Preclinical Considerations for Stem Cell-Based Therapies: CBER Perspective

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CIRM Webinar:
Preclinical Animal Model Considerations for Stem Cell Therapies
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Overview

- CBER/OCTGT Organization
- Regulatory Review Principles
- Properties of Stem Cells
- Questions to Ask…
- CMC Considerations
- Preclinical Study Design(s)
  - Animal Species/Model Considerations
  - The Cellular Product Used
  - Cell Implantation Modalities
  - Pharmacology/Proof-of-Concept (POC)
  - Preclinical Study Design Considerations - Specifics
- Transitioning to a Clinical Trial
- Working with FDA/CBER/OCTGT

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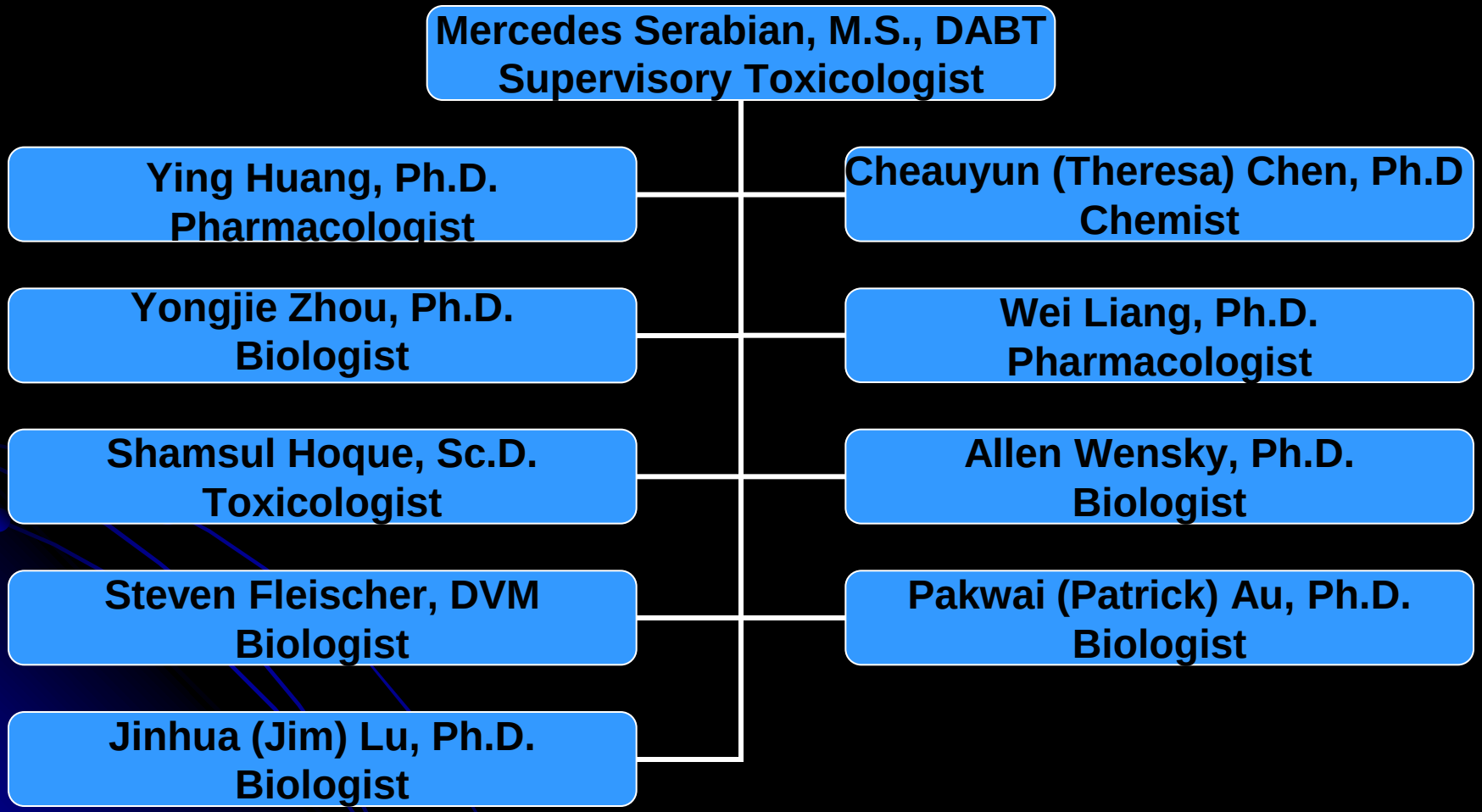


