Clinical Development of hESC-Derived Oligodendrocyte Progenitor Cells for the Treatment of Spinal Cord Injury

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Human Spinal Cord Injury Causes Tissue Destruction and Ectopic Tissue Formation in the Spinal Cord

- Trauma to the spinal cord causes hemorrhagic necrosis
- Secondary damage includes cell death, cavity formation, demyelination, and scarring
- Chronic stage: gray matter replaced by either a lesion cavity or collagenous scar
- Typical spared rim of white matter

Cervical SCI at C5; 10 days post-injury

Kakulas, Paraplegia, 25:212-216, 1987

Normal Spinal Cord  Solid Cord Injury  Contusion Cavity

Pathology of the lesion provides rationale for oligodendrocyte progenitor transplantation

Aubourg, P., Nature Genetics 2007
Obermair, Schröter and Thallmair, Physiology 2008
AST-OPC1: hESC-Derived Oligodendrocyte Progenitor Cells

AST-OPC1

- Cryopreserved Allogeneic Cell Population
- Derived from Human Embryonic Stem Cells (hESCs)
- Characterized Composition of Cells:
  - Oligodendrocyte progenitors
  - Neural progenitors
  - Infrequent mature neural cells and
  - Rare other characterized cell types
- Three identified functions
  - Produces neurotrophic factors
  - Induces remyelination
  - Induces vascularization
- “Off the shelf” administration
- First indication: spinal cord injury
- Potential line extensions in other neurodegenerative diseases
Production of AST-OPC1 for Therapeutic Use

- **Characterization of Starting Material**
  - Source of Cells
  - Donor Medical History
  - Adventitious Agents

- **Characterization of Production Procedure**
  - Qualification of Reagents
  - Qualification of Procedures

- **Characterization of Cells**
  - Composition and Function
  - Stability and Durability
  - Delivery Efficiency

- **Release Testing and Assay Qualification**
  - Composition of Cells
  - Identity of Cells
  - Cell Viability
  - Potency
  - Sterility

- **Stability**
AST-OPC1: Three Major Physiologically Relevant Functional Activities

1. Wraps host neurons and forms compact myelin sheaths

2. Produces neurotrophic factors and stimulates neurite outgrowth

3. Stimulates neovascularization
AST-OPC1 Reduces SCI Cavity Formation and Induces Persistent Myelination

Rat Thoracic Spinal Cord Injury Model

9 months vehicle

9 months post-transplant with AST-OPC1

Cavity forms in untreated SCI lesion

Myelinated axons do not extend across cavity

Brown: antibody to human nuclear antigen labels AST-OPC1; Blue: Eriochrome Cyanine stains myelin

AST-OPC1 in SCI Lesion; Significantly Reduced Cavity Formation

Robust AST-OPC1 survival (brown)

Myelinated Fibers (blue)
Models of Spinal Cord Injury Used to Evaluate Safety/Activity of AST-OPC1

- Midline Contusion Injury at T10
- Unilateral Contusion Injury at C5/C6

Transplant AST-OPC1 7 days post-injury at injury site

Evaluate
- Efficacy & Activity
- Histological Effects
- Cell Survival
- Cell Phenotype
- Cell Migration
- Toxicity
Safety/Efficacy Profile of AST-OPC1 in Nonclinical Studies

28 Animal Studies
>3000 Rodents and Pigs

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

- Survives in the Spinal Cord
- Predominantly Neural Cell Types
- Greatest Activity in Subacute Injury
- Improves Locomotor Activity
- Reduces Parenchymal Cavitation
- Active Doses Established
- Migrates Up 5cm in Spinal Cord
- No Distribution Outside CNS
- Does Not Increase Mortality
- Does Not Induce Allodynia
- Does Not Induce Systemic Toxicity
- Does Not Produce Teratomas
- Produces Low Frequency (1-2%) Small Ectopic Tissue at Injury Site
- Not Highly Susceptible to Direct Immune Responses
### Patient Population
- **Specifics**: Neurologically complete (AIS A), thoracic (T3-T11) SCI; 7-14 days post-injury
- **Rationale**: Minimize risk of ascending injuries; Post-inflammatory, prior to onset of glial scar

