Protection and Repair after Spinal Cord Injury: Accomplishments and Future Directions

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Disclosure and Conflict of Interest
(W. Dalton Dietrich, PhD)

- NIH/NINDS – Grant Funding
- DOD – Grant Funding
- Zoll Medical Corp. – Speaker’s Bureau
- QOOL Therapeutics, Inc – Consultant
- Mission Connect – External Review Committee
- Pfizer – Safety Monitoring Board
- InflamaCORE, LLC/Managing Meml
The First Maurice Albin Keynote Lecture Outline

I. Introduction
II. Neuroprotective Strategies
   ➢ Pathophysiology
   ➢ Pharmacological Treatments
   ➢ Therapeutic Hypothermia
III. Reparative Strategies
   ➢ Intrinsic/Extrinsic Mechanisms of Axonal Regeneration
   ➢ Cell Therapies
   ➢ Schwann Cell Program
IV. Neurorehabilitation
   ➢ Locomotor Training
   ➢ Electrical Stimulation
   ➢ Bootcamp
   ➢ Brain-Machine Interface
V. Quality of Life Issues
   ➢ Neuropathic Pain
   ➢ Deep Brain Stimulation
VI. Future Directions
CNS Research
Bench to Bedside/Bedside to Bench Research Program

Pipeline for Success
The Miami Project Mission Statement

“To discover and test new therapies that will improve function and quality of life issues in people living with paralysis”

Neurological Disorders:

- Spinal cord injury ✓
- Traumatic brain injury
- Cerebrovascular disease and stroke
- Neurodegenerative diseases
- Epilepsy

Cross-fertilization between research areas is important for new advances
SCI Epidemiology

- As many as 500,000 people worldwide suffer an SCI each year.
- Over 10,000 new cases each year in the U.S. Average age 43 yrs.
- Approximately 1.275 million Americans living with paralysis as a result of SCI.
- Motor vehicle accidents followed by falls, acts of violence and recreational activities are the leading causes of SCI in the U.S.
- Since 2000, about 78% of SCIs reported to the national database have occurred in males.
- 7% of SCI victims due to accident or injury occurring while serving in the military.
- Currently it is believed that 5.3 million people are living in the US with paralysis due to some type of CNS injury/disorder.
- Worldwide problem.
CNS Injury Research

- Neuroprotection/Pathophysiology
  - Can we protect?
- Transplantation/Regeneration
  - Can we repair?
- Rehabilitation
  - Can we retrain and enable circuit function?
- Quality of Life
  - Can we improve life?
- Clinical Trials
  - Can we improve functional outcome?
- Education/Training
  - Can we train the next generation of scientists?
Pathophysiology of SCI

Severed axons
Demyelination
Apoptosis and necrosis
Inflammation
Edema
Excitotoxicity and oxidative damage, etc.
Hemorrhage
Cavitation
Glial reactivity and inhibitory scar formation
Ischemia/vasospasm and occlusion

Mothe and Tator, J Clin Inves, 2014
Cytoprotective Strategies and Treatments Targeting Spinal Cord Injury

- Critical Care Management/Limiting Secondary Insults/Emergency Medicine
- Surgical Interventions/Decompression
- Methylprednisolone
- GM-1 ganglioside
- Erythropoietin
- Minocycline
- Cethrin® (Rho antagonist)
- Riluzole (Na⁺ channel blocker)
- Rolipram (Next generation PDE inhibitors)
- Therapeutic Hypothermia
- Combination Therapies
• NASCIS (National Acute Spinal Cord Injury Study) II and III trials led to the widespread adoption of a high-dose MP regimen for patients treated within 8 hours of injury
• Subsequent studies have called into question the validity of NASCIS conclusions
• Further evidence of the ineffectiveness of the MP protocol has led to declining confidence in the treatment over the last decade
• At the present time, high-dose MP cannot be recommended as a standard of care, but it remains an option until supplanted by future evidence-based therapies.
Surgical Interventions in Patients with Traumatic SCI

