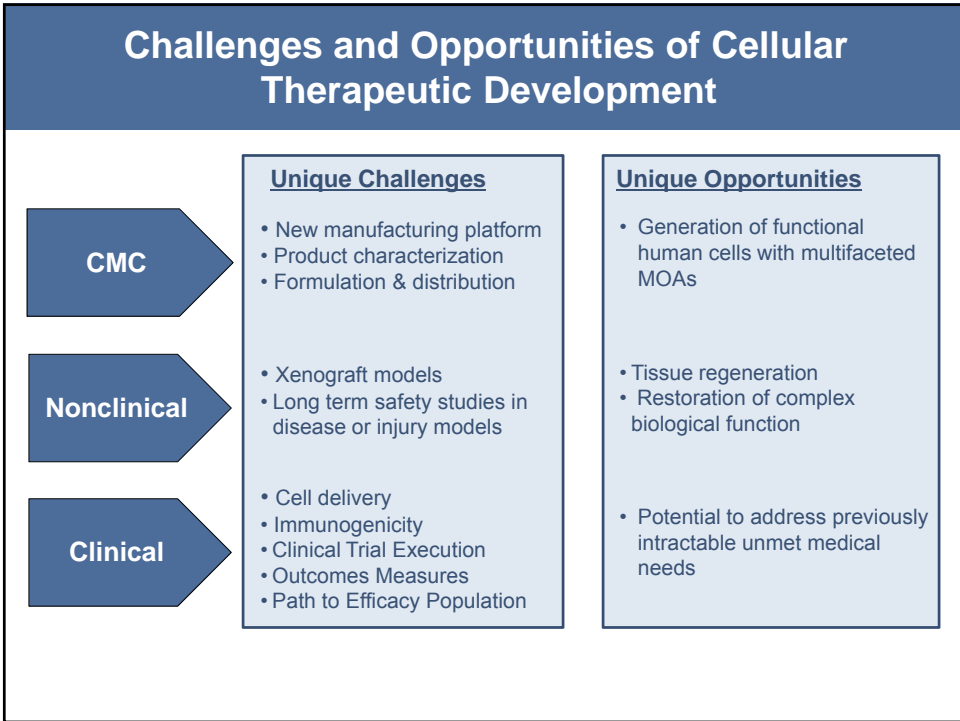


**Case Study:**  
**Human Embryonic Stem Cell Based Therapy for SCI: Challenges for Entry and Execution of Phase 1 Clinical Trials**

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NHLBI-PACT Workshop Sept 15, 2011



## GRNOPC1: Oligodendrocyte Progenitor Cells

- Cryopreserved Allogeneic Cell Population
- Derived from Human Embryonic Stem Cells
- Characterized Composition of Cells
- Contain Oligodendrocyte Progenitor Cells
- Produces Neurotrophic Factors
- Induces Myelination of Denuded Axons



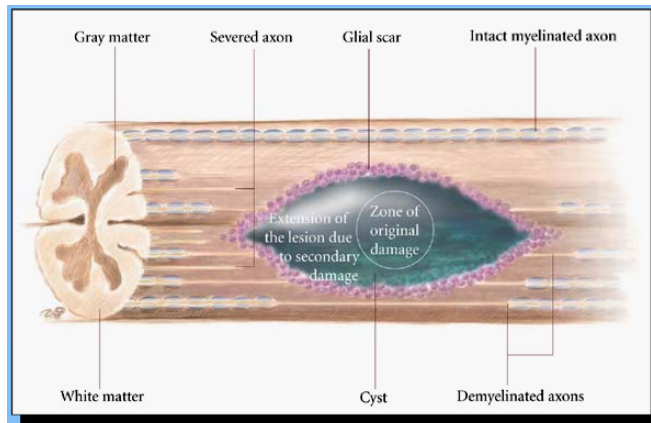
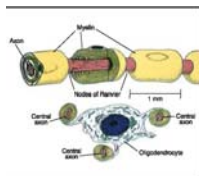
### Intended Application

- "Off-the-Shelf" Product
- Spinal Cord Injury
- Other CNS Disorders

## Spinal Cord Injury: Pathology at the Lesion



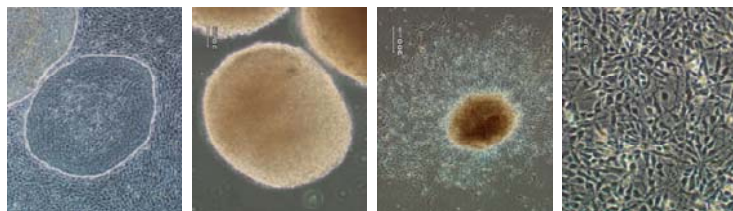
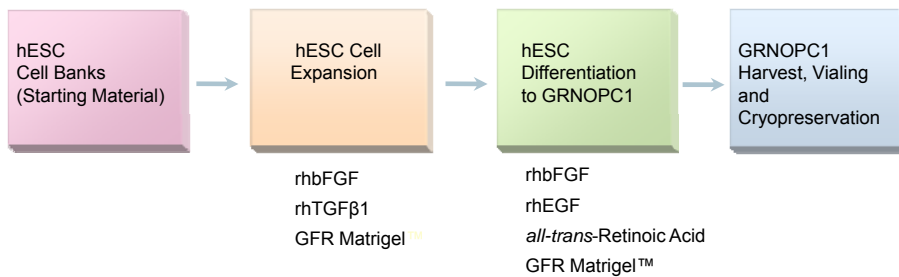
Postmortem human spinal cord with bony fracture, compression of cord (The Miami Project to Cure Paralysis © 2004)



