

# **Monitoring the Safety of Stem Cell Based Therapeutics in Clinical Trials**

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# Disclosure

- Received salary & ownership interest from Geron Corporation as an employee.

# **Multiple Considerations in Designing a Clinical Protocol to Test a Stem Cell Therapy**

- **What is the Clinical Indication?**
- **What is the Source of Stem Cells: Allogeneic or Autologous?**
- **Are There Risks of Infection?**
- **What is the Delivery Route?**
- **How Long Do the Cells Need to Survive to Be Effective?**
- **Will Immunosuppression Be Required?**
- **What is the Anticipated Mechanism of Action?**
- **What Are the Potential Benefits?**
- **Are There Toxicological Concerns?**
- **Are There Tumorigenicity Concerns?**

# Example of GRNOPC1

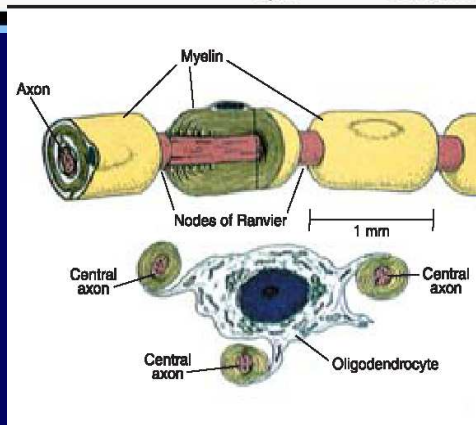
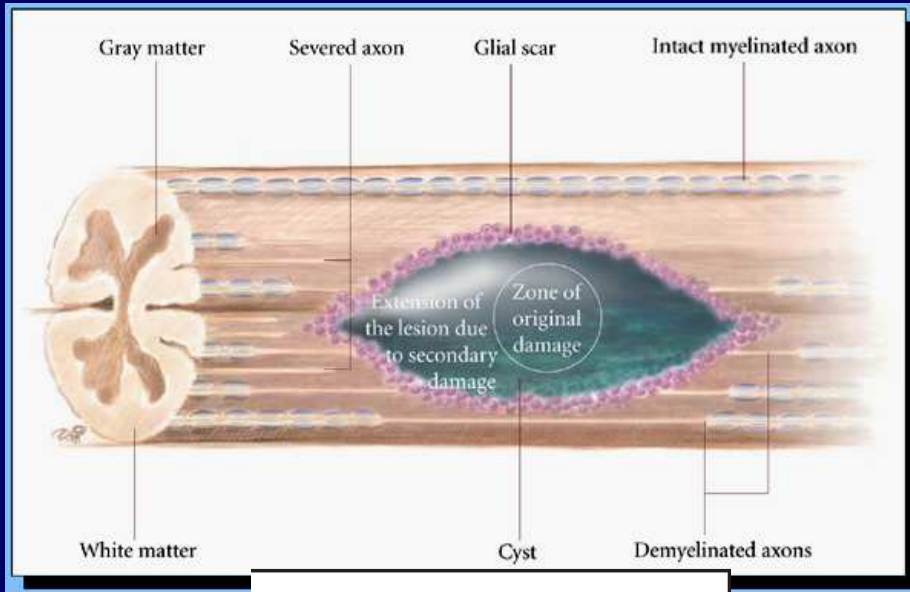


- Cryopreserved Allogeneic Cell Population
- Derived from Human Embryonic Stem Cells
- Characterized Composition of Cells
- Contain Oligodendrocyte Progenitor Cells
- Produces Neurotrophic Factors
- Induces Myelination of Denuded Axons