- Realignment and stabilization of the spine
- Decompression surgery

“Time is Spine”
Timing of Decompressive Surgery of Spinal Cord after Traumatic Spinal Cord Injury: An Evidence-Based Examination of Pre-Clinical and Clinical Studies

- Primary literature using Medline
- 19 experimental studies and 22 clinical studies
- Studies indicated that patients who underwent early surgical decompression can have similar outcomes to patients who received delay operation
- However, evidence to suggest that early intervention is safe and feasible
- Recommend that early intervention should be considered in all patients for 8 to 24 hrs following acute traumatic SCI
Replication studies carried out as part of the Facilities of Research Excellence-Spinal Cord Injury (FORE-SCI) program launched by NIH/NINDS in 2003.

Important issues

- Replication
- Reproducibility
- Potential translation to clinical trials

"Many published SCI studies cannot be successfully replicated"
Exact replication studies are very challenging.
Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury

Steven Casha,1 David Zygun,1,2 M. Dan McGowan,1 Ish Bains,1 V. Wee Yong1 and R. John Hurlbert1

1 Department of Clinical Neurosciences and the Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada
2 Department of Critical Care Medicine and the Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada

- Single center double-blind randomized placebo controlled study.
- Seven days of IV minocycline treatment, N=27, placebo, N=25.
- Overall patients treated with minocycline experienced 6 points greater motor recovery.
- Difference of 14 points were observed in cervical SCI with motor incomplete showing largest differences.

“Findings are encouraging and warrant further investigation in a multicenter Phase III”
Prospective multicenter phase I trial by NACTN to investigate pharmacokinetics and safety and neurological outcome after acute SCI.

Thirty-six patients with AIS A-C.

50mg of Riluzole twice daily within 12 hrs of SCI for 14 days.

No serious adverse effects related to Riluzole.

Increase in 31.2 points in mean motor score of cervical SCI compared to 15.7 points for 26 registry patients.

Patients with cervical injuries had more robust conversions to higher grades than the comparison group.
CSF concentrations of IL-6, IL-8, MCP-1, Tau, S100b, and GFAP at 24 h post-injury are correlated with baseline injury severity (ASIA A, B, or C).
The inflammatory response is divided into innate and adaptive immunity.
The Inflammasome is a multiprotein complex involved in the activation of caspase-1 and the pro-inflammatory cytokines IL-1β and IL-18. There are different types of inflammasomes and ASC is common to all of them.

ASC = apoptosis associated speck-like protein containing caspase recruitment domain
NLRP = nod-like receptor family, pyrin domain-containing
ASC neutralization improves histopathological and functional outcomes after SCI

de Rivero Vaccari J et al., 2008
Is Moderate Hypothermia Protective in Experimental and Clinical SCI?
Clinical trials with SCI were begun in the 1960s following promising experimental reports.

Techniques of local cooling were feasible for acute SCI because the practice of surgical decompression allowed exposure of the spinal cord.

Evaluation of these studies was difficult due to:

- limited number of patients
- lack of randomized control groups
- concomitant interventions, e.g. spinal cord decompression, steroid use (methylprednisone)
## Effects of Spinal Cord Cooling in Experimental Spinal Cord Trauma

