Regenerative Therapies for Spinal Cord Injury: Rationale, Evolution and Current Status

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International Colleagues for Guidelines Development to Manage Spinal Cord Injury

Fehlings MG (U Toronto); Harrop J (Jefferson, Delaware Valley); Aarabhi B (U Maryland, Shock Trauma); Kurpad SN (MCW, CNTR); Kwon B (ICORD, UBC, Vancouver); Kotter M (U Cambridge)
The Art and Science of “Restoring Humanity to Human Beings”
Sir Henry Marsh

“Do No Harm: Stories of Life, Death and Brain Surgery” Orion Books 2014

The Status Quo Sucks
George Carlin

Academic Medicine is an opportunity for a doctor to leave the field better than (s)he found it.
CENTER OF NEUROTRAUMA RESEARCH

TRANSLATIONAL NEUROTRAUMA RESEARCH
Advancing the Science of Neurotrauma: Brain and Spinal Cord Injury

Basic Science
- Neurosurgery Research Laboratories & Biomechanics
- MCW Neuroscience Research Center
- MCW Center for Imaging Research (CIR)

Basic Science of TBI/SCI
- Neuro-imaging Biomarkers for TBI/SCI

Clinical Translation
- Traumatic Brain and Spinal Cord Injury
- Clinical Neurotrauma Trials
- Pediatric TBI/SCI
- Rehab & Outcome

Clinical Science
- Traumatic Brain & Spinal Cord Injury
- MCW Neurosurgery, Neurointensive Care, Neuropsych
- MCW Neurosurgery, Trauma Surgery
- Pediatric Neurotrauma
- MCW & VA Neurosurgery and PM&R

Collaborative Partners
- U.S. DOT/TSB
- NIH/NINDS
- Dept. of Defense/Veterans Affairs
- CDC/Public Health
- Academic Partners
- Industry Sponsors
- Organized Sports
- Foundation
Spinal Cord Injury
Facts and Figures
If you drive a car...Or ride a motorcycle

- **Incidence**
  - 3-5/100,000 in the US
- **New cases**
  - 12,000/year in the US, 250,000 total
  - with deficits
- **Survival**
  - 90%, near-normal life span
- **Costs**
  - $6 billion/year in the US
- **Age**
  - Average: 33.4 years
  - most common age: 19 years
The Dark Side of Summer

24 Year Old Male
Medical Student

Diving Accident

Quadriplegic at Scene and in ER
Topics

• History
• Developing the “Drug”: 2001-2015 and ??
• Developing the “Map”: 2006-Present
• Delivering the “Drug”: Surgical Considerations
• Funding!
Edwin Smith Papyrus (2500-1700 BC)

- Five Cases reported
- Crushed vertebra- “He is unconscious of neck and arms, speechless and urine dribbles”.. An ailment not to be treated
- Sprained vertebra- Treat with application of fresh meat and honey
Galen of Pergamon (AD 129-210)

- Lived under Emperors Antonius Pius and Marcus Aurelius
- Studied Gladiators in the Coliseum
- Transection of spinal cord results in paralysis
- Injury to one half of spinal cord results in paralysis on same side of the body (earliest concept of localization)
- **First to Treat Spinal Cord Injury (Traction)**
Neuron Doctrine and Concept of Localization (1850-1910)
Santiago Ramon Y Cajal and Charles Edouard Brown Sequard

- Spinal Cord composed of Predictable and Definable Nerve Cell Connections
- Different Parts of the Spinal Cord Serve Different Functions
  - Front or Ventral – Motor
  - Back or Dorsal - Sensory
What Has Been Available?

- Early Diagnosis
- Intravenous Medication (Methylprednisolone)
- Surgical Reconstruction of the Spine (if indicated)
- Long Term Rehabilitation
What Do We Do?

- Plus Long Term Rehabilitation and Re-integration
What Happens after Spinal Cord Injury?

- Tissue Swelling from Inflammation
- Release of toxic substances into the zone of injury
- Loss of normal tissue
- Disruption of normal nerve connections
- Scar Formation
- Creation of environment hostile to regrowth of nerves
1. Developing the “Drug”
Breakthrough of the Year

Stem Cells Show Their Potential
Timeline (Stem Cell Strategies)

- 2005-2008: Application of concept to Human Stem Cells to generate Transplantable Myelin Making Cells
- 2009: GERON Stem Cell Study Starts. Terminated in 2011 (FUNDING Shortages!)
- 2015: Asterias Stem Cell Study Starts
  - Human Embryonic Stem Cells
  - Genetically Engineered to form Oligodendrocytes
Strategies for Spinal Cord Repair
Karolinska Institutet 2001
Neural Stem Cells integrate into the spinal cord

Green: GFP in stromal cells; Red: Neurofilament-IR
Grafting of neural stem cells genetically engineered to express Neurogenin2 allows for recovery of hindlimb sensory function.
Grafting Ngn-2 transduced neuronal stem cells into the injured spinal cord