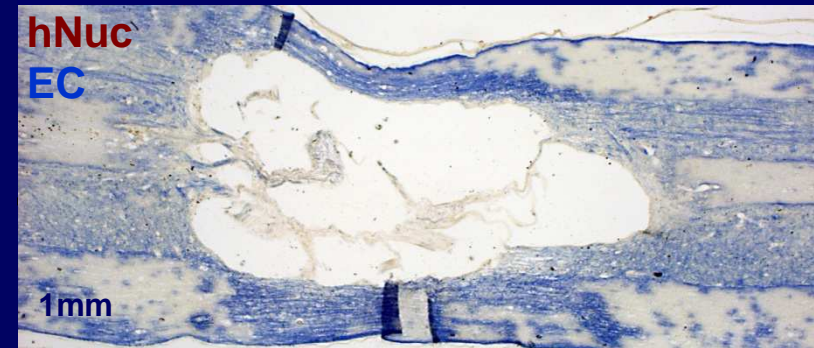
## Intended Application

- “Off-the-Shelf” Product
- Spinal Cord Injury
- Other CNS Disorders

# Spinal Cord Injury: Pathology of the Lesion Provides Rationale for Oligodendrocyte Progenitor Transplantation



9 months vehicle

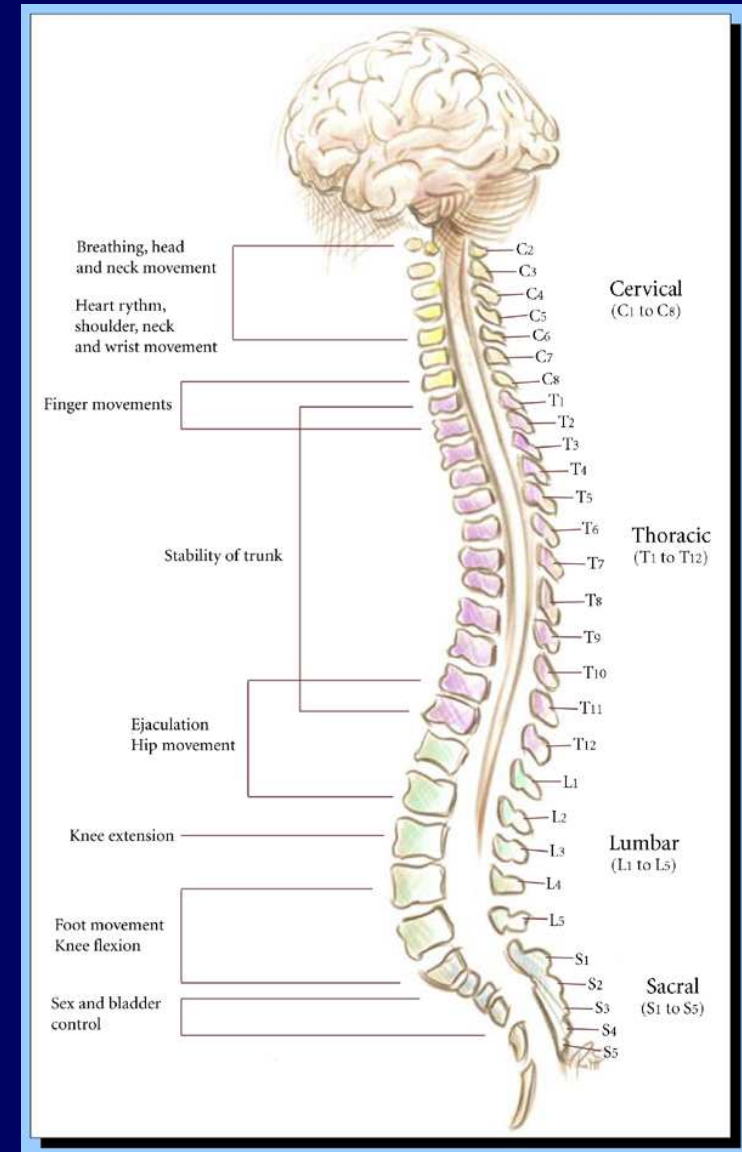


9 months post-GRNOPC1



# GRNOPC1 Phase 1 Multi-Center Trial

- Open Label Trial
- Subacute, Functionally Complete T3-T10 Lesions
- $2 \times 10^6$  Cells
- Transplant 7-14 Days Post Injury



# **Infectious Disease Risk Due to Adventitious Agents in Stem Cell Product**

**Are There Adventitious Agents Administered Due to the Source of the Cells or the Reagents Used to Prepare the Stem Cell Product?**