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Species</th>
<th>Level</th>
<th>Method</th>
<th>Cooling Start</th>
<th>°C, Duration</th>
<th>Other</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Albin et al.</td>
<td>1965</td>
<td>Dog</td>
<td>T10</td>
<td>WD</td>
<td>Immediate</td>
<td>12 SC, 2.5 h</td>
<td>DO</td>
<td>Positive</td>
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<td>Albin et al.</td>
<td>1967</td>
<td>Dog</td>
<td>T10</td>
<td>WD</td>
<td>Immediate</td>
<td>5 SOL, 2.5 h</td>
<td></td>
<td>Positive</td>
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<td>Albin et al.</td>
<td>1968</td>
<td>Monkey</td>
<td>T10</td>
<td>WD</td>
<td>4 h post</td>
<td>10 SC, 3 h</td>
<td>DO</td>
<td>Positive</td>
</tr>
<tr>
<td>Ducker/Hamit</td>
<td>1969</td>
<td>Dog</td>
<td>T11</td>
<td>WD</td>
<td>3 h post</td>
<td>3 SOL, 3 h</td>
<td>DO</td>
<td>Positive</td>
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<tr>
<td>Kelly et al.</td>
<td>1970</td>
<td>Dog</td>
<td>T10</td>
<td>WD</td>
<td>Immediate</td>
<td>12 SC, 2.5 h</td>
<td>DO</td>
<td>Positive</td>
</tr>
<tr>
<td>Black/Markowitz</td>
<td>1971</td>
<td>Monkey</td>
<td>T10</td>
<td>WD</td>
<td>1 h post</td>
<td>4-8 SOL, 5 h</td>
<td>Some DO</td>
<td>Negative</td>
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<tr>
<td>Tator/Deecke</td>
<td>1973</td>
<td>Monkey</td>
<td>T9-10</td>
<td>ICD</td>
<td>3 h post, 3 h post</td>
<td>5, 3 h, 36, 3h</td>
<td>Some DO</td>
<td>Positive</td>
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<tr>
<td>Campbell et al.</td>
<td>1973</td>
<td>Cat</td>
<td>T9</td>
<td>WD</td>
<td>3 h post</td>
<td>4 SOL, 3 h</td>
<td>DO</td>
<td>Positive</td>
</tr>
<tr>
<td>Hansebout et al.</td>
<td>1975</td>
<td>Dog</td>
<td>T13</td>
<td>ICD</td>
<td>Immediate</td>
<td>4 EP, 4 h</td>
<td></td>
<td>Positive</td>
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<tr>
<td>Kuchner/Hansebout</td>
<td>1976</td>
<td>Dog</td>
<td>T13</td>
<td>ICD</td>
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<td>Positive</td>
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<tr>
<td>Eidelberg et al.</td>
<td>1976</td>
<td>Ferret</td>
<td>Mid-T</td>
<td>SWL</td>
<td>1 h post</td>
<td>10 EP, 3 h</td>
<td></td>
<td>Positive</td>
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<tr>
<td>Wells/Hansebout</td>
<td>1978</td>
<td>Dog</td>
<td>T13</td>
<td>ICD</td>
<td>4 h post</td>
<td>6 EP, 1-18 h</td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td>Green et al.</td>
<td>1973</td>
<td>Cat</td>
<td>T10</td>
<td>WD</td>
<td>1 &amp; 4 h post</td>
<td>6-18°C, 3h</td>
<td>DO</td>
<td>Positive</td>
</tr>
<tr>
<td>Martinez/Green</td>
<td>1992</td>
<td>Rat</td>
<td>T8</td>
<td>WD</td>
<td>Pre &amp; post</td>
<td>31-32°C, 4h</td>
<td>DI</td>
<td>Positive</td>
</tr>
<tr>
<td>Yu et al.</td>
<td>2000</td>
<td>Rat</td>
<td>T10</td>
<td>WD</td>
<td>Post</td>
<td>33°C, 4 h</td>
<td>DI</td>
<td>Positive</td>
</tr>
<tr>
<td>Chatzipanteli et al.</td>
<td>2000</td>
<td>Rat</td>
<td>T10</td>
<td>WD</td>
<td>Post</td>
<td>33°C, 4 h</td>
<td>DI</td>
<td>Positive</td>
</tr>
<tr>
<td>Dimar et al.</td>
<td>2000</td>
<td>Rat</td>
<td>T10</td>
<td>WD</td>
<td>Post</td>
<td>19°C, 2h</td>
<td>DI</td>
<td>Positive/Neg</td>
</tr>
</tbody>
</table>

Guest and Dietrich, 2005
Therapeutic Hypothermia and Targeted Temperature Management

The Breakthrough: Where?

