Human Embryonic Stem Cells: Considerations for Therapeutic Product Development

Jane Lebkowski Ph.D.
Geron Corporation

EMA Stem Cell Workshop
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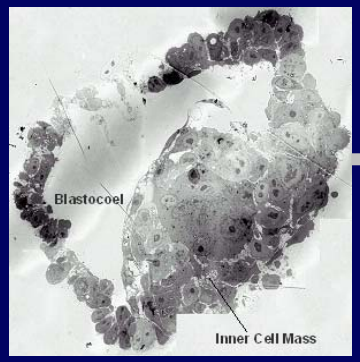
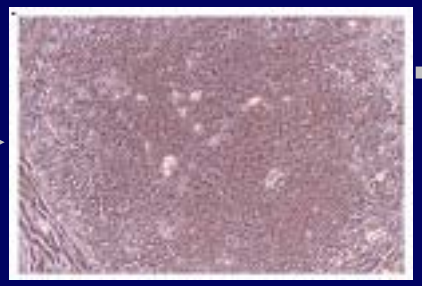
Human Embryonic Stem Cells

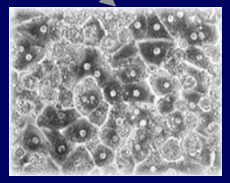


Blastocyst

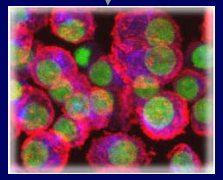


Human Embryonic Stem Cells

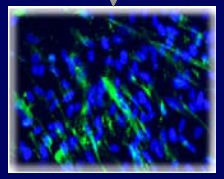
Large Characterized cGMP Banks



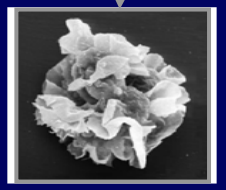
Hepatocytes



Chondrocytes

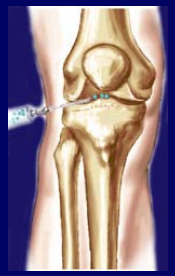


Osteoblasts

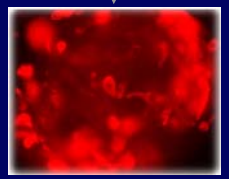


Dendritic Cells

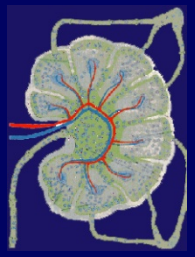
Drug Discovery
Liver Failure



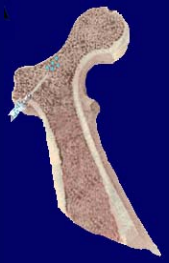
Arthritis



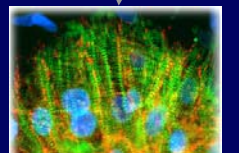
Islets



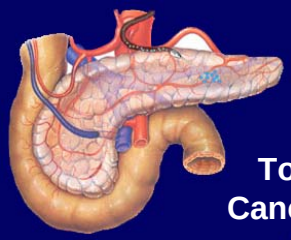
Tolerance Induction
Cancer Immunotherapy