# H1 hESC Line and GRNOPC1 Were Qualified for the Production of Human Biologics

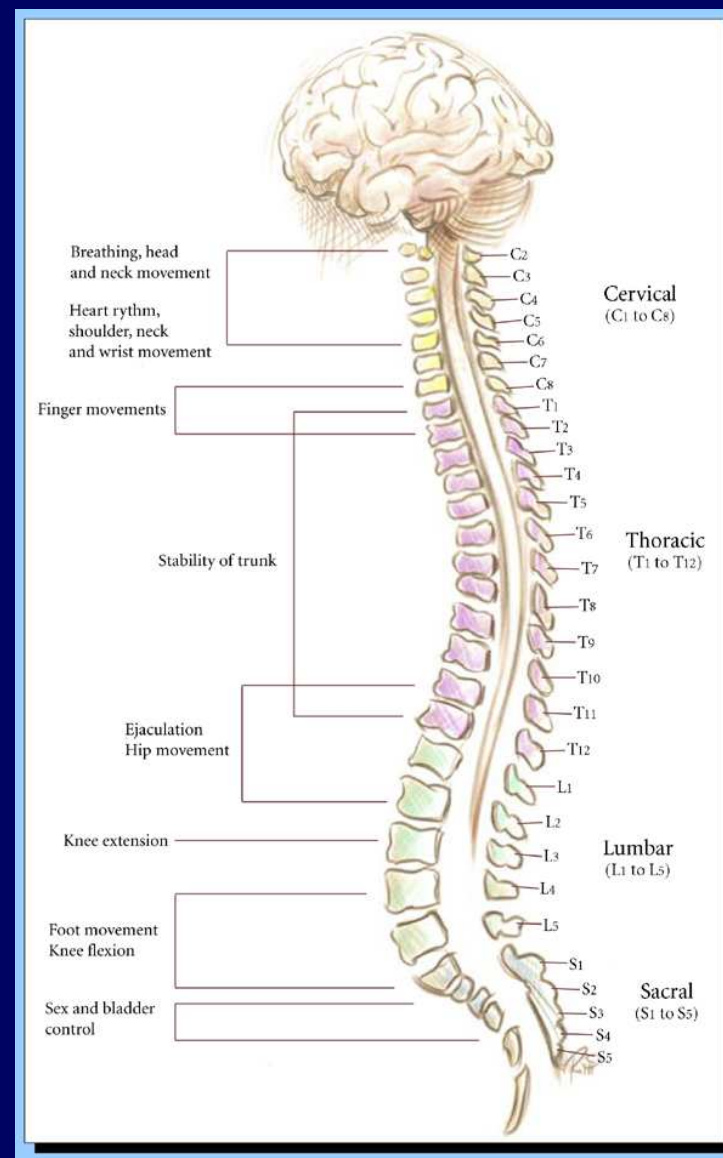
## **No Evidence Of:**

- 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
- Qualified According to FDA Guidance
  - No Evidence of Adventitious Agents of Human or Animal Origin
  - Normal Karyotype By G-Banding

# GRNOPC1 Phase 1 Multi-Center Trial: Adventitious Agent Monitoring

## Precautionary Activities in Clinical Trial

- Patients Monitored Routinely for Infectious Disease
- Vials of Product Retained in Case of Suspected Infectious Disease Transmission
- Peripheral Blood Samples Collected Stored Periodically to Monitor Suspected Changes in Pathological Agent Status