- In the laboratory, mild to moderate HYPOThERMIA is the most powerful therapy for any type of CNS injury.
  - Global Cerebral Ischemia
  - Focal Cerebral Ischemia
  - Traumatic Brain Injury
  - Spinal Cord Injury
  - Subarachnoid Haemorrhage
Temperature Mechanisms in Ischemia and Trauma

1. Metabolism (1970)
2. pH (1992)
8. Cerebral blood flow (1954)
11. Calcium accumulation (1992)
12. Protein synthesis (1991)
13. Protein kinase-C activity (1991)
15. Platelet function (1987)
16. NMDA neurotoxicity (1991)
18. Growth factors (1994)
19. Calcium-dependent protein phosphorylation (1990)
22. NOS activity (1999)
24. microRNA (2011)
25. Inflammasome activation (2012)

Dietrich, 2012

Small variations in CNS temperature influences many secondary injury cascades
Temperature Experimentation in CNS Injury Models

Therapeutic Value

Experimental Tool

Is Moderate Hypothermia Protective in Experimental and Clinical SCI?
Beneficial effects of modest systemic hypothermia on locomotor function and histopathological damage following contusion-induced spinal cord injury in rats

Chen Guang Yu, M.D., Ph.D., Omar Jimenez, M.D., Alexander E. Marcillo, M.D., Brian Weider, M.D., Kurt Bangerter, M.D., W. Dalton Dietrich, Ph.D., Santiago Castro, and Robert P. Yezierski, Ph.D.

The Miami Project, and Departments of Neurological Surgery and Anatomy and Cell Biology, and the Neuroscience Program, University of Miami, Miami, Florida
Systemic Hypothermia Improves Histological and Functional Outcome After Cervical Spinal Cord Contusion in Rats

THOMAS PANG LO, JR.,1 KYOUNG-SUOK CHO,2 MANEESH SEN GARG,1 MICHAEL PATRICK LYNCH,1 ALEXANDER EDUARDO MARCILLO,1 DENISE LEIGH KOIVISTO,1 MONICA STAGG,1 ROSA MARIE ABRIL,1 SAMIK PATEL,1 W. DALTON DIETRICH,1,3–5 AND DAMIEN DANIEL PEARSE1,46

Behavior

Pathology
Systemic Review and Meta-Analysis of Therapeutic Hypothermia in Animal Models of Spinal Cord Injury

Batchelor et al., 8:e71317, PLoS One, 2013

- Literature review to determine the efficacy of systemic and regional hypothermia in SCI
- Three databases were utilized: PubMed, ISI Web of Science and Embase
- Inclusion criteria consisted of (i) reporting efficacy of hypothermia on functional outcome (ii) number of animals and (iii) mean outcome and variance in each group
- Systemic hypothermia improved behavioral outcome by 24.5%
- Behavioral improvement with regional hypothermia was 26.2%
- Systemic hypothermia appears to be a promising potential method of treating acute SCI on the basis of meta-analysis of pre-clinical literature and the results of high quality animal studies
Research Protocol at UMMSM/JMH

- No clinical guidelines or protocols establishing efficacy for the use of therapeutic hypothermia after human SCI have been published in peer reviewed journals.

- The Department of Neurological Surgery/Miami Project at the UMMSM/JMH is currently conducting an IRB approved SCI research protocol.

- Modest hypothermia (33°C/92°F) is induced via a cooling catheter that is placed in a large blood vessel.

- Cooling is maintained for a 48hr period followed by a slow re-warming of one degree every 8 hours.
Clinical Application of Modest Hypothermia after Spinal Cord Injury

- Fourteen patients cooled 48 hrs using systemic modest hypothermia (33°C)
- Average time between injury and induction of hypothermia was 9.17 hrs
- Positive correlation between temperature and heart rate
- Minimum variation of body temperature during cooling phase
- No increase in risk factors associated with modest hypothermia
- Provides critical baseline data for future outcome studies including multicenter randomized trials

*Currently cooled over 52 patients
Table 1. Inclusion and Exclusion Criteria for Modest Hypothermia Protocol

