Cellular Therapy Products and Immune Rejection: Preclinical Perspective

CIRM Webinar: Immune Response in Stem Cell-based Therapy

September 27, 2012

FDA/CBER/OCTGT/DCEPT/PTB

Theresa Chen, Ph.D.

Overview

- Types of Cellular Therapy Products
- Safety Concerns
- Preclinical Considerations
- Immune Rejection
- Needs and Challenges

Cellular Therapy Products

- Stem/Progenitor cells
  - hESC and iPS derived cell products (e.g., neural progenitor cells, retinal pigment epithelial cells, insulin-producing cells)
  - Fetal, perinatal tissue derived cell products
  - Adult stem cells - mesenchymal stem cells (MSCs), hematopoietic stem cells
- Mature fully differentiated cells (e.g., hepatocytes, chondrocytes, islet cells)
- Different donor sources - autologous, allogeneic, xenogeneic

Cellular Therapy Products (cont)

- Mechanism of action
  - Repair, replace, or restore injured/diseased tissue
  - Secretion of growth factors or use intercellular signaling and interactions to induce host tissue regeneration
  - Immunomodulatory
- Desired duration of cell survival/engraftment (dependent on the mechanism of action)
  - Short term
  - Long term

Cellular Therapy Products (cont)

- Systemic administration or direct administration into a target anatomic site
- Single or multiple administrations
- Can be administered in combination with a device component
  - Catheter
  - Scaffold
  - Encapsulation (may protect against immune rejection)

Potential Safety Concerns for Cellular Therapy Products

- Uncontrolled proliferation (e.g., hypercellularity, tumor/mass formation)
- Inappropriate differentiation (e.g., ectopic tissue formation, teratoma)
- Distribution to non-target sites
- Undesirable host response (e.g., inflammatory/ immune response, allodynia)
- Delivery/surgical procedure-related risks
- Adverse interactions with concomitant therapies (e.g., immunosuppressive agents)

What Regulations Govern the Conduct of Preclinical Studies?

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

"…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, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations."

Goals of Preclinical Studies

- Discern mechanism of action/toxicity of the product
- Provide rationale for the proposed therapy, (e.g., feasibility, bioactivity, potential benefit)
- Recommend a safe starting clinical dose level and dose-escalation scheme
- Support patient eligibility criteria
- Support clinical monitoring plan (e.g., safety and activity parameters, staggering intervals, follow-up intervals)

Risk:Benefit

Preclinical Expectations for Early-Phase Clinical Trials

- Provide scientific rationale/'Proof-of-concept' (POC) for conducting clinical trial
  - Establish pharmacologically effective dose(s) and minimal effective dose
  - Select optimal route of administration and dosing regimen
- Determine distribution of administered cellular therapy product in target and non-target tissues

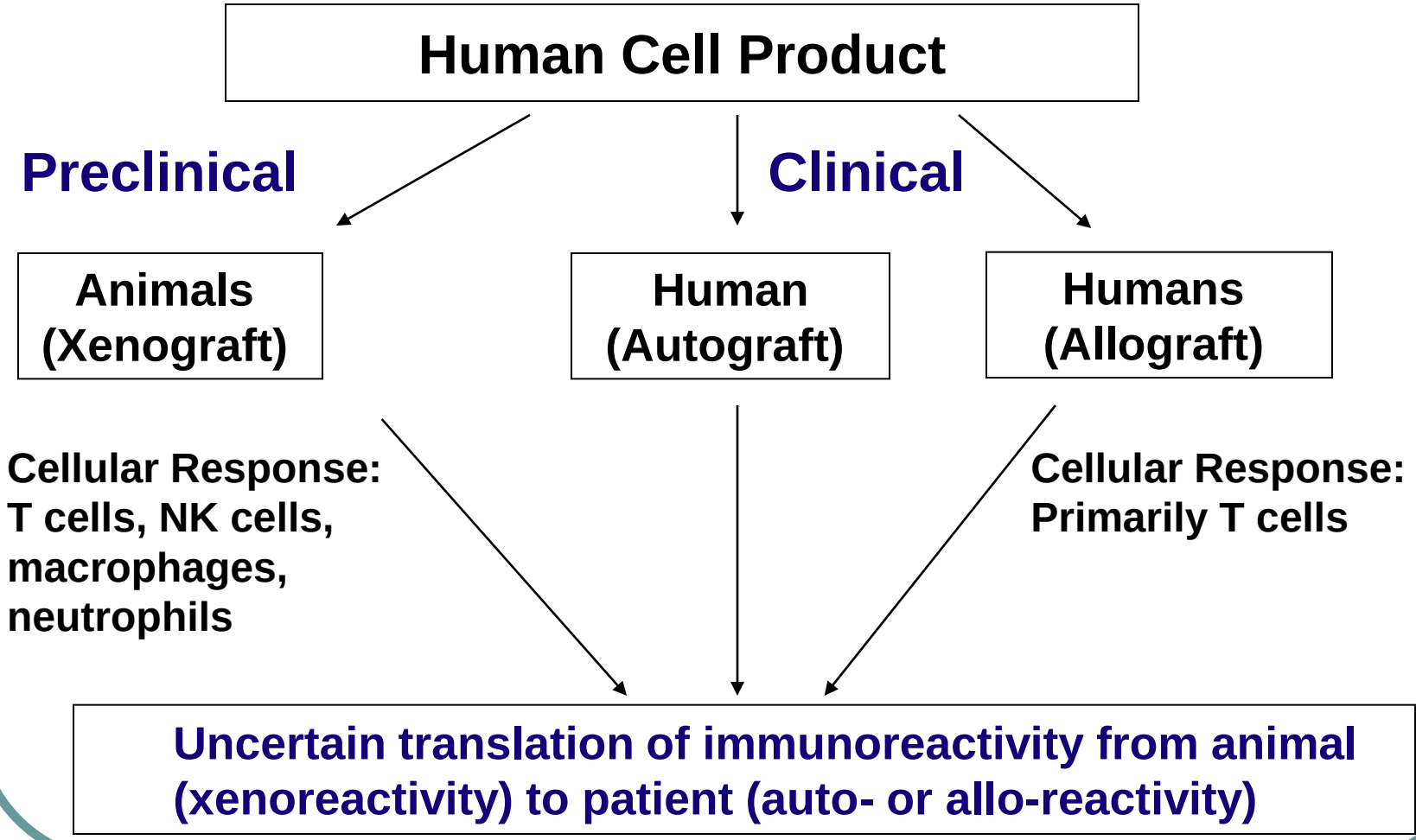
Preclinical Expectations (cont)