Critical Path Development of Biotherapeutic Agents

- FDA Regulatory & Scientific Input
- ICH documents
- FDA guidances/21 CFR

Clinical Trials

IND Submission

- Basic Research
- POC Studies
- Toxicology/Safety
- Biodistribution/Cell fate

- Pre-PreIND interaction with FDA/CBER
- PreIND discussion with FDA/CBER

Biologics License Application

Product License Granted

Discovery Phase/Safety Assessment

How are Preclinical Studies Integrated into the Proposed Clinical Plan?

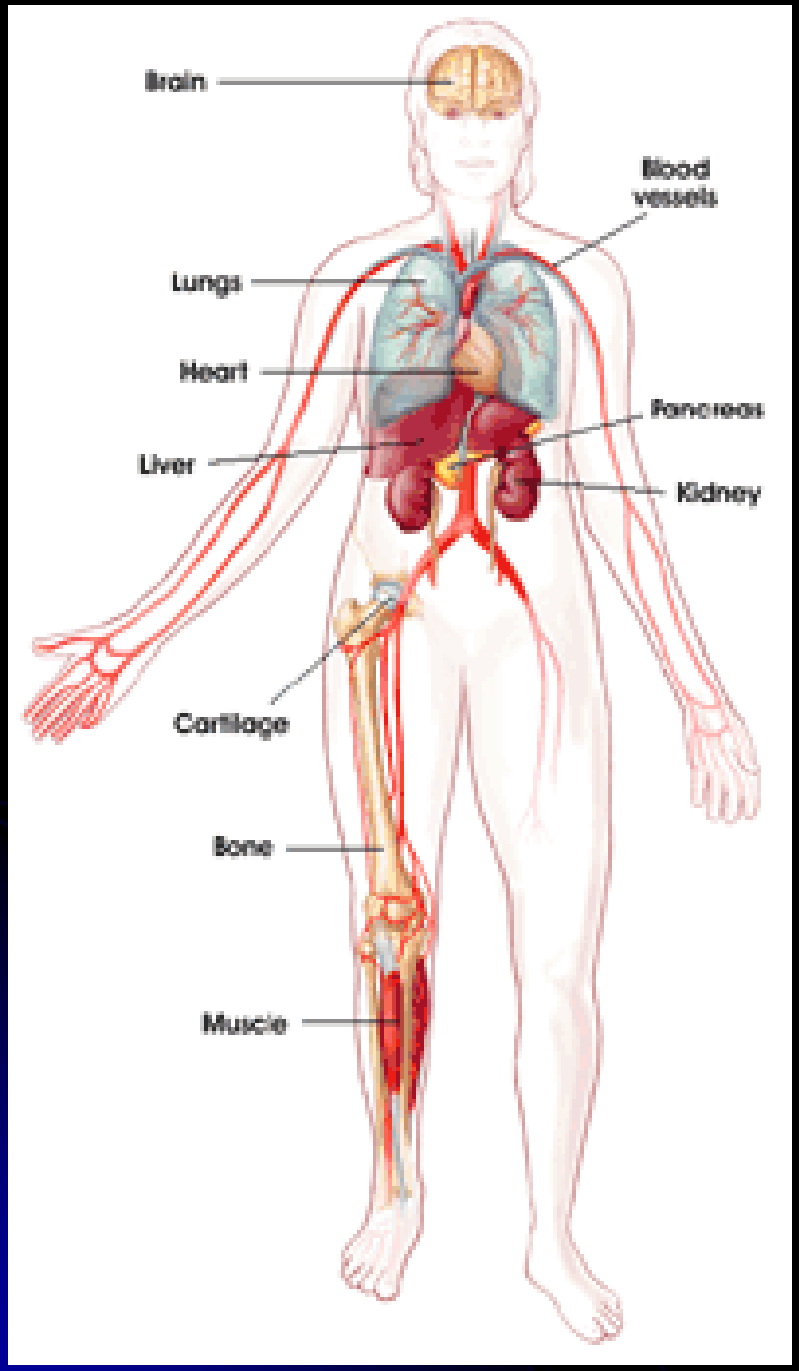
Pharmacologic & Toxicologic Studies

"…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."