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Age 16–65 years</td>
<td>Age &lt;16 or &gt;65 years</td>
</tr>
<tr>
<td>AIS score A</td>
<td>AIS score B, C, or D</td>
</tr>
<tr>
<td>Nonpenetrating injury</td>
<td>Hyperthermia &gt;38.5°C on admission</td>
</tr>
<tr>
<td>Surgically treated patients were included in the study</td>
<td>Severe systemic injury</td>
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<td>Severe bleeding</td>
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<td>Pregnancy</td>
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<td>Coagulopathy</td>
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<td>Thrombocytopenia</td>
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<td>Prior known cardiac history</td>
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<td>Blood dyscrasias</td>
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<td>Pancreatitis</td>
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<td></td>
<td>Reynaud syndrome</td>
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<td>Spinal cord transaction</td>
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<td></td>
<td>Improvement in neurological examination within 12 hours of injury</td>
</tr>
</tbody>
</table>

AIS, American Spinal Injury Association and International Medical Society of Paraplegia, Impairment Scale.
Adapted from Levi et al., 2010 (55).
Systemic cooling

SURFACE COOLING

- Arctic Sun / ArcticGel Pads (Medivance/Bard)

- Criticool / Cool Wrap 3500 (MTRE Advanced Technologies)

ENDOVASCULAR COOLING

- Zoll intravascular temperature management system / ICY catheter (Zoll)
Cooling Profile of SCI Patient

Early reduction/sustained hypothermia/controlled rewarming
Case Study

- Patient, 20 yo male, C6-7 fracture with bilateral dislocation and disk herniation at C6-7 after doing a gymnastic flip.
- ASIA A complete at admission.
- Underwent anterior cervical dislocation and fusion.
- Received modest hypothermia treatment within <8 hours from trauma.
- Improved to ASIA D at acute care discharge from the hospital.

“Good result most likely the combination of several factors including early stabilization, hypothermia tx, established ICU protocols and rehabilitation”

A) Pre-op CT demonstrating a severe bilateral facet-fracture dislocation at C6-7.
B) An MRI performed 4 days post-injury demonstrates re-establishment of canal diameter and spinal cord decompression with intrinsic spinal cord change at the level of injury.

State-of-the-art Neuroimaging for spinal cord injury
Clinical outcomes using modest intravascular hypothermia after acute cervical spinal cord injury, Levi et al., Neurosurgery, 2010

AIS Outcome at 1 year

ASIA A conversion ratio of 43%
Therapeutic Hypothermia for Acute Severe Spinal Cord Injury: Ready to Start Large Clinical Trials?

- Supportive pre-clinical data
- Positive findings replicated using different SCI models in multiple laboratories
- Single institutional studies showing safety and some evidence of efficacy
- Lack of successful treatments for acute SCI
ARCTIC
Acute Rapid Cooling Trial for Injuries of the spinal Cord

Clinical Protocol

• 200 patients
• 17 centers - NETT
• 4 patients per center per year
• 5 year project (3.5 year enrollment, 1 year minimum f/u, 6 month start-up)
• $12,000,000 total project costs
• PI: Michael Wang, MD
Therapeutic Hypothermia (Michael Wang, MD (PI)) – The Department of Neurological Surgery and The Miami Project to Cure Paralysis have launched a significant initiative to study hypothermia treatment for acute spinal cord injury. A multicenter randomized clinical trial application has been submitted to NIH with the neurological emergencies trials group (NETT) to evaluate the efficacy of moderate hypothermia after severe SCI.

The Dream Team
CNS Injury Research

- Neuroprotection/Pathophysiology
  - Can we protect?
- Transplantation/Regeneration
  - Can we repair?
- Rehabilitation
  - Can we retrain?
- Quality of Life
  - Can we improve life?
- Clinical Trials
  - Can we improve functional outcome?
- Education/Training
  - Can we train the next generation of scientists?
Potential Mechanisms of Spinal Cord Repair Following Cell Transplantation

Mothe and Tator, J Clin Inves, 2014
Helper Cells to Promote Regeneration and Repair

- Peripheral nerve/Schwann cells
- Olfactory ensheathing glia
- Astrocytes
- Macrophages
- Genetically engineered cells
  - Fibroblasts
  - Schwann cells
- Stem Cells
  - Fetal
  - Embryonic
  - Adult/MSCs
  - Induced Pluripotent SCs (iPS)

Clinical trial (http://www.clinicaltrials.gov)
Uncertainty exists on the extent to which a cellular therapy needs to demonstrate efficacy in the preclinical setting to justify the initiation of a lengthy, expensive, potentially risky clinical trial.

