

Unique Issues Associated with Stem Cell Therapeutics

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NAS Symposium on Translation of Stem Cells into Clinical
Stem Cell Therapeutics

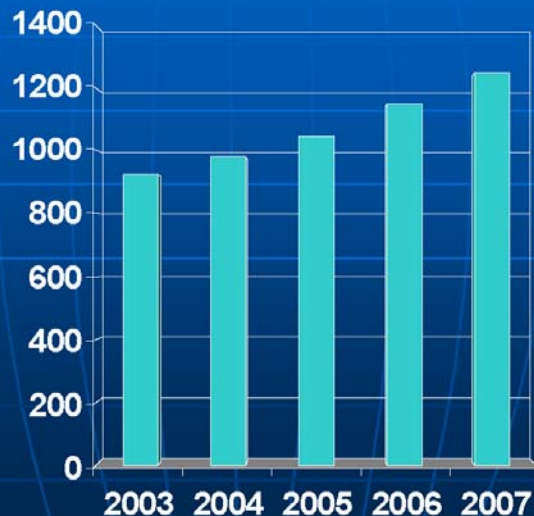
Washington, DC 20-November 2008

Outline

- What's unique and not unique with stem cell therapeutics
- The roles of in vitro and in vivo characterization in mitigating potential risks unique to stem cell therapeutics
- Addressing unique stem issues in context of clinical trials
- Summary

What's not Unique about Stem Cell Therapeutics

Total Active Files in OCTGT
(IND, IDE, MF) FY 2003-2007



C. Witten – CBER/OCTGT
ISCT SCT Mtg., September 2008

- Significant broad experience at FDA with variety of cell-based therapies
 - Lessons learned
- Many stem cell therapies in clinical trials
 - Hematopoietic
 - MSCs
 - Number of others

What's Unique about Stem Cell Therapeutics?

□ Some examples:

- In vitro expansion potential
- In vitro differentiation potential
- In vivo differentiation potential
- Persistence potential
- Donor genetic/medical history might be clinically relevant to recipients

Development of Safe & Effective Stem Cell Therapeutic Products

- Characterize the cell product in vitro
 - Starting materials
 - During differentiation
 - Final product composition
- Evaluate cell product in vivo in appropriate animal model
 - Efficacy
 - Pharmacology
 - Toxicity
 - Tumorigenicity
 - Biodistribution
- Test stem cell therapeutics in clinical trials
 - Safety
 - Efficacy

REMINDER

Must balance need for safety against need for efficacy

What's Unique about Stem Cell Therapeutics – Product Characterization

□ Some examples:

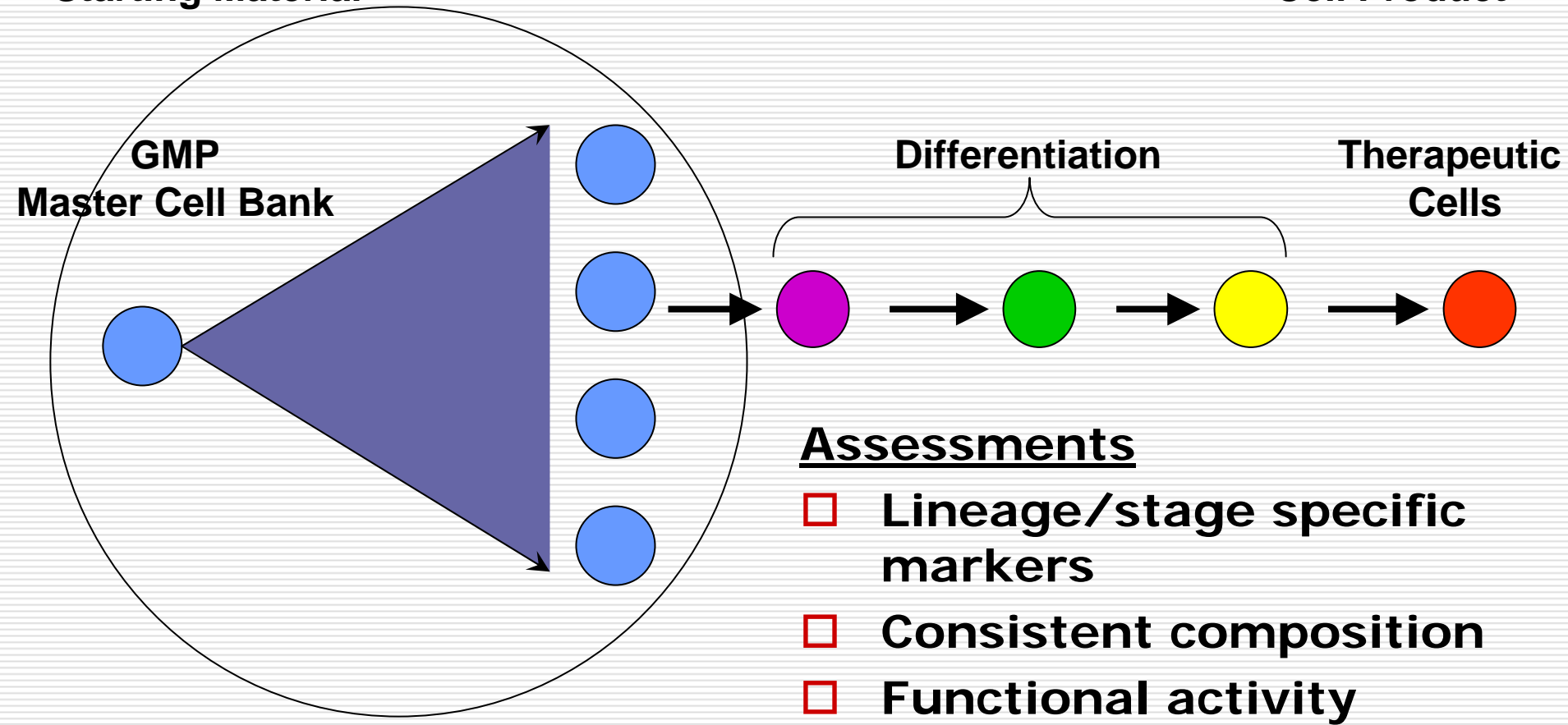
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In Vitro Characterization of Starting Materials