# Safety of Delivery

## Some Risk Due to Administration of Cells

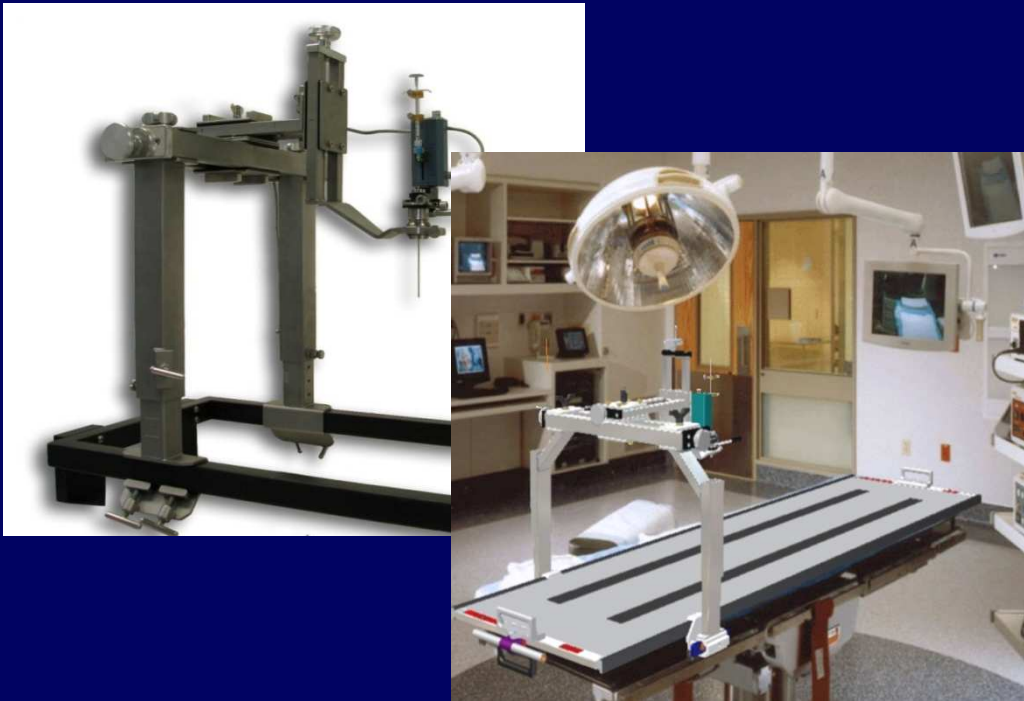
Highly Depends on the Route of  
Administration and Cell Dose  
Administered