27 SCI researchers were surveyed and a focus group organized to conduct discussion around a number of translational issues including

- Use of injury models and mechanisms
- Window for demonstrating efficacy
- Independent replication
- Defining relevant meaningful efficacy
- Expectation of therapeutic benefits for cellular interventions
Randomized control study with single-blinded primary assessment.

Determine efficacy of autologous incubated macrophage treatment in patients with acute complete SCI (L5-T11).

AIS A to B or better conversion was experienced by 7 treated and 10 control participants; AIS A to C conversion was experienced by 2 control patients.

Analysis failed to show a significant difference in outcome between the two groups.

Importance of standardization and measurement of key practice parameters may be important independent variables for future clinical trials.

“Let’s learn from completed studies”
To investigate the safety and therapeutic efficacy of autologous olfactory ensheathing cell transplantation in chronic SCI.

Eight patients were recruited to the study.

Three months after treatment, ASIA and FEM scores improved significantly compared to pretreatment.

Return of substantial sensation and motor activity in various muscles below the injury was observed in 3 patients.

Bladder function was restored in 2 patients.

No serious complications.

Excellent Result
Sources of Stem Cells for Transplantation into the Injured Spinal Cord

Mothe and Tator, J Clin Inves, 2014
Phase I/II open-label multinational study evaluating safety and preliminary efficacy of HuCNS-SC® human fetal neural stem cells.

First clinical trial in stem cell transplantation to complete enrollment.

12 subjects (7 complete AIS A and 5 AIS B).

At 12 months, multisegment gains in sensory function in two/three AIS A subjects. One subject converted from complete to incomplete.
FDA approved Phase I safety trial for Neuralstem’s NSI-566 neural stem cells.

Trial will enroll 8 chronic SCI patients with thoracic spinal cord injury (T2-T12) AIS A.

Patients will receive 6 injections in or around the injury site.

Patients will receive physical therapy and immunosuppressive therapy.

Trial study will end 6 months post-injury with a 1 year Phase I completion goal.

Question: Is immunosuppression in SCI patients?
Neural stem cell expressing GFP were embedded in fibrin matrices containing growth factor cocktails and grafted to sites of severe SCI (10 factors).

Grafted cells differentiated into multiple cell phenotypes including neurons.

Large numbers of extended axons over remarkable distances forming abundant synapses with host cells.

Two human cell lines embedded in growth factor containing fibrin exhibited similar growth.
Intrinsic and Extrinsic Neuronal Mechanisms Facilitating Axonal Regeneration

- Insufficient intrinsic growth capacity.
  - Cell transplantation
  - Neurotrophin supplementation
  - Growth promoting small molecules
  - Genes, transcription factors, microRNAs
  - Bioengineered scaffolds

- Extrinsic factors/inhibitory environment
  - Chondroitin sulfate proteoglycans
  - NOGO and other myelin inhibitors
  - Glial scar
  - Fibroblast
  - Perineuronal nets

Kadoya et al., 2009
Qiu et al., 2002
Busch and Silver, 2007
Fawcett, 2003
Schwab, 2004
VP16-KLF7 enhances regeneration of corticospinal tract axons

Blackmore et al., PNAS, 109:7517, 2012
FDA SCI Clinical Trials
Miami Project

- Human Schwann Cell Transplantation Targeting Subacute SCI (2012)
- Brain/Computer Interface Technology for Chronic Cervical SCI Patients (2013)
- Deep Brain Stimulation for Neuropathic Pain and Autonomic Dysreflexia after SCI (2013)
- Mesenchymal Stem Cell Treatment for Subacute SCI (2014)
Why Schwann Cells?