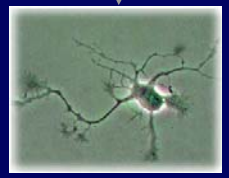
Osteoporosis
And Bone
Fractures



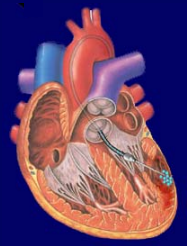
Cardiomyocytes



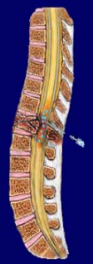
Diabetes



Neural Cells



Heart Failure



Spinal Cord
Injury

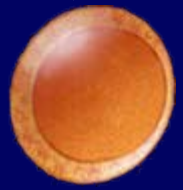
Therapeutic Cells

hESC-Based Cell Therapy Distribution Scheme

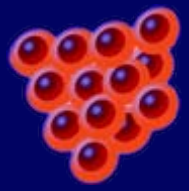
Central Manufacturing Facility

Frozen
Final Product

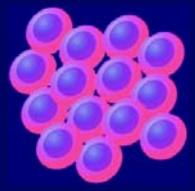
Hospital



hESC
Starting
Material

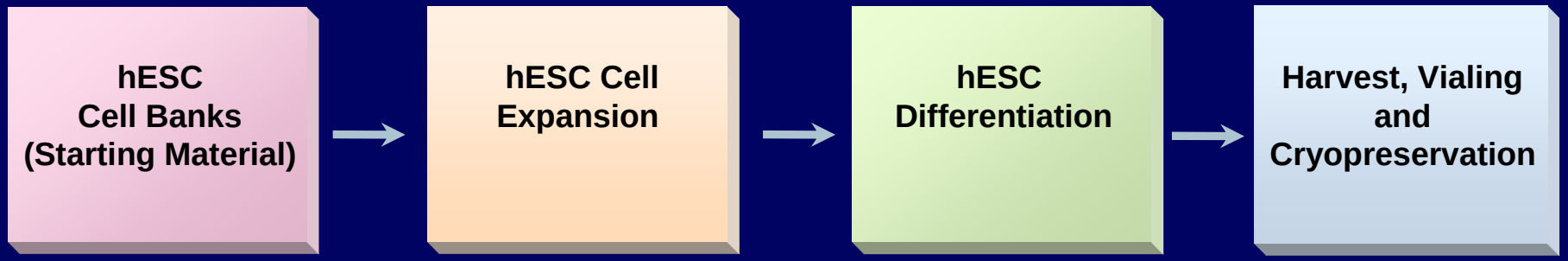


Differentiation



Formulation for
Transplantation

Production Process for hESC Therapeutics



Critical Technology Enabling Therapeutic Development of hESC Products

Culture & Differentiation

Scalable cGMP Production

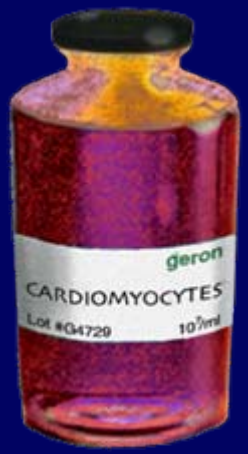
Cryopreserved Formulations

Preclinical Efficacy

Preclinical Safety

Delivery

Clinical Development



Qualification of hESC Lines for Cell Therapy Production

No Evidence Of:

- × Mycoplasma
- × HIV 1 &2
- × HTLV I/II
- × CMV
- × HBV or HCV
- × HHV-6
- × EBV
- × Parvovirus B-19
- × Mouse Adventitious Agents
- × Porcine Adventitious Agents
- × Rabbit Adventitious Agents
- × Eco-, Xeno- or Amphotropic Retroviruses
- × Adventitious Agents Detected In Vitro & In Vivo PTC Assays

- ✓ History Files
- ✓ Adventitious Agents
- ✓ Karotype
- ✓ Phenotype
- ✓ Performance

