Cell fate - influence of local microenvironment
  - Survival/engraftment
  - Integration (anatomical/functional)
  - Differentiation/phenotype expression
  - Migration/trafficking (ectopic tissue formation)
  - Proliferation

Tumorigenic Potential

- Tumorigenic potential - hyperplastic or unregulated growth
  - What is the cell source?
  - What is the ‘stemness’ of the cells?
  - What is the extent of ex vivo manipulation?
  - Where is the site of implantation?
  - What patient population is targeted?

Tumorigenic Potential

- Test the intended clinical (human) cells
  - Intended ROA/site of implantation
  - Maximum feasible dose
  - Controls – assurance of engraftment; spontaneous tumors, etc…
  - Adequate study duration – rodent lifespan
  - Interpretation of data
    - Inappropriate proliferation- without malignant transformation [IHC, Ki67]
    - Frequency of tumor formation
    - Origin of tumor cells (human?)

CBER Approach to Preclinical Assessment

- Data-driven
- Problem-solving, creative
- Should be based on best available science, technology to date
- Novel therapies mean novel testing paradigms
- Follow the CFR, FDA guidances, ICH
- Careful design of preclinical studies results in judicious use of animals

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 targeted discussion of specific issues - a “two-way street”
- PreIND meetings
  - Summary data and sound scientific principles to support use of a specific product in a specific patient population

Thanks!