### Dose
- **Specifics**: 2 million cells
- **Rationale**: Started with absolute cell dose tested in tumorigenicity studies

### Delivery
- **Specifics**: Custom “syringe positioning device”
- **Rationale**: Minimize risk of injection procedure

### Immuno-suppression
- **Specifics**: Short term (60 d) low dose tacrolimus
- **Rationale**: Low allogenicity of OPC1; Minimize IS risk in vulnerable SCI patients

### Follow-up
- **Specifics**: Frequent MRIs and Neurological Exams; Extensive immune monitoring; Long term (5 yr in person, 15 yr total)
- **Rationale**: Monitor safety; Evaluate IS regimen; Long term safety data
SCHEMA

SUBJECT

Acute complete SCI
Day -14
Day -11
Day -3
Day -2
Day -1
Day 1
Day 0
Day 120
Day 180
Day 270
1 Year
5 Years
15 Years

Protocol CP35A007

Day 1
Day 7
Day 30
Day 60
Day 90
Day 120
Day 180
Day 270

15 Years

Days 46-60

Immunosuppression taper

Discontinue Immunosuppression

GRNOPC1 INJECTION
Begin immunosuppression

screening
baseline

MRI

Protocol CP35A008

In person visits
Phone f/u

AST-OPC1
Phase 1 Thoracic Trial Study Schema
Summary of Findings from First in Human Study of AST-OPC1

All 5 Patients Now Followed for > 5 Years

<table>
<thead>
<tr>
<th>Well Tolerated</th>
<th>• AST-OPC1 well tolerated, with no SAEs to date deemed related to the cells, delivery method, or immunosuppressive regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Immune Responses</td>
<td>• No evidence of immune responses to AST-OPC1, even 10 months after removal of all immunosuppression</td>
</tr>
<tr>
<td></td>
<td>• Despite significant HLA mismatches between AST-OPC1 and subjects</td>
</tr>
<tr>
<td></td>
<td>• Suggests low dose, transient immunosuppressive regimen may be sufficient to enable long term engraftment of cells</td>
</tr>
<tr>
<td>Engraftment</td>
<td>• MRI results consistent with reduced cavity formation at injection site in 4 of 5 subjects</td>
</tr>
<tr>
<td>No Changes Neurological Function</td>
<td>• No evidence of significant changes in neurological function</td>
</tr>
<tr>
<td></td>
<td>• No evidence for ascending loss of function from cells or delivery</td>
</tr>
<tr>
<td></td>
<td>• Efficacy not anticipated in this study due to low dose (5-10x below predicted efficacious range) and suboptimal patient population (complete thoracic injuries)</td>
</tr>
</tbody>
</table>
• Devastating impact on quality and duration of life with no treatment options

• In cervical cord repair/regeneration of axons only required over a short distance to reinnervate motor neurons for arms & hands

• Better outcome measures for cervical spinal cord injury

**Two Methods to Measure Improvement in Motor Function**

**UEMS**

Upper Extremity Motor Score: Sum of All Motor Function Measured at all Levels of the Upper Extremities C5-T1; 50 Points Maximum for Both Sides (25 per Side)
Improvements of two or more motor levels of function translate to:
- Clinically significant improvements in ability to self-care
- Significant reductions in cost of care

AST-OPC1 Clinical Development Plan in Cervical SCI

Objectives of Trial

- Establish safety of AST-OPC1 in cervical sensorimotor complete SCI
- Assess effects on upper extremity motor function
- Investigate effects on additional measures of neurological function

Cohort 1
3 subjects with C5-C7 cervical SCI
• Dose $2\times 10^6$ AST-OPC1

Cohort 2
5 subjects with AIS-A C5-C7 cervical SCI
• Dose $1\times 10^7$ AST-OPC1

Cohort 3
5 subjects with AIS-A C5-C7 cervical SCI
• Dose $2\times 10^7$ AST-OPC1

Cohort 4
5 subjects with AIS-B C5-C7 cervical SCI
• Dose $1\times 10^7$ AST-OPC1

Cohort 5
5 subjects with AIS-B C5-C7 cervical SCI
• Dose $2\times 10^7$ AST-OPC1

AIS-A
AIS-B

Dosing complete
Currently enrolling
Future enrollment

Confirm Low Dose Safety Activity
Confirm Mid Dose Safety Activity
Confirm High Dose Safety Activity