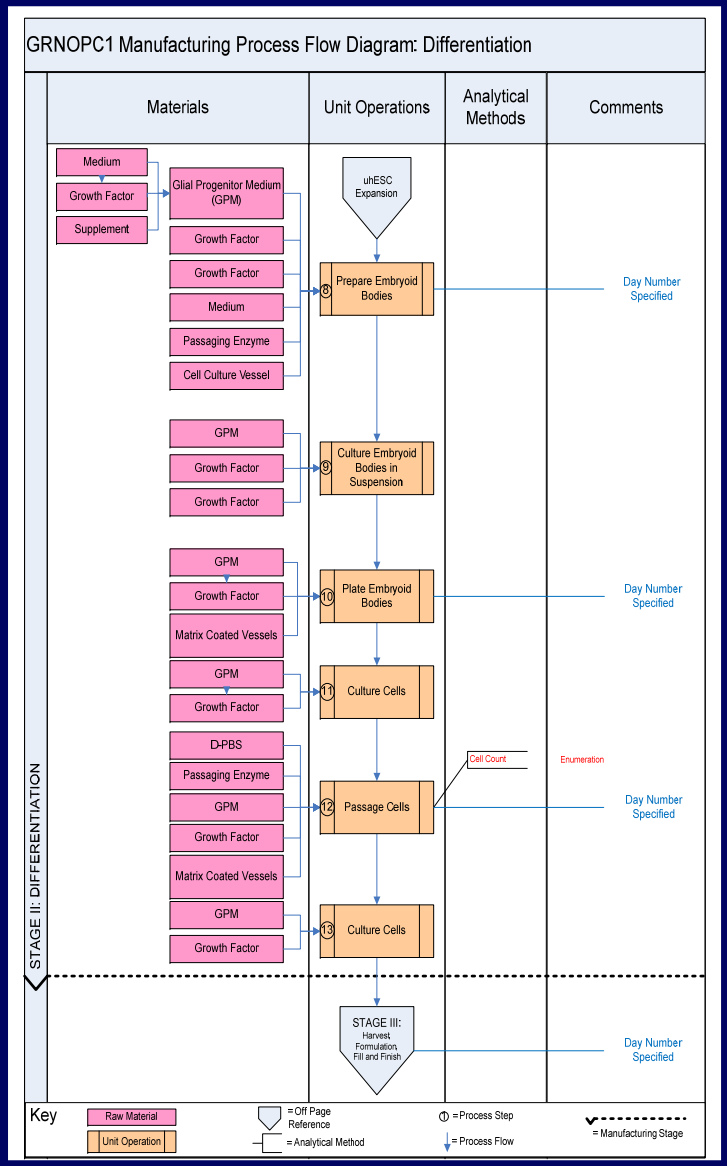
hESC Cell Therapy Production Process

Requires Rigorous Detailed Development of Production Process

Considerations/Challenges

- **Characterization of Materials**
  - **Starting Material**
  - **Reagent Performance**
- **Characterization of Unit Operations**
  - **Cell Density**
  - **Culture Format**
  - **Scale**
  - **Timing of Induction**
- **Stability of Storage Conditions**

Example for GRNOPC1



Characterization of hESC-Based Therapeutics

Attributes

- Identity
- Purity
- Strength
- Potency

Challenges

- Multiple Markers Required
- Lineage Specific Markers
- Marker Specificity
- Antibody Specificity
- Detection and Quantitation Limits of Assays
- Potency Assays

Example for GRNOPC1

Lineage	Marker
Neural Progenitors	Nestin
Oligodendroglial Progenitors	Olig 1
Oligodendroglial Progenitors	NG2
Oligodendroglial Progenitors	PDGFRa
Early Ectoderm	Pax 6
Early Ectoderm	Sox 10
Neurons	βTubIII
Astrocytes	GFAP
Early Endoderm	HNF3β
Endoderm	AFP
Early Mesoderm	GATA4
Mesoderm	MSA
Undifferentiated hESCs	OCT4
Undifferentiated hESCs	Tra-1-60

Considerations for Nonclinical Studies for hESC-Based Therapeutics

Final Product:

- What is the Product Designed to Do?
- What is the Target Site for Activity?

Formulation:

- Cryopreserved Format?
- Selective Cell Survival?
- Cellular Debris?

Clinical Administration:

- Site of Administration?
- Dose Required?
- Effects on Performance and Potential Adverse Events?
- Need for Immunosuppression?

Activity & Efficacy of the hESC-Based Therapies

Considerations/Challenges

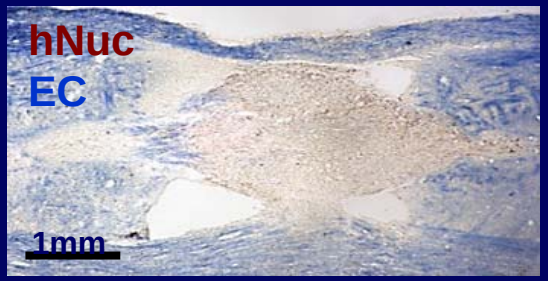
In Vitro Activity

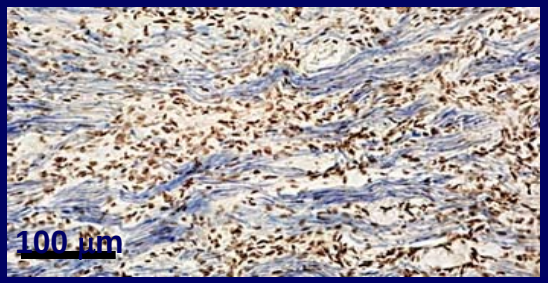
- Protein and Gene Expression
- Factor Production
- Structural/ Metabolic Activity