- No approved therapies
- No single conventional drug or biologic likely to impact the multiple mechanisms of degeneration

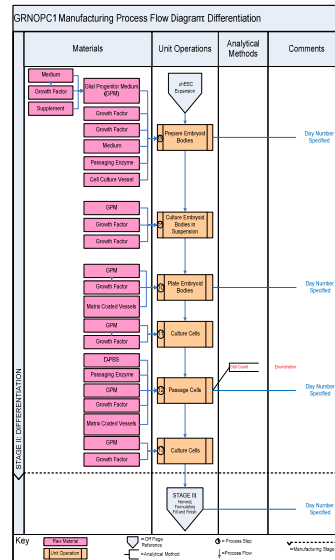
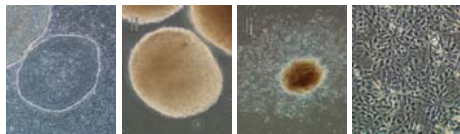
## Challenge: Robust, Scalable Manufacturing Process and Product Characterization

### Production Process for GRNOPC1

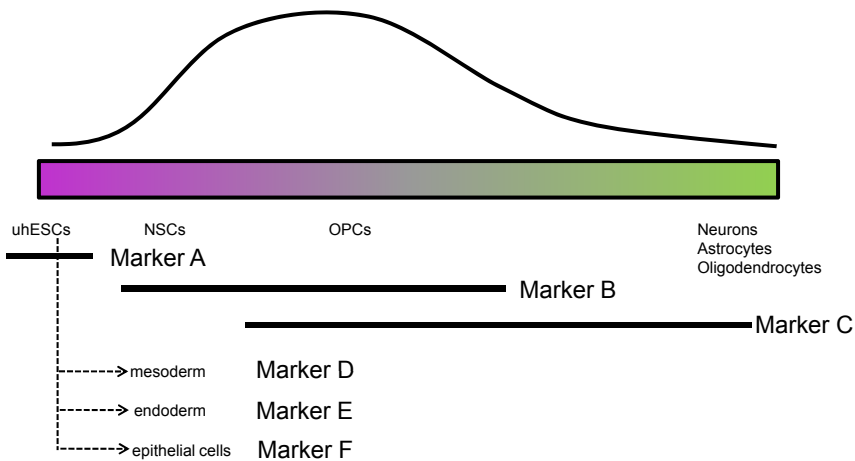


## Challenge: Controlled Production Process

- Characterization of Materials
  - . Starting Material
  - . Adventitious Agents
- Characterization of Unit Operations
  - . Cell Density
  - . Culture Format
  - . Timing of Induction
- Storage



## GRNOPC1: Characterized Composition of Cells



- Multiple cell types may be important for function
- Single marker may not definitively identify a particular cell type

## GRNOPC1: Characterized Cellular Composition

GRNOPC1 Characterized for Phenotypic Properties Associated with Multiple Cell Types

- Whole Genome MicroArray Analysis
- Quantitative RT-PCR
- Flow Cytometry
- High Content Imaging
- Biological Assays for Specific Cell Types



*Composition Correlated with In Vivo Activity in Animal Models*

*Critical for Establishing Cell Composition Specifications*

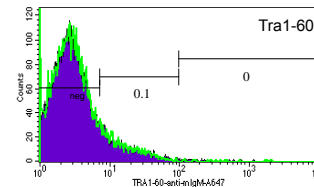
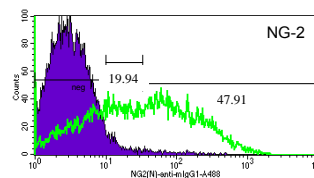
## GRNOPC1 Product Release

GMP Lot QC Testing

- Morphology
- Viability
- Cell composition
  - OPC Phenotype
  - Extraneous Phenotypes
  - Undifferentiated hESCs
- Adventitious Agent Testing
- Sterility and Mycoplasma
- Endotoxin

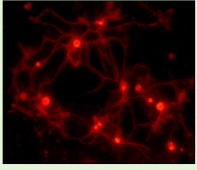


NG-2 and Tra1-60 Expression in GRNOPC1



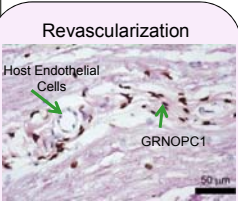
## GRNOPC1 Has Three Properties To Support CNS Repair