- Promote regeneration of axons in the PNS
- Produce growth factors, ECM components
- Myelinate, ensheathe axons in CNS
- Restore axonal conduction upon myelination
- Enter cord in substantial numbers/ SCI
- Are readily accessible/ PN
- Can be transplanted autologously
- Can be obtained in large numbers
- Promising preclinical data in multiple species
Inclusion Criteria

- Traumatic thoracic spinal cord injury between levels T3-T11
- ASIA Impairment Scale grade A
- 18-50 years of age

Dose Escalation

<table>
<thead>
<tr>
<th>Dose to be Studied</th>
<th>Target dose</th>
<th># of injections</th>
<th>Total Volume</th>
<th># subjects in cohort</th>
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<tbody>
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<td>Cohort</td>
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</tr>
<tr>
<td>1</td>
<td>$5 \times 10^6$</td>
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<td>50 $\mu$l</td>
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<tr>
<td>2</td>
<td>$10 \times 10^6$</td>
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<tr>
<td>3</td>
<td>$15 \times 10^6$</td>
<td>1</td>
<td>150 $\mu$l</td>
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</table>
CNS Injury Research

- Neuroprotection/Pathophysiology
  - Can we protect?
- Transplantation/Regeneration
  - Can we repair?
- Rehabilitation/Locomotor Training
  - Can we retrain?
- Quality of Life
  - Can we improve life?
- Clinical Trials
  - Can we improve functional outcome?
- Education/Training
  - Can we train the next generation of scientists?
Conditioning Strategies for Living and Aging with SCI

Nash and colleagues
Gross UE Movement

Pinch

Field-Fote and colleagues

Pinch with rotation

Grip

Grip with rotation
Assess the effects of an intervention combining body weight support, functional electrical stimulation and treadmill training on overground walking speed, treadmill walking speed, speed and distance and lower extremity motor scores.

In 19 ASIA C patients at least one year post injury.

All subjects showed improvement in treadmill training on overground walking speed and overall lower extremity strength.

“Subjects with incomplete SCI, who retain some capacity for ambulation, would likely benefit from a walking program that combines BWS, FES, and treadmill training”
Advanced Robotic and Rehabilitation Technologies

Lokomat

ZeroG

Exoskeleton

RiceWrist
Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans

Claudia A. Angeli,1,2 V. Reggie Edgerton,3,4 Yury P. Gerasimenko3,5 and Susan J. Harkema1,2

- Four individuals showing voluntary movement occurring with epidural stimulation including two who were diagnosed with sensory and motor complete lesion.
- Part of a stand and step training program.
- Neuromodulation of the spinal cord circuitry with epidural stimulation enables paralyzed individuals to process conceptual auditory and visual input.
- The subthreshold motor state of excitability of the lumbosacral spinal networks was the key to recovery.
- “Conceivably, after repetitive epidural stimulation and training, plasticity of these disrupted pathways could have resulted in a more functional state”
- A better understanding of the biological mechanisms underlying these types of functional results is required.
Exercise devices used for spinal cord injured rats. (A) A motorized exercise wheel. (B) Motorized cycles. (C) Step training.
Miami Project Boot Camp
Preparing People with Chronic SCI for Cellular Therapies

Upper Limb Conditioning

Motor Rehabilitation

Endurance

Balance and Conditioning
“Boot Camp” for Chronic Schwann Cell Trial

Goal: To provide conditioning/exercise regimens to promote better recovery.

T2-T12 AIS Grade A, B, or C
C5-T1 AIS Grade A, B, or C
Interventions

• **Exercise conditioning protocol:**
  – Upper Extremity Circuit Resistance Training (45min; 3 days/week at home)
  – Lower Extremity Functional Electrical Stimulation cycling (15min; 2 days/week on-site)

• **Body-weight supported locomotor training protocol:**
  – Lokomat for AIS A-B (45min; 2 days/week on-site)
  – Overground for AIS C (45min; 2 days/week on-site)
Proposed Logistics

Screening to determine eligibility

Exercise & training period

Wk 1
Wk 2-13
Wk 14
Wk 15
Wk 16
Wk 17-19
Month 1-6 post-transplant

Nerve harvest

Baseline 1
Baseline 2
Post-op recovery
2 month
6 month

Resume exercise & training as medically stable

Exercise & training period

Clinical Protocol to be Submitted to the FDA for Consideration
President’s BRAIN Initiative