In Vivo Activity

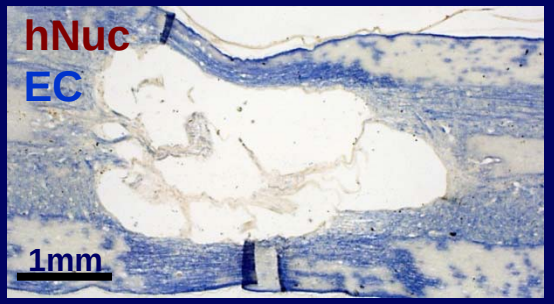
- Delivery Site and Method
- Cell Survival
- Immune Responses
- Phenotype Over Time
- Proliferative Capacity
- Clinical Efficacy
- Histological Efficacy
- Dose Requirements
- Human Equivalent Dose
- Timing of Treatment

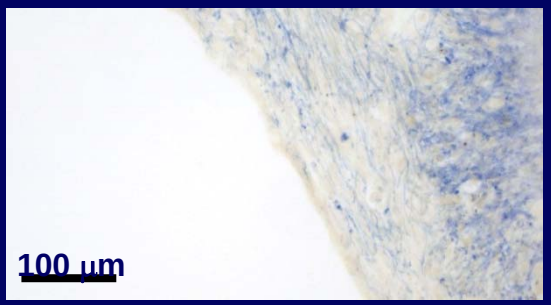
9 mos GRNOPC1





9 mos vehicle





Biodistributuion: Where Do The Cells Go?

Safety and Efficacy Implications

- **Site for Intended Activity**
- **Sufficient Cells at Site**
- **Distribution Outside Target Site**
- **Migration at Local Site**
- **Over Extended Time**
- **QPCR & Histological Methods**

Example for GRNOPC1

- Not Detected Outside of CNS
- Not Detected in the Brain
- Greatest Concentration at the Injection, Injury Site
- Migrates Up to 5 cm from the Injury Site
- Migration Not Dependent on Dose
- Migration Dependent on Time
- No Evidence of Migration Beyond 9 Mos

Toxicology Studies

Considerations/Challenges

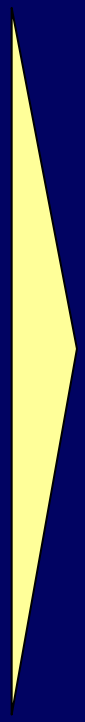
- Doses of Product
- Tox Model
- Feasibility of Model
- Duration of Studies
- Duration of Human Cell Survival

Example GRNOPC1

- Toxicity of Delivery
- Animal Survival
- Clinical Observations
- Systemic Toxicity
- Hematological
- Coagulation Parameters
- Clinical Chemistries
- Macropathology
- Micropathology
- Allodynia

Tumorigenicity Studies

- Teratomas
- Ectopic Tissues
- Local Injection Site
- Distal Sites



Challenges

- Human Dose
- Long-Term Cell Survival
- Large Numbers of Animals
- Mimic Human Setting
- Large Animals?
- Homologous ESC Systems?