IND Regulations [21 CFR 312.23 (a)(8)]

Translation from Preclinical to Early Phase Clinical Trials

- Proof-of-concept [POC] – *in vitro*/*in vivo*
  - Potential mechanism of action [regeneration, paracrine secretion, 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



Potential For Stem Cells :

Repair

Replace

Restore

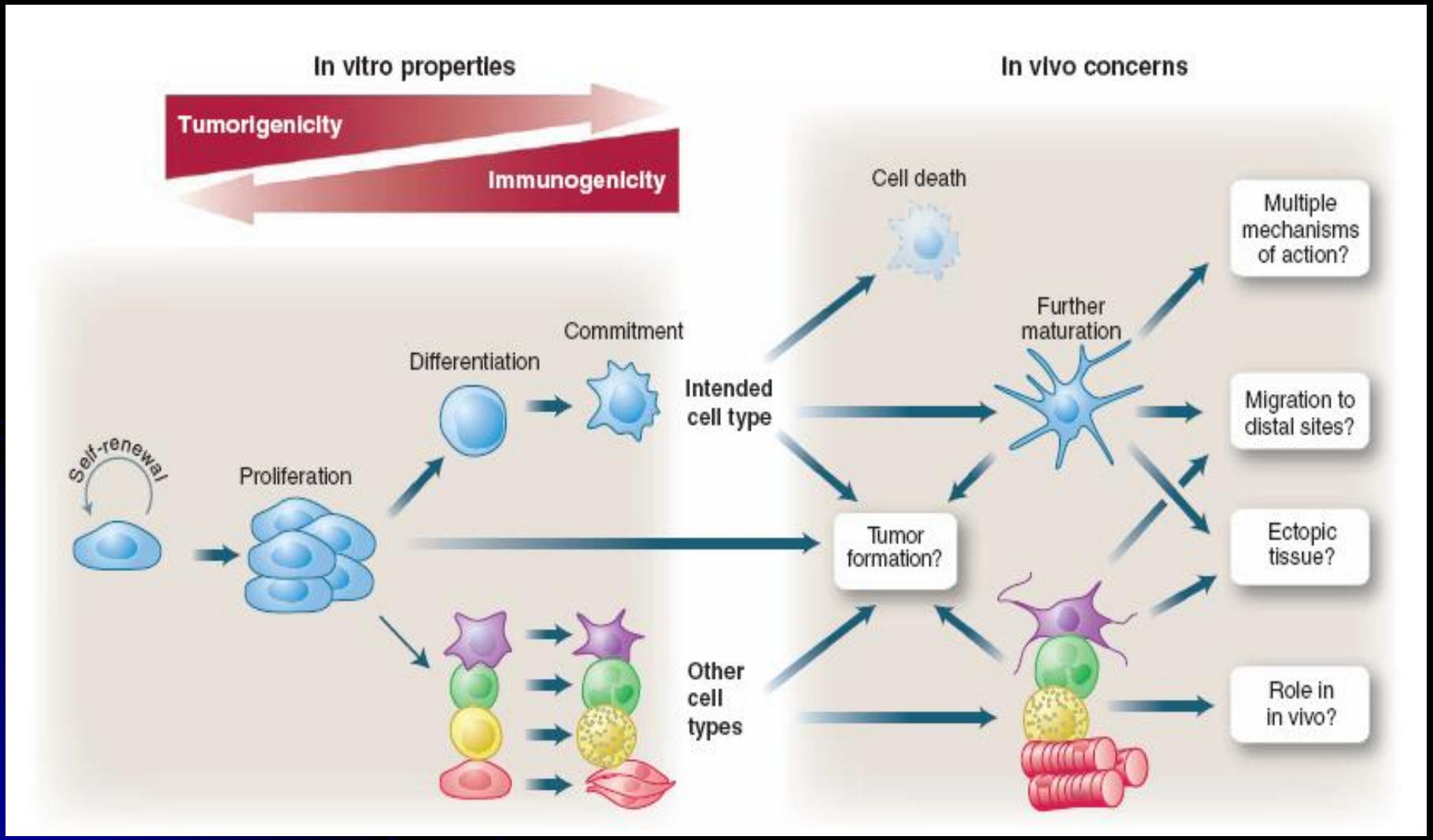
Regenerate

Properties of Stem Cells

- Capable of self-renewing proliferation
- Stem cells may be entirely unspecialized or possess restricted specialization potential; do not have tissue-specific structures or perform specialized functions
- Unspecialized stem cells give rise to specialized cells through differentiation

All of the Above Pose Challenges

Stem Cell Biology – Potential Risks?



D.W. Fink. Science 2009;324: 1662

Potential Safety Concerns for Stem Cell-Based Therapies

- Risks of the delivery procedure
- *Ex vivo* modification (i.e. expansion, genetic modification, encapsulation, scaffold seeding)
- Host response - inflammatory/immune response to the administered cellular product
- Inappropriate cell differentiation (i.e. ectopic tissue formation)
- Cell migration/trafficking to non-target sites
- Uncontrolled cell proliferation or tumor formation
- Interactions with concomitant therapies

[Some] Questions that Should be Asked…

- What cell population(s) will be administered?
  - 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 the intended mode of action of the cells to achieve the desired ‘efficacy’ outcome?
  - Is cell survival/engraftment necessary?... For how long?
  - Do the cells prevent further damage or compensate for what has already been damaged?
  - Do the administered cells replace lost/damaged cells?...do they stimulate endogenous mechanisms of repair?
  - Do the cells secrete growth factors/cytokines?
  - Do the cells act as immunomodulators?

[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 genetically modified?...now a ‘gene therapy’?
- What is/are the biologically responsive animal species for your product?
