

Preclinical Considerations for Stem Cell-Based Products

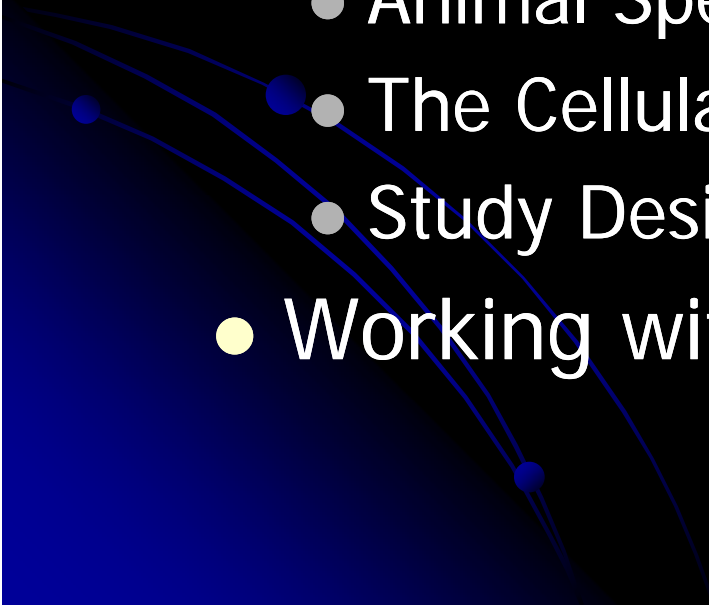
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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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
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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?

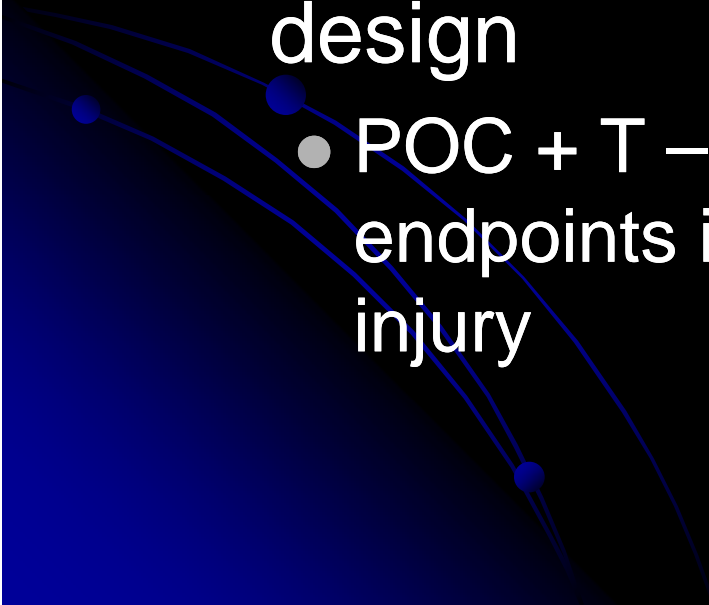
[Some] More Questions...

- 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
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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

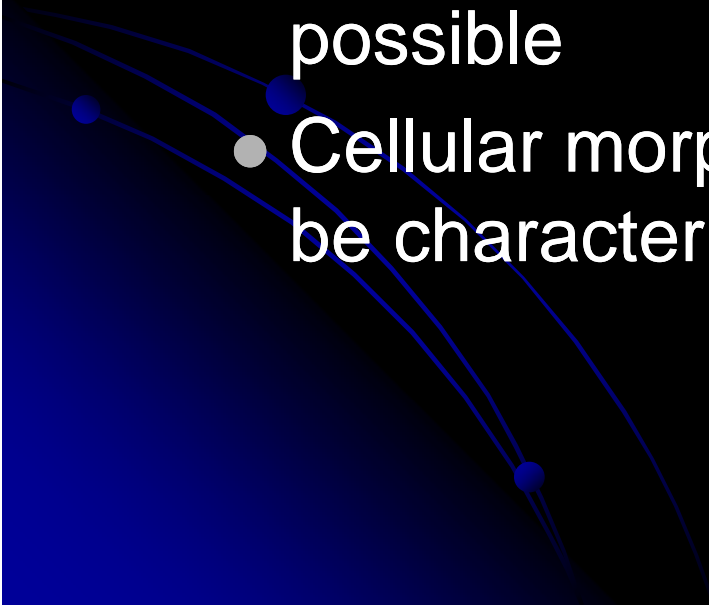
Animal Species/Model Considerations

- 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
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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

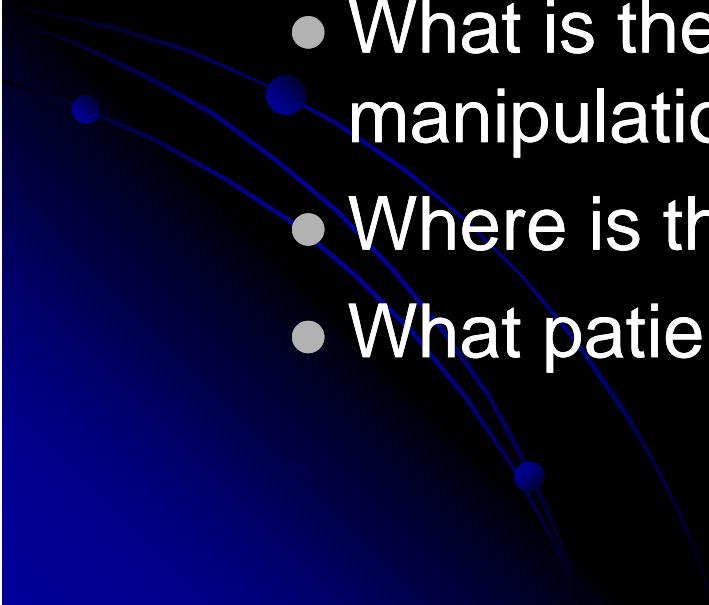
Preclinical Study Design: Specifics

- '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
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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?
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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!