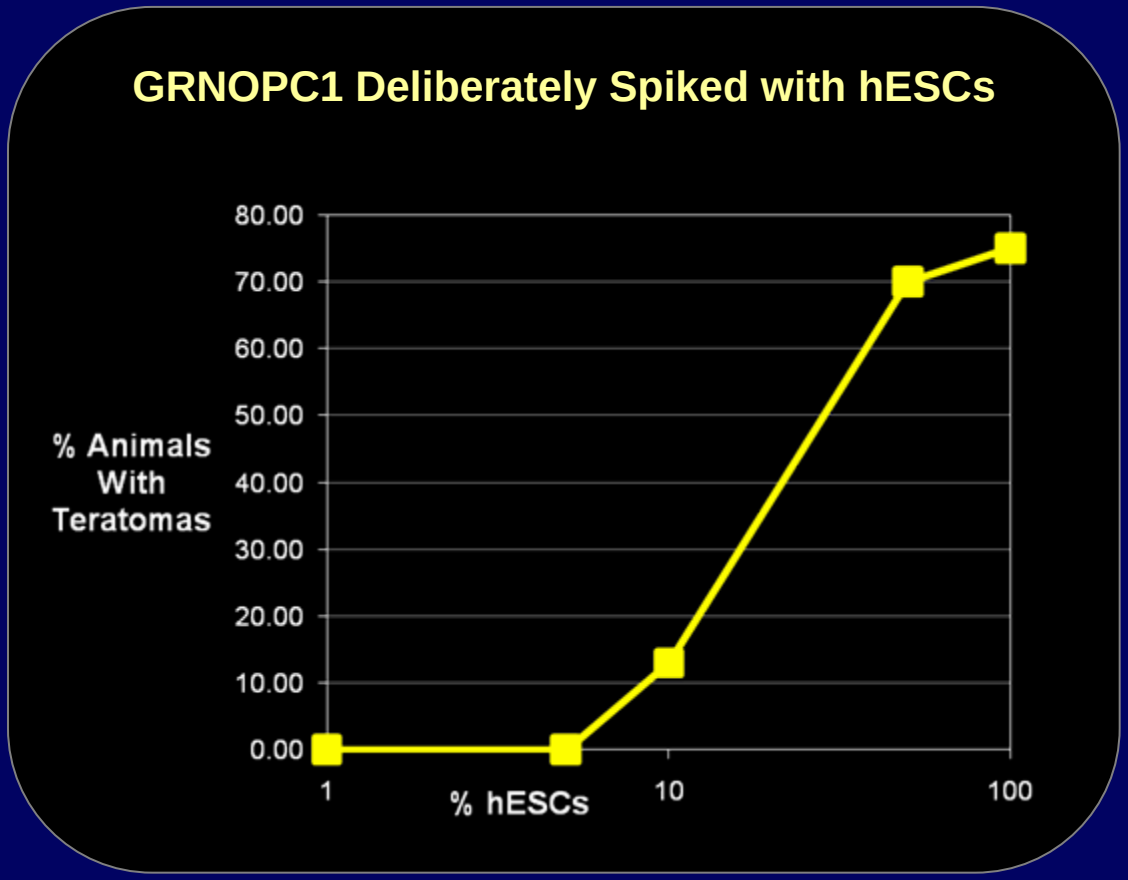
Considerations

- Location of Ectopic Tissue
- Clinical Consequences
- Treatment Strategies

Tumorigenicity Studies

Important Factors In Teratoma Formation

- **hESCs Cell Number**
- **Site of Implantation**
- **Cell Aggregation State**



2 x 10^6 Cells
Intraspinal Cord Injection
Assessment 12 mos.

Allogenicity Studies

- Immunosuppression Required?
- Duration of Immunosuppression?

Challenges

- hESC-Based Products are Xenografts in All Animal Models
- Allogenicity of Maturing Cells In Vivo
- Humanized Models
- Tracking of Surviving Cells in Clinical Trial Subjects

No Excellent Solutions

- Allogenicity In Vitro
- Utilize Immunosuppression Regimens Compatible with Human Clinical Indication
- Monitor Outcomes

Design of Clinical Trials
Key Consideration: Patient Safety & Risk Mitigation

Multidisciplinary Team of Physicians, Ethicists, Regulatory Bodies, Patients Advocates, etc to Develop Clinical Protocol Based on Potential Risks and Benefits of the Therapy

- Protocol
- Delivery
- Logistics of Trial
- Minimize Potential Risks
- Define Adverse Events
- Monitor for Adverse Events
- Monitor Cell Survival
- Assess Outcome Measures
- Short & Long-Term Follow-up

Risk Mitigation

- Frequent & Long-term Monitoring for Ectopic Tissue/Masses
- Real-time Review of Adverse Events
- Independent DMC
- Follow-up of AEs
- Suspension Rules
- Treatment Strategies if AEs Related to Product Occur

Conclusions

- Numerous Considerations in Developing Cell Therapies
- Some Challenges Common To All Cell Therapies
- Some Challenges More Specific to hESC-Based Therapies
- Some Challenges Vary in Importance Depending on Clinical Indication
- Specific Nonclinical Study Designs Based on Clinical Considerations
- Clinical Trial Designs Require Interdisciplinary Input
- Risk Mitigation Strategy Required