Ng-2 stem cells (GFP) have become oligos (MBP) ensheathing host nerve fiber (Tuj1)

What about Chronic Spinal Cord Injury?
<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Cell Dose</th>
<th>Location</th>
<th>Follow-up as of 7/2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lysosomal storage disorder</td>
<td>6/6</td>
<td>500 M to 1 B</td>
<td>BRAIN: Frontal lobe, Parietal lobe, Lateral ventricle</td>
<td>&gt; 5 year (n=3)</td>
</tr>
<tr>
<td>Age range: 2 to 9 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypomyelination disorder</td>
<td>4/4</td>
<td>300,000</td>
<td>BRAIN: Frontal lobe</td>
<td>&gt; 4 years (n=4)</td>
</tr>
<tr>
<td>Age range: 12 mo. to 5 yrs</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thoracic SCI</td>
<td>12/2</td>
<td>20 M</td>
<td>SPINAL CORD: thoracic intramedullary</td>
<td>&gt; 12 months (n=12)</td>
</tr>
<tr>
<td>Age range: 19 to 53 yrs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age-related macular degeneration</td>
<td>15/5</td>
<td>200,000 to 1 M</td>
<td>EYE: subretinal space</td>
<td>&gt; 12 months (n=14)</td>
</tr>
<tr>
<td>Age range: 63 to 92 yrs</td>
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</tbody>
</table>
Clinical Trial Structure

- Age 18 to 60
- C5 – C7
- **Chronic cervical** spinal cord injury A-C
- 4-24 months from injury
- Injection fetal derived HuCNS-SC®
- Peri-lesional injections
- Immunosuppression x 6 months
Summary

• Neural Progenitors can be harvested and propagated in culture

• Regardless of source, NPC can be partially differentiated in vitro into OPC and can induce remyelination in animal models of SCI
2. Developing the “Map”
Imaging Biomarker Development
A Reverse Translational Model to Guide Prognostication and Drug Delivery
Index Case I

29 Year Old Male in Rollover MCA

Quadriplegic at Scene and ER

Large Body Habitus (380 lb)
Emergent OR

ORIF, Posterior Approach

ASIA E at 6 month Follow Up

Index Case II

24 Year Old Male Medical Student

Diving Accident

Quadriplegic at Scene and in ER

ASIA A at 1 year
Human Spinal Cord DTI: C-Spine

(Ellingson et al AJNR 2008)
Translational Collaborative Efforts in Spinal Cord MRI (DTI)
CNTR/CIR

Remote Cord Imaging
Brian Schmit, PhD

Imaging Near Hardware
Kevin Koch, PhD

Acute Cord Injury Assessment
Matthew Budde, PhD

Disk Degeneration
Tugan Muftuler, PhD
Lesion Site Imaging Limitation
Rationale for Remote Imaging

Secondary Injury in SCI

DTI Proximal to Injury Site
Hind Limb Motor Function

Correlation between MD and BBB

Average Mean Diffusivity in the Cervical Segments

White and Gray Matter Differences
Axial FA maps at the high cervical level and injury zone in a single acute SCI patient (right)
Corresponding FA maps in healthy control (left)

hcDTI metrics within white matter funiculi change predictably in SCI patients vs controls

Vedantam et al, World NS 2017
11 patients with cervical cord injury, 11 controls
Underwent DTI of the cervical cord at a median duration of 3.5±0.9 days post-injury
DTI metrics measured at 2 levels:
  High cervical cord (C1-C2 level)- hcDTI
  Injury zone- izDTI

Lateral funiculi  Ventral funiculus  Dorsal funiculus

SCI  Control  SCI  Control  SCI  Control

L tract  V tract  D tract

SCI  Control  SCI  Control  SCI  Control
Improving Specificity and Efficiency
Double Diffusion Encoding (DDE)
Isolated Evaluation of Spinal Cord WM
Budde MD et al

Perpendicular “Filter”
Suppress edema/CSF

Parallel “Detection”
Probes axonal injury

Combined
Measure axonal injury without contamination from edema/CSF

Main Confounding Signals:
CSF
Edema
Other Inflammation

- Reduced Acquisition time (< 3 mins)
- No regions of interest
- Immediate quantification
- No post-processing
- Eliminates variance between scanners
Clinically Viable
rFOV DDE

Acute (48 hrs)

Chronic (30 days)
Summary

• Current Gray Scale MRI Imaging is not useful as a planning or a prognostic tool
• Diffusion Imaging of the Spinal Cord shows promise in both and is already being harnessed in clinical trials as a secondary outcome measure
3. Delivering the “Drug”: Surgical Considerations

Bringing it Together for use in Patients
Evaluation of AST-OPC1 in Subacute Cervical SCI

A Phase 1/2a Dose Escalation Study of AST-OPC1 in Subjects With Subacute Cervical Spinal Cord Injury