Infection

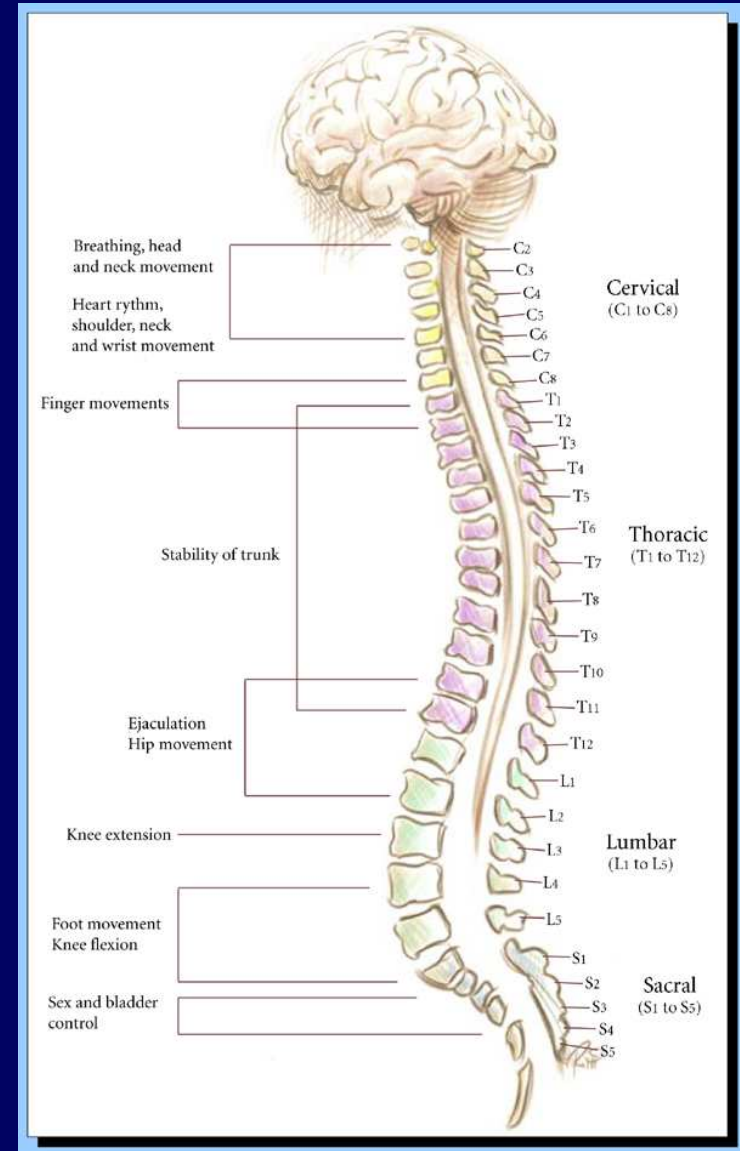
Surgical Risk

- Minimize Invasiveness of Delivery
- Minimize Damage Done By the Delivery
- Design Specific Subject Monitoring Standards in Peri-Transplant Period

# GRNOPC1 Phase 1 Multi-Center Trial: Safety of Delivery



- Intralesional Injection 7-14 Days Post Injury
- Guided By Prior MRI and Intra-Operative Ultrasound
- Syringe Positioning Device
- Training of Surgeons on Cadavers
- DVT Prophylaxis
- Detailed Subject Monitoring



# Stem Cell Product Survival In Vivo

- **Ideally Track Cells In Vivo in Subjects**
  - **Track Cells Using Biopsy Material**
  - **Track Products Produced By Cells**
    - **Look for Evidence of Rejection**



**Challenge for Most Trials  
Imaging Technology Improving  
But Not Sufficient Yet for Many  
Applications**

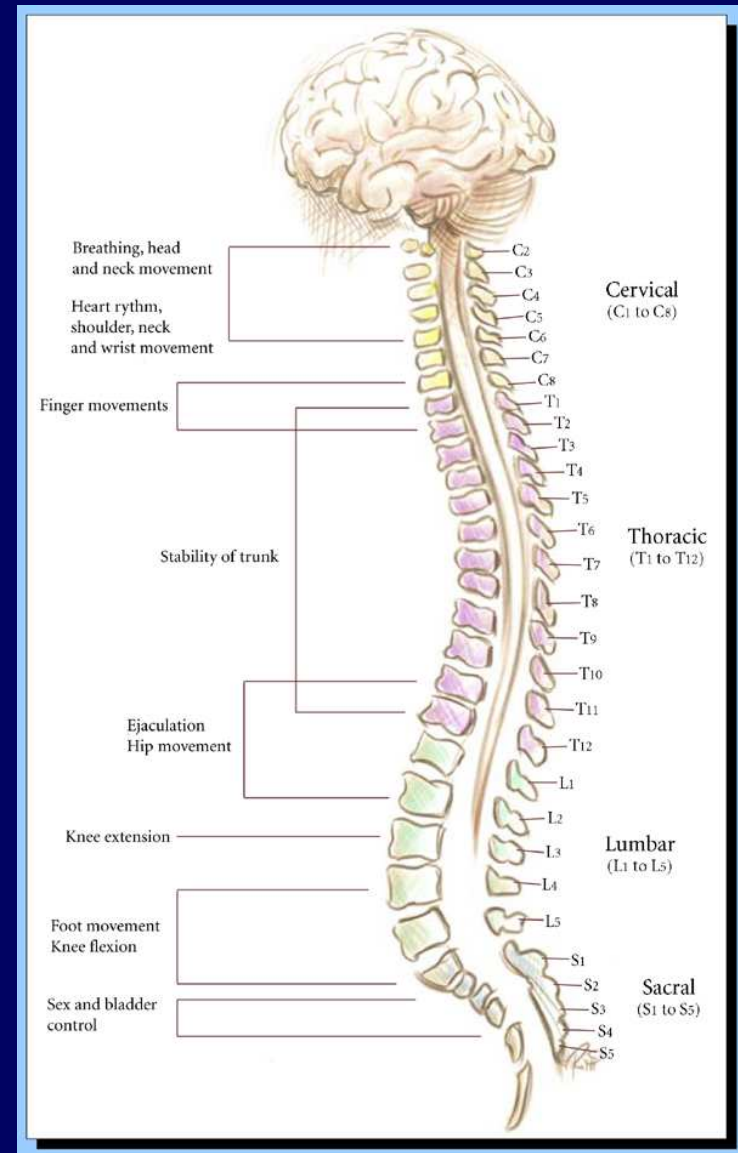
# GRNOPC1 Phase 1 Multi-Center Trial: Cell Survival Monitoring