Dose Escalation
Dose Escalation
Dose Escalation
AST-OPC1 Cervical Phase 1/2a Study Schema

- Open Label Trial
- Multi-Center (8-12 sites)
- Complete cervical SCI (C5-C7)
- Temporary Immunosuppression

Primary Assessment: Safety
Secondary Assessment: ISNCSCI exams
Exploratory Assessments: SCIM, GRASSP

Protocol AST-OPC1-01
Protocol AST-OPC1-02

Days 46-60
Immunosuppression Taper

Discontinue Immunosuppression

Acute complete cervical SCI

Screening Baseline

AST-OPC1 Injection 14-30 Days Post-SCI

Day -11 Day -3 Day -1 Day 0 Day 7 Day 30 Day 60 Day 90 Day 180 1 Year 5 Years 15 Years

In person visits Phone f/u
Cervical Phase 1/2a Clinical Trial: Enrolling Sites To Date

Enrolling Sites

Dr. Donald Leslie
Dr. Richard Fessler
Dr. Gary Steinberg
Dr. Steve McKenna
Dr. Charles Liu
Dr. Shekar Kurpad
Dr. Eric Horn
AST-OPC1 Injection Procedure

• Injections performed using a table-mounted syringe positioning device (SPD)

• Direct intra-parenchymal injection into the spinal cord lesion

• Single 50µL injection for both the 2M & 10M doses

• No intraoperative complications to date
Safety Profile Remains Positive

• Safety profile from all AST-OPC1 patients enrolled to date remains positive:
  ➢ 5 subjects followed 5+ years in previous thoracic safety trial
  ➢ 3 subjects followed 1+ year from Cohort 1 of SCiStar study
  ➢ 6 subjects followed 9+ months in Cohort 2

• No SAE’s associated with injection procedure

• Immunosuppression with tacrolimus has been well tolerated

• Safety profile of AST-OPC1 cells has been favorable, including no SAEs related to AST-OPC1 and no adverse findings on MRI scans to date
Low Dose 2 Million Cell Cohort Has Motor Recovery Similar to Matched Historical Controls

Cohort 1 data supports safety of AST-OPC1

EMSCI (www.emsci.org) is the most complete and most current SCI database available for comparison (> 3300 patients, ~300 new patients added annually)
- Actively managed database
- Best available ISNCSI SCI dataset

As expected, UEMS recovery in low dose 2 million safety cohort tracks with historical controls
AIS-A 10 Million Cell Cohort Experienced Greater UEMS Recovery than Matched Historical Control Group

- Change in UEMS from baseline over time
- Error bars at 1 Standard Error
- Matching criteria for historical controls:
  - Traumatic injury
  - Baseline assessment between 16-40 days from injury
  - AIS A at baseline
  - Age 18-69
  - NLI of C5-C7 at baseline
  - UEMS at baseline 7-32
Cohort 2 Motor Level Recovery for 6 Subjects at Latest Follow-up Visit Through 9 Months

Cohort 2 (10 million cells) motor level recovery vs. matched historical controls from EMSCI database

Control Data Consistent with Steeves et al. 2012 which indicated 26% of cervical AIS-A subjects recover 2 motor levels at 1 year

Motor level improvement vs. baseline measurement
Clinical Translation of Two Level Motor Improvement

- Improved Arm and Hand Function
- Greater Independence in Self-care
- Greater Independence in Transfers and Transport
- Greater Independence in Activities of Daily Living

• Safety Profile of Injection Procedure and AST-OPC1 Excellent with No Associated SAEs

• Immunosuppression with tacrolimus has been well tolerated

• UEMS improvement in Cohort 1 (2 million cells) was similar to matched controls which is indicative of safety in this low dose safety cohort

• Subjects in Cohort 2 have also shown a greater degree of motor score and motor level recovery than matched historical controls in the EMSCI database

• Improvements in motor function reported for Cohort 2 (10 million cells) have been maintained or further increased through last date of follow up at 9 months

• 2 motor level improvement translates into increased arm and hand function along with improved independence in activities of daily living.
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Gabriel Nistor

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Steering Committee
Data Monitoring Committee
Radiology Committee
Outcomes Committee

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