Six Sites Currently Enrolling

ClinicalTrials.gov: NCT02302157
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
Syringe Positioning Device
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; Two injections for the 20M dose
- No intraoperative complications to date
Summary of Findings from First in Human Study of AST-OPC1

All 5 Patients Now Followed for > 5 Years

**Well Tolerated**
- AST-OPC1 well tolerated, with no SAEs to date deemed related to the cells, delivery method, or immunosuppressive regimen

**No Immune Responses**
- No evidence of immune responses to AST-OPC1, even 10 months after removal of all immunosuppression
- Despite significant HLA mismatches between AST-OPC1 and subjects
- Suggests low dose, transient immunosuppressive regimen may be sufficient to enable long term engraftment of cells

**Engraftment**
- MRI results consistent with reduced cavity formation at injection site in 4 of 5 subjects

**No Changes Neurological Function**
- No evidence of significant changes in neurological function
- No evidence for ascending loss of function from cells or delivery
- Efficacy not anticipated in this study due to low dose (5-10x below predicted efficacious range) and suboptimal patient population (complete thoracic injuries)
**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

**Dosing complete**
- Currently enrolling
- Future enrollment
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

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

In person visits
Phone f/u

Discontinue Immunosuppression

Immunosuppression Taper

Days 46-60

AST-OPC1 Injection 14-30 Days Post-SCI

Baseline

Screening

MRI

MRI

MRI

MRI

MRI

MRI

MRI
Cervical Phase 1/2a Clinical Trial: Enrolling Sites To Date

Enrolling Sites

Shepherd Center
Dr. Donald Leslie

Rush University Medical Center
Dr. Richard Fessler

Santa Clara Valley Medical Center
Dr. Gary Steinberg
Dr. Steve McKenna

Rancho Los Amigos National Rehabilitation Center
Dr. Charles Liu

Medical College of Wisconsin
Dr. Shekar Kurpad

Indiana University
Dr. Eric Horn
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 ISNCSCI dataset

As expected, UEMS recovery in low dose 2 million safety cohort tracks with historical controls

Matched historical control from EMSCI Database
Cohort 1 – 2 million (n=3)
Error bars at 1 Standard Error
AIS-A 10 Million Cell Cohort Experienced Greater UEMS Recovery than Matched Historical Control Group

Change in UEMS from baseline over time

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

Matched historical control from EMSCI Database
Cohort 2 – 10 million (n=6)
Error bars at 1 Standard Error

Time post baseline
Months

Months of Follow-up

Change in UEMS from baseline over time
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

Motor level improvement vs. baseline measurement

HuCNSC: Stem Cells Inc Trial

- Phase II Proof of Concept Trial in Cervical ASIA A patients
- Derived from Fetal Brain Tissue
- Cell Injection approx 14 weeks and up to 104 weeks Post SCI
- Objectives
  - Primary: Dose Escalation
  - Secondary: Imaging Biomarker Validation

**J Neurotrauma.** 2018 Sep 5. doi: 10.1089/neu.2018.5843. [Epub ahead of print]
Clinical Outcomes from a Multi-Center Study of Human Neural Stem Cell Transplantation in Chronic Cervical Spinal Cord Injury.
Levi AD\(^1,2\), Anderson KD\(^3\), Okonkwo DO\(^4\), Park P\(^5\), Bryce T\(^6\), Kurpad SN\(^7\), Aarabi B\(^8,9\), Hsieh J\(^10\), Gant K\(^11\).

Levi AD\(^1\), Okonkwo DO\(^2\), Park P\(^3\), Jenkins AL 3rd\(^4\), Kurpad SN\(^5\), Parr AM\(^6\), Ganju A\(^7\), Aarabi B\(^8\), Kim D\(^9\), Casha S\(^10\), Fehlings MG\(^11\), Harrop JS\(^12\), Anderson KD\(^1\), Gage A\(^13\), Hsieh J\(^13\), Huhn S\(^13\), Curt A\(^14\), Guzman R\(^15\).
Phase I/II Thoracic SCI HuCNS-SC Transplantation
A phase 2 single-blind, randomized, parallel arm study of the safety and efficacy of HuCNS-SC transplantation in cervical spinal cord injury

Cell dose manually injected above and below injury based on MRI and ultrasound
Cell Injection Strategy

Cohort I (Injection rate = 20 μL / minute)
Where are we NOW?

- AST-OPC1 cells are safe.
- No serious adverse effects so far
- Early recovery of meaningful function
  - Improved Arm and Hand Function
  - Greater Independence in Self-care
- Greater Independence in Transfers and Transport
- Greater Independence in Activities of Daily Living
Time and Resources for Outcome?

- Concept TO (2001) (Funding)
- Research TO (2001-10) (Funding)
- Clinical Trial TO (2010-Present) (Funding)
- Standard of Care
Thank You