- Does a relevant animal model(s) of the disease/ injury of interest exist?

[Even Some] More Questions…

- What is the optimal procedure/route/anatomical site for product delivery?
- What is the optimal timing for product administration relative to the onset of the disease/ injury?
- What happens to the cells *in vivo* following delivery?
- Will repeat administration be needed?
- Will immunosuppression be needed?
- What is the risk/benefit ratio for the planned patient population?

Chemistry, Manufacturing & Controls (CMC) Considerations

- Demonstrate capability of manufacturing process to reproducibly generate an investigational cellular product of defined quality intended for commercial distribution:
  - Within and between clinical trials
  - Throughout the entirety of clinical/product development
- CMC Assessments
  - Source Controls
  - Control of Raw Materials Quality
  - Manufacturing Process Controls
  - Detailed Product Characterization

Preclinical Study Design(s)

- Assess pharmacology/POC/cell fate in biologically relevant animal model(s) of disease/injury
- Assess safety/toxicology (T)/cell fate in biologically relevant healthy species and/or model(s) of disease/injury
- Hybrid pharmacology-toxicology study design – POC + T + cell fate in an animal model of disease/injury
- Apply the 3 R'S – **Reduce, Refine, Replace** – in preclinical study designs

Animal Species/Model Considerations

- Predictability of bioactivity & safety profile of the cellular product from animals to humans
  - Comparative anatomy, physiology, age, etc… to humans
  - Microenvironmental niche
  - Route of administration - comparable to clinical
    - Systemic vs. targeted delivery
    - Delivery system/delivery procedure
- Immune response to the clinical (human) product
  - Immune competent animals given immunosuppressive drugs
  - Genetically immunodeficient strains
- Conduct small pilot studies to determine the survival potential of the implanted cells in the animal species before embarking on large, pivotal studies

Animal Species/Models (2)