**Neurotrophic Factors**



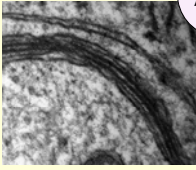
Induces Axonal Sprouting

**Revascularization**



Host Endothelial Cells  
GRNOPC1  
Associated With Vessel Growth

**Remyelination**



Induces Myelin Wrapping

**GRNOPC1**

- Produces Defined Neurotrophic Factors
  - TGF- $\beta$ 2, HGF, BDNF, Activin A, Midkine
- Induces Revascularization at Lesion Site
- Remyelinates Denuded Axons

**Challenge for Mechanism of Action Studies and Potency Assays**

## Challenge: Long, Large Nonclinical Studies to Evaluate Safety

**Xenograft Models  
Injury Models**

## Safety/Efficacy Profile of GRNOPC1

- Activity/ Efficacy
- Biodistribution
- Dosing/Delivery
- Toxicity
- Tumorigenicity
- Ectopic Tissue
- Immune Rejection

**>26 Studies and >2000 Rodents**

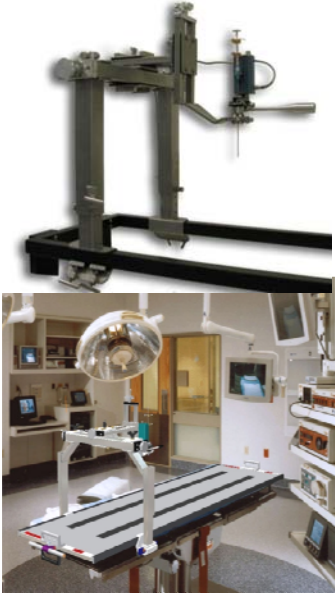
**GRNOPC1**

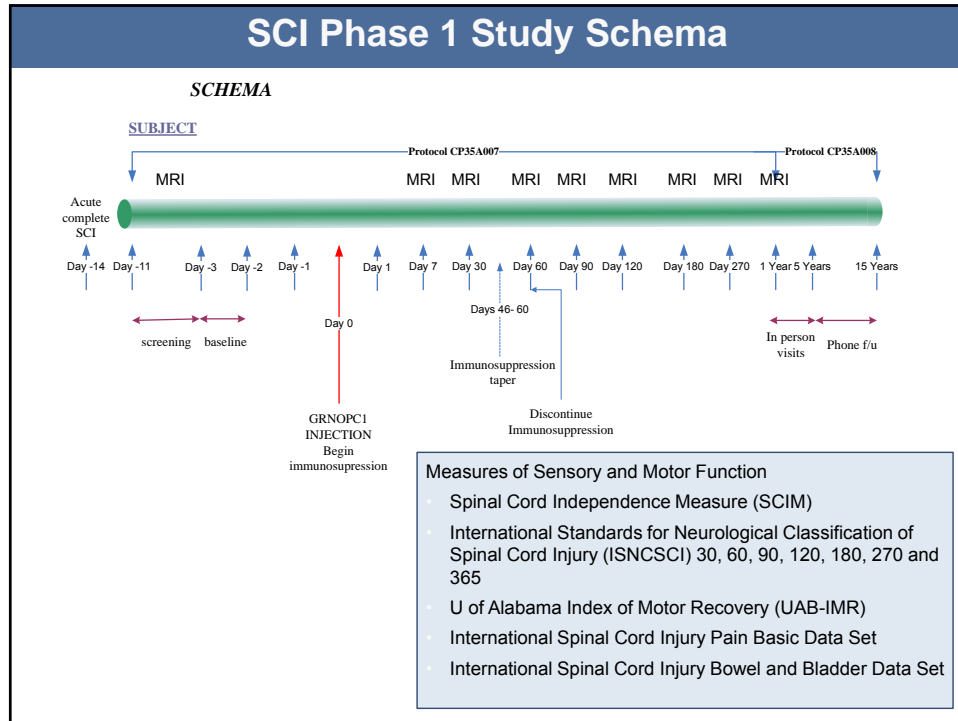
- Survives in the Spinal Cord
- Predominantly Neural Cells Types
- Improves Locomotor Activity
- Reduces Parenchymal Cavitation
- Migrates Through the Spinal Cord
- Does Not Increase Mortality
- Does Not Induce Allodynia
- Does Not Induce Systemic Toxicity
- Does Not Produce Teratomas
- Infrequent Ectopic Structures Observed Restricted to the Injury Site
- Not Highly Susceptible to Direct Immune Responses

## Delivery of GRNOPC1: Elective Surgical Delivery

**Delivery**

- $2 \times 10^6$  GRNOPC1
- 50 uL Injection
- 5mm Caudal of Injury Epicenter
- Injection Performed Using Syringe Positioning Device
  - Support Frame
  - Microdrive
  - Syringe and Needle





- ### Challenge: Clinical Trial Execution
- Initial Restrictive Inclusion/Exclusion Criteria
  - Multiple Clinical Trial Sites
  - Numerous Committee Approvals
  - Outcome Measures for Novel Indications
  - Rigorous Follow-up
  - Staged Expansion of Inclusion Criteria to Target Efficacy Population