- Perform preliminary safety assessment
  - Determine a No-Observed-Adverse-Effect Level (NOAEL)
  - Characterize adverse findings following product administration
    - Local or systemic effects
    - Acute, delayed, or persistent findings
    - Identify target tissue(s) of toxicity

Preclinical Assessment

- Should mimic the proposed clinical study
  - Use product comparable to the intended clinical product
    - Human cellular product
    - Analogous animal cells
  - Biologically relevant animal species/model
  - Clinically relevant site of administration
  - Clinically relevant delivery device/procedure
- Sufficient study duration for safety and bioactivity assessment

Challenges of Immune Rejection – Translation



Immune Rejection: 'Solutions'?

- The implanted cell product needs to survive in the animal for a sufficient duration to allow for safety/bioactivity assessment
- Immune rejection of the implanted cells can be partially overcome by
  - Use of immunosuppressive (IS)/immunotolerance (IT) inducing agents in immunocompetent animals
  - Use of genetically immune deficient animals (e.g., NOD mice, NSG mice, nude rats)
  - Use of immunoprotective devices
  - Administration to possible immune-privileged sites
  - Use of analogous animal product

**Graft failure may not always be immune-related, such as with cell senescence

Immune Rejection: 'Solutions'? (cont)

Immunocompetent animals given IS/IT-inducing agents

Pros

- May allow the use of large animal species
  - Comparative physiology to human
  - Similar anatomy to human
  - Able to use clinically relevant delivery system/delivery procedure

Cons

- Need to identify IS/IT regimen that prevents/mitigates immune rejection of xenograft
- Uncertain engraftment of human cells
- Effect of IS on administered cells
- IS/IT-related toxicity may compromise the study

Immune Rejection: 'Solutions' (cont)

Genetically immune-deficient animals

Pros

- Better defined degree of immunodeficiency
- No IS toxicity concerns

Cons

- Often limited to rodents
- Limited life span of animals
- Relevant pathophysiology/disease condition may be lacking
- Physically fragile/susceptible to disease
- Limited pathology database

Needs & Challenges...

- IS and/or IT regimen that can be used to prevent/mitigate immune rejection of the implanted cell product in immunocompetent biologically relevant animal species and/or animal models
  - What are the currently available IS and IT regimens that can be used to address these concerns?
  - What are the currently available methods that can be used to circumvent immune rejection in animals and/or in humans (with acceptable risk/benefit profile)?
  - What level of IS or IT is needed in animals to prevent or mitigate immune rejection of the implanted human cells?

Needs & Challenges (cont)...

- Appropriate animal models to study clinically relevant immune response profile to the implanted human cells (e.g., humanized mice)
- Information to support the proposed clinical IS or IT therapies/regimens
  - Rationale
  - Dosing regimen and duration
- Improved immunoprotective devices that are engineered to be:
  - Safe and biocompatible (to the human cells and to the animal and human hosts)
  - Allow for adequate cell survival/factor secretion in animals and humans
- Others…

Needs & Challenges (cont)...

To what extent will the data generated from the animals translate to ‘prediction’ of safety and efficacy in the patient population?

Early Communication with OCTGT

- Pre-preIND interactions for novel products
  - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (Pharm/Tox and CMC) and the sponsor
- PreIND meetings
  - Formal scientific discussions with CMC, preclinical, and clinical review disciplines
  - Sponsor should provide summary data and sound scientific principles to support use of a specific product in a specific patient population and study design

OCTGT Regulatory Resources

- OCTGT Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- General information for OCTGT and related regulatory references
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Guidance Documents for Cell and Gene Therapies
  http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm

Contact Information for CBER / OCTGT

Theresa Chen, Ph.D.

Theresa.chen@fda.hhs.gov

301-827-9072

Regulatory Questions:

Contact the Regulatory Management Staff in OCTGT at: CBEROCTGTRMS@fda.hhs.gov or Lori.Tull@fda.hhs.gov or by calling (301) 827-6536

Public Access to CBER

CBER website:
http://www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)
Email: ocod@fda.hhs.gov
Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch (MATTB)
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