- Use of a large, non-rodent species
  - Comparative physiology
  - Ability to access the anatomic site for product administration using the intended clinical delivery device
  - Organ/tissue size comparable to human to allow for administration of absolute human dose levels and extrapolation for targeted delivery
- Use of a rodent species
  - Ability to use robust numbers of animals
  - Transgenic or knockout models available
  - Genetically immune deficient rodents available for evaluation of human cells

Animal Models for Evaluating Human Cells

Immunocompromised

- **Pros**
  - Consistency and ease of use
  - Allows certain disease/injury modeling
  - Defined degree of immunodeficiency with various genetic rodent models
- **Cons**
  - Limited to using rodents
  - Not predict immunoreactivity to transplanted cells
  - Physically fragile/susceptible to disease
  - Limited pathology database

Immunosuppressed

- **Pros**
  - Allow use of large animal species
  - Wider array of disease models
- **Cons**
  - Hard to achieve consistent immunosuppression (IS)
  - IS agent might affect transplanted cells
  - Need to discriminate IS toxicity from cell product toxicity
  - Uncertain translation of immunoreactivity from animal (xenoreactivity) to patient (alloreactivity)

Use of Animal Model(s) of Disease/Injury to Assess Safety and Activity

- Advantages
  - Evaluate the safety of the product under local microenvironment & pathophysiology condition
  - Provide insight regarding dose/activity and dose/toxicity relationships
  - Define the risk:benefit ratio of novel, first-in-human products
    - Invasive delivery routes
    - Assumed ‘permanent’ nature of the product
    - Lack of disease exacerbation - activity & safety benefit
  - Identify effectiveness/risk biomarkers that may be applicable for monitoring in the clinical trials
- Limitations
  - Inherent variability
  - A paucity of robust historical/baseline data
  - Technical limitations with the physiological and anatomical constraints
  - Potential need for immunosuppressive agents
  - Animal care issues
  - Ethical issues

What Cells Should be Used in the Preclinical Studies?

- ‘Clinical’ product (human cells)
  - Immune tolerance of the animal(s) to the implanted human cells
    - Immune competent animals given immunosuppressive drugs
    - Genetically immunodeficient strains
  - ‘Immune privileged’ implantation sites/‘immune privileged’ cells
    - Loss of this advantage due to differentiation of implanted cells
    - Loss of this advantage due to the inflammatory disease pathology
- Use of analogous cellular product

Comparability of Cells Delivered to Animals to the Clinical Product

- Manufacturing process of the cellular product used in the preclinical studies should be as similar to the intended clinical product as possible
  - Tissue/sample harvest, cell isolation, expansion, culturing, formulation/scaffold seeding, storage conditions, etc..
- Adequate product characterization
  - Cellular morphology and phenotype
  - Molecular/biochemical markers

Regarding Analogous Cells…

- Uncertainties:
  - Potentially different biological activity(ies) or cell regulation
  - Limited characterization of the animal cells due to lack of reagents
  - Potentially different impurities/contaminants
- Comparability between animal & human cells necessary to understand the safety of the proposed cell therapy

Cell Implantation Modalities: Encapsulation

- Capsule
  - Device biocompatibility tests
  - *In vitro*/*in vivo* chemical/mechanical durability & strength
  - Permeability to oxygen & nutrients
  - Immunoprotection for cells/for host
- Cells - dose, cell growth, cell function, cell-capsule interaction
- Safety assessment of encapsulated cells
  - Use the intended clinical capsule
  - Use identical encapsulation procedure as proposed clinically

Cell Implantation Modalities: Scaffolds

- Scaffold material selection – biocompatibility testing
- Scaffold design - resorbable/permament/2D-3D
  - Structure & biomaterial decomposition products
- Cell seeding – ‘dose’, cell growth, cell function, cell-scaffold interaction
- Safety assessment of cell-scaffold clinical product
  - Use the intended clinical scaffold & cell seeding procedure
  - Biochemical. morphological, functional analysis
  - Durability of repair
  - Construct biodegradation profile *in vivo*