## Monitoring Cells in Spinal Cord

- Current Tracking Technologies Not Applicable for Long-Term Monitoring
- Biopsy Material Not Available



- Periodic MRIs
- Sample CSF and Blood for Cell Specific Products
- Monitor Immune Responses



# Immunogenicity

- **Are the Cells Rejected ?**
- **Consequences for Follow-up Treatments?**
- **Sensitization?**

**Careful Selection of Patient Inclusion/Exclusion Criteria to Mitigate Negative Impact on Potential Downstream Clinical Options**

# Toxicological Effects of Stem Cells Based Products

- **Abnormal Local Tissue Responses**

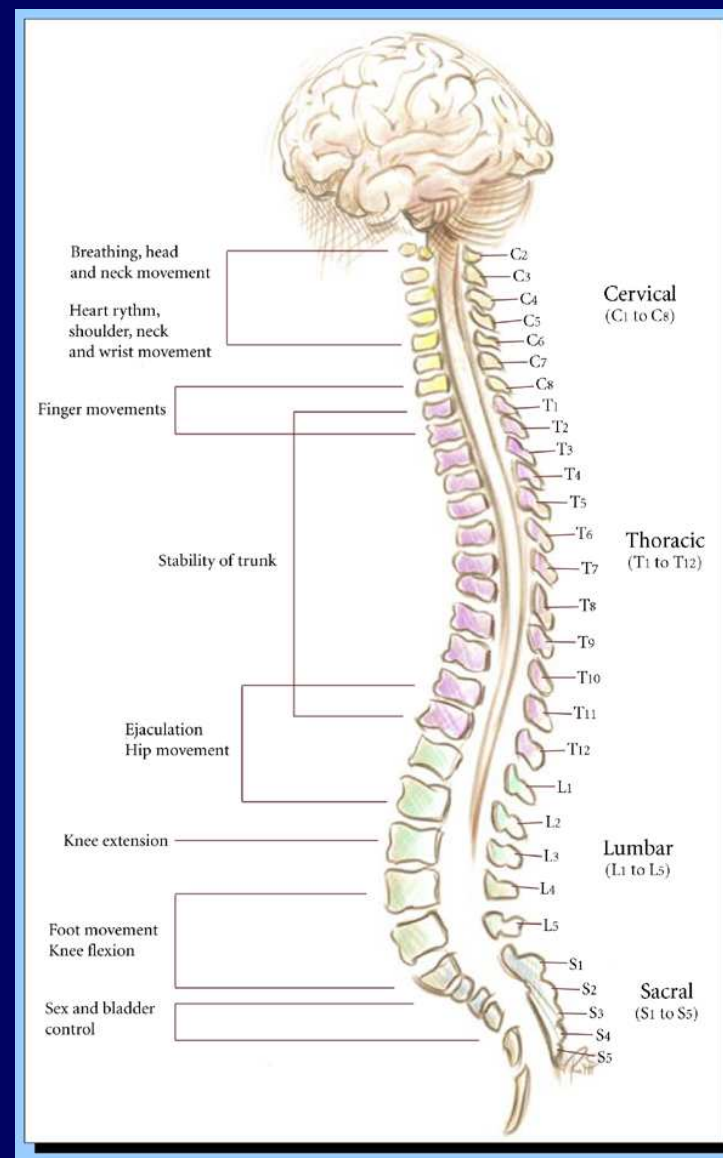
- **Metabolic Changes**
- **Structural Changes**
- **Neurological Changes**
- **Induction of Pain Responses**



- **Careful Selection of Inclusion Exclusion Criteria to Minimize Harm**
- **Theoretical and Observed Potential Toxicities in Preclinical Studies Need to Be Assessed in Human Trials**