- Stem cell markers
 - Undifferentiated cells
 - Potency
 - Ability to form the three germ layers
 - Genetic fingerprint
 - Identity
 - Authentication
 - Disease markers
 - Relevant to intended clinical application
 - Cancer
 - Karyotyping
 - Normal complement
 - XX or XY
 - Genetic stability over time
- Quality
- Safety

In Vitro Characterization of Stem Cell Differentiation Process

Starting Material  Cell Product



Assessments

- Lineage/stage specific markers
- Consistent composition
- Functional activity
- Stable karyotype

In Vitro Characterization of Therapeutic Cell Product

- Sterility, Mycoplasma, Endotoxin
- Identity
- Purity (composition)
 - Therapeutic cells
 - Accessory cells
 - Undifferentiated cells
 - Process residuals
- Potency
- Stability



In vitro Characterization Challenges

- Multiple markers required
 - Different markers at start, middle and end
- Availability of specific antibodies and lineage specific markers
 - FACS, IHC
- Potency Assays
 - Predictive of clinical outcome
- Linearity, specificity and sensitivity of assays

What's Unique about Stem Cell Therapeutics? – Preclinical Assessments

□ Some examples:

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Desirable or Undesirable attributes of Stem Cell Therapeutics?



- Migration
- Differentiation
- Integration into host physiology
- Functional activity
- Persistence

In vivo Stem Cell Therapeutic Characterization

- Efficacy
 - Relevant animal model of disease
 - Provides rationale for proposed clinical studies
- Pharmacology
 - In vivo survival
 - In vivo activity
- Biodistribution
 - Migration to sites distal to implant
- Toxicity
 - Local
 - Systemic
- Tumorigenicity
 - Teratoma
 - Ectopic tissue formation

Difficult to correlate findings in animals to humans due to limitations

What's Unique about Stem Cell Therapeutics – Clinical Aspects

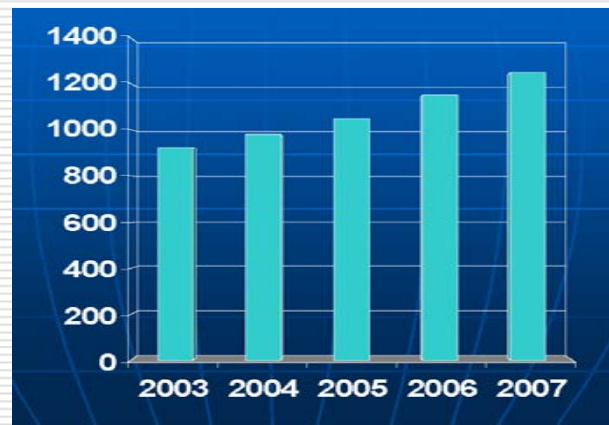
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Patient monitoring for specific concerns – Some Thoughts

- Persistence, in vivo differentiation
 - Deliberate Chimerism
 - Biopsy
 - Metabolic markers deficient in recipients, restored by therapy
 - Restoration of function, behavioral, QOL
- Genetic risks, aberrant tissue formation
 - Donor history; testing of cells for disease markers
 - Testing of recipients at baseline and post-therapy
 - Genetic fingerprint of cells in patient's medical record

Patient Populations for Early Trials of Stem Cell Therapeutics



Cell & Gene Therapy
INDs –FDA/CBER

- ❑ Stem cell therapeutics more similar than different to most cell therapies
- ❑ First in human studies with novel therapies typically with populations failed standard therapies or for which no good therapy exists
- ❑ Stem cell specific concerns are additive to usual safety concerns; must assess risks preclinically and via patient monitoring

Suitability of Stem Cell Therapeutics for Clinical Use



- ❑ Requires global assessment based on:
 - Clinical indication, patient population, implant site, trial design
 - Data from preclinical efficacy & safety
 - Specific product characteristics
- ❑ Approaches to mitigate potential risks

Wish List

- Move away from 'case by case' approach to more general principles
- Preclinical guidance from FDA
- Clinical safety guidelines
- Development of more predictive animal models
 - Disease
 - Safety (tumorigenicity)
- Better characterization tools
 - Robust, sensitive; in vitro & in vivo

Summary

- ❑ Greater emphasis on characterization of stem cell therapeutics is needed to assess quality and safety concerns
- ❑ Despite limitations data from animal models of efficacy and safety are required
- ❑ An integrated approach to risks from stem cell therapies is needed
- ❑ Emphasis on 'safety' must be balanced against need for efficacy

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