Pharmacology/POC Studies

- *In vitro* / *ex vivo* activity/mechanism of action
  - Neurotrophic activity (nerve cells) - protection of neuron from cell death/differentiation into neurons
  - 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 scaffold?
  - Optimize ROA/cell administration procedure
  - Optimize timing of cell administration
  - Identification of non-terminal biomarkers/activity endpoints

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/injection 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 (2)

- Adequate numbers of animals/group to ensure statistically & biologically robust interpretation
- Sufficient study duration and multiple time points - depending on the biology of the product - 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
  - Cell fate

Preclinical Study Design: Specifics (3)

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

Preclinical Study Design: Specifics (4)

- Product-dependent endpoints
  - Inflammatory/immune response
  - Scar formation
  - Tumorigenicity
- Disease-dependent endpoints
  - Functional outcomes (cardiac, neurological, ophthalmic, etc…)
  - Biochemical and morphological parameters
- Cell fate following administration
  - Survival/engraftment
  - Integration (anatomical/functional)
  - Differentiation/phenotype expression
  - Transdifferentiation/de-differentiation, fusion
  - Migration/trafficking
  - Potential for ectopic tissue formation
  - Proliferation

Tumorigenic Potential

- Tumorigenic potential - hyperplastic or unregulated growth is a safety concern:
  - What is the cell source?
  - What is proliferation & self-renewing capacity ('stemness') of the cellular product?
  - What is the extent of *ex vivo* manipulation?
    - Genetically modified – transgene concern?
    - Genetically modified – vector concern?
  - Where is the site of implantation?
  - What patient population is targeted?
  - What immunosuppressive agents are administered to support cell engraftment?

Tumorigenic Potential

- Test the intended clinical product
  - Intended ROA/site of implantation
  - Controls – sensitivity of the test, 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?)

Transitioning to a Clinical Trial

Regulatory Issues for Clinical Trials

- Does the submission contain sufficient information to assess risks to the subjects in the proposed trial?
  - Are source materials, manufacturing process, and final product sufficiently characterized to provide adequate assurance of safety?
  - Were adequate preclinical studies performed?
  - Were data submitted in sufficient detail to conduct an independent review?
  - Does the design of the clinical trial contain adequate safeguards for subject safety?
  - Is the design of the clinical trial adequate to achieve stated aim?
- If sufficient data are present, are the risks to human subjects unreasonable?

Assessment of Safety/Activity

Early Communication with CBER/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 exchange'
- PreIND meetings
  - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  - Summary data and sound scientific principles to support use of a specific product in a specific patient population

Resource Information…

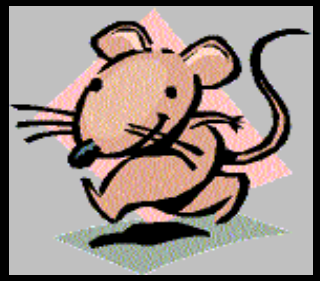
- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy IND Applications http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Xenotransplantation/ucm092705.pdf
- ICH Documents http://www.fda.gov/cber/guidelines.htm
- CBER/FDA Biological Response Modifiers Advisory Committee Mtg:

  Human Stem Cells as Cellular Replacement Therapies for Neurological Disorders (July 13-14, 2000)

  Transcript Available at: http://www.fda.gov/ohrms/dockets/ac/cber00.htm#Biological%20Response%20Modifiers%20Advisory%20Committee
- CBER/FDA Cellular, Tissue and Gene Therapies Advisory Committee Mtg:

  "Cellular Therapies Derived from Human Embryonic Stem Cells: Scientific Considerations for Pre-Clinical Safety Testing." (April 10-11, 2008)
  Transcript Available at: http://www.fda.gov/ohrms/dockets/ac/cber08.html#CellularTissueGeneTherapies
- DW Fink, Jr., and Bauer, SR. "Stem Cell-based Therapies: FDA Product and Preclinical Considerations." In The Essentials of Stem Cell Biology (Second Edition). Ed. R Lanza, J Gearhart, B Hogan, D Melton, R Pedersen, J Thomson, E Thomas and I Wilmut; Elsevier Academic Press: Burlington, MA, pp. 619-630, 2009

Contact Information



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Thanks!