# GRNOPC1 Phase 1 Multi-Center Trial: Toxicology Assessments

- Subacute, Functionally Complete ASIA A T3-T10 Lesions
- Temporary Immunosuppression with Tacrolimus
- Primary Endpoint: Safety
  - Neurological
  - Overall
- Secondary Endpoints: Safety/Efficacy
  - ASIA Grade and Score
  - UAB-IMR
  - Independence Measurements
  - Bowel and Bladder Function
  - Pain Assessments



# Tumorigenicity of Stem Cell Based Products

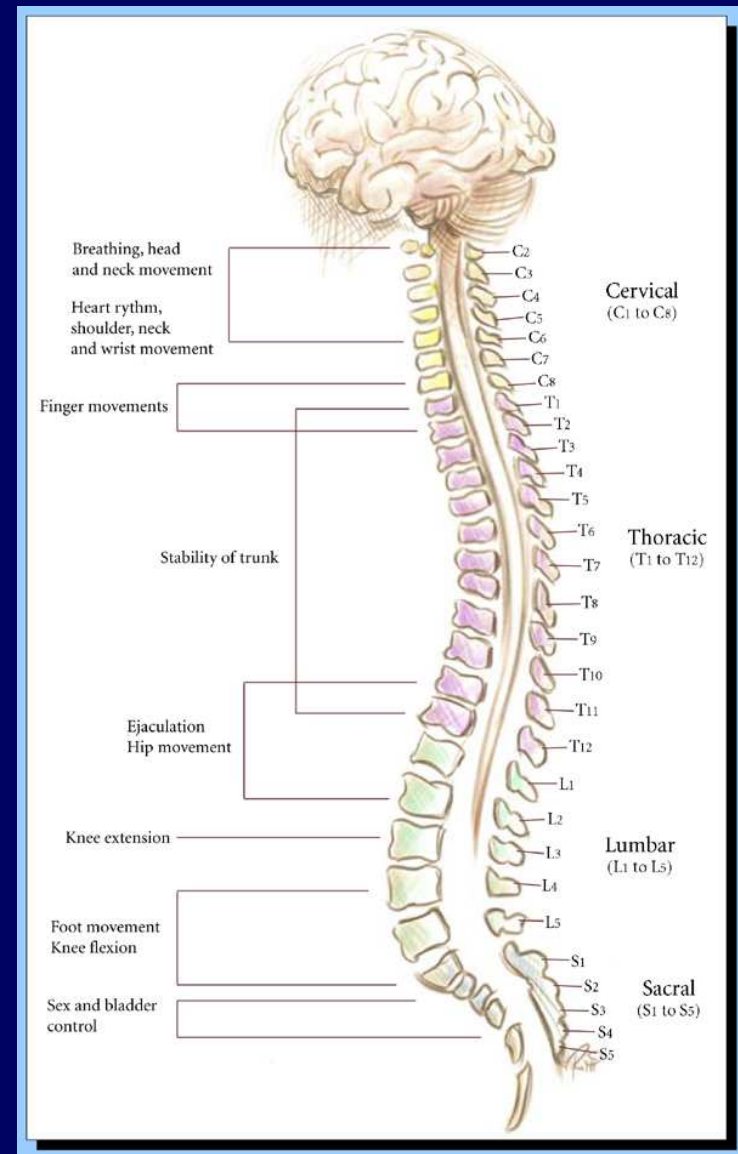
- **Do the Cells form Masses?**
- **Do the Cells form Ectopic Tissue?**
- **Are the Cells Proliferative In Vivo?**
- **Do the Cells Produce Adverse Clinical Consequences Associated with Ectopic Tissue Formation?**

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- **Monitor for Expansile Tissue Masses**
  - **Monitor Clinical Symptoms for Evidence of Expansile Tissue**
  - **Long-term Follow-up**

# GRNOPC1 Phase 1 Multi-Center Trial

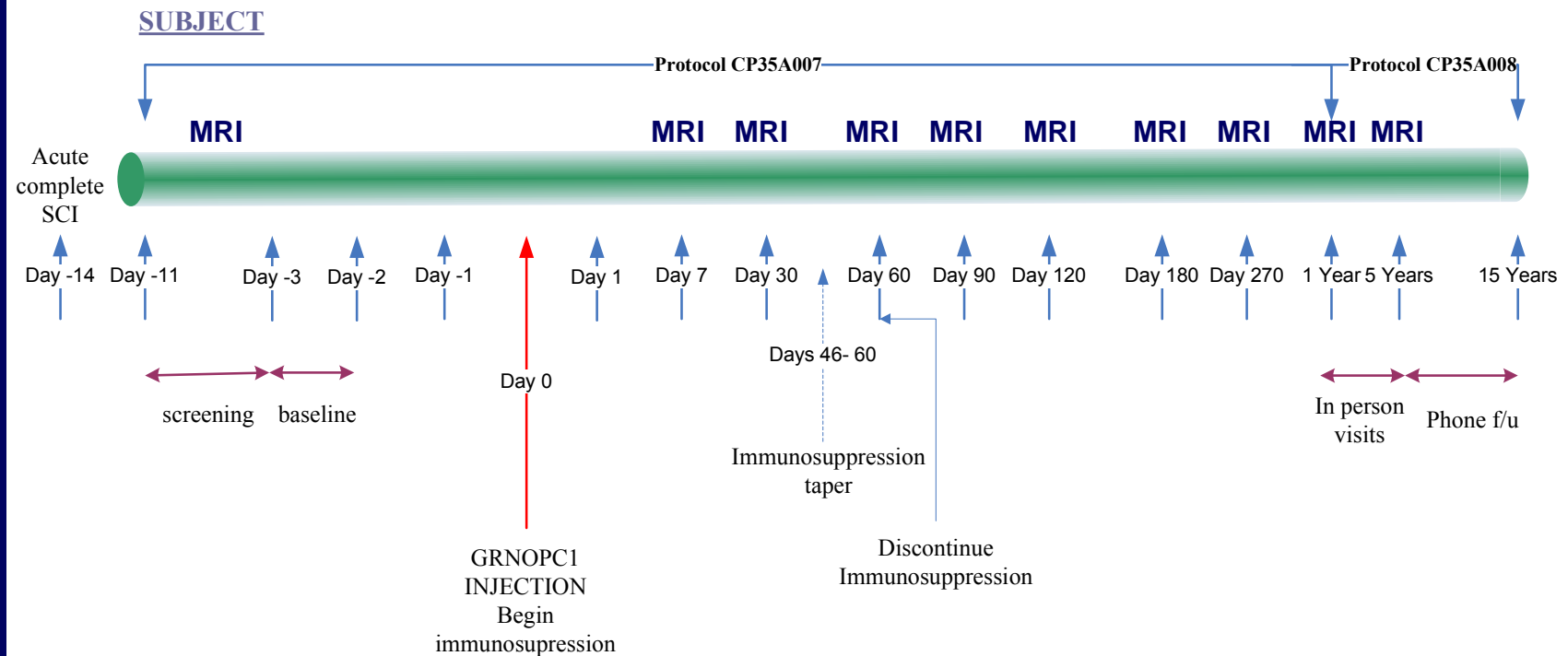
## Monitor Clinical Adverse Reactions

- Neurological Deterioration
- Overall Clinical Deterioration
- Increased Evidence of Pain
- Frequent MRIs
- 15 Year Follow-up



# MRI Monitoring Scheme for GRNOPC1 Clinical Trial

## *SCHEMA*



# Risk Mitigation Strategy

- Initial Staggered Enrollment
- Build in Frequent Monitoring to Detect Potential Adverse SUSARs
  - Real Time Event Review by Data Monitoring Committees
    - Plan For Follow-up of SUSARS
  - Assess Treatment Options in the Event of a SUSAR
    - Defined Trial Suspension Rules

# Summary

- **Careful Design and Execution of Clinical Trials Are Required to Monitor the Safety of Stem Cell Based Therapeutic Products**
- **Specific Risks to be Examined Include Those Associated with the Survival, Rejection, Integration, Proliferation and Ectopic Tissue Formation By the Cells.**
- **Risk Mitigation Strategies Must Be Developed to Minimize the Impact of SUSARS**