- Timing is right to make a strong push toward clinical testing in humans.
“High-Profile” SCI Neurotechnology Therapies

Present Goal: A fully implantable brain/machine interface for fully restoring grasp and arm extension after SCI
Objectives – Motivated by Need

• Restore three fundamental upper extremity functions to quadraplegics (C5/C6 level).
  – Direct neural control of tricep contraction
  – Direct neural control of thumb and index finger pinch
  – Movement and control of both arms independently

Restoration of these functions leads to independence.
Brain/Computer Interface Concept

Deliver a fully implantable, bi-directional interface in human SCI.

PI: Justin Sanchez, PhD
CNS Injury Research

- Neuroprotection/Pathophysiology
  - Can we protect?
- Transplantation/Regeneration
  - Can we repair?
- Rehabilitation
  - Can we retrain?
- Quality of Life
  - Can we improve life and aging with SCI?
- Clinical Trials
  - Can we improve functional outcome?
- Education/Training
  - Can we train the next generation of scientists?
ACTIVE CLINICAL STUDIES
AT THE MIAMI PROJECT
www.themiamiproject.org

- ACTIVITY AND NUTRIENT MODIFYING STUDIES (PI: Mark S. Nash, PhD, FACSM) (9 studies)
- FERTILITY STUDIES (PI: Nancy Brackett, PhD, HCLD)
- SPASTICITY STUDIES (PI: Christine Thomas, PhD)
- PAIN STUDIES (PI: Eva Widerstrom-Noga, DDS, PhD)
- PSYCHOLOGY STUDIES (PI: Larry Brooks, PhD)
- SLEEP STUDIES (PI: Mark Nash, PhD, FACSM) (2 studies)
- MOBILITY STUDIES (PI: Rachel Cowan, PhD)
- EDUCATION OUTREACH (PI: Kim Anderson, PhD)
Research papers

Metabolite concentrations in the anterior cingulate cortex predict high neuropathic pain impact after spinal cord injury

Eva Widerström-Noga a,b,c,d,e,*, Pradin M. Pattany f, Yenisel Cruz-Almeida a,b,e,1, Elizabeth R. Felix a,d, Salome Perez g, Diana D. Cardenas a,d, Alberto Martinez-Arizala b,g.

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>A-B (n = 22) Mean ± SEM</th>
<th>SCI-noNP (n = 14) Mean ± SEM</th>
<th>SCI-LPI (n = 24) Mean ± SEM</th>
<th>SCI-HPI (n = 16) Mean ± SEM</th>
<th>ANOVA F; P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA</td>
<td>6.21 ± 0.12</td>
<td>6.22 ± 0.14</td>
<td>6.04 ± 0.16</td>
<td>6.18 ± 0.10</td>
<td>0.422; .738</td>
</tr>
<tr>
<td>Ins</td>
<td>5.37 ± 0.09</td>
<td>5.65 ± 0.15</td>
<td>5.12 ± 0.11</td>
<td>5.75 ± 0.10</td>
<td>6.700; .0001</td>
</tr>
<tr>
<td>Glx</td>
<td>7.95 ± 0.22</td>
<td>8.28 ± 0.46</td>
<td>7.59 ± 0.22</td>
<td>7.22 ± 0.24</td>
<td>2.258; .0891</td>
</tr>
<tr>
<td>Cr</td>
<td>5.07 ± 0.39</td>
<td>5.20 ± 0.41</td>
<td>4.95 ± 0.48</td>
<td>5.35 ± 0.25</td>
<td>4.139; .0091</td>
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<tr>
<td>Cho</td>
<td>1.45 ± 0.17</td>
<td>1.46 ± 0.09</td>
<td>1.42 ± 0.20</td>
<td>1.56 ± 0.12</td>
<td>2.945; .0391</td>
</tr>
<tr>
<td>NAA/Ins</td>
<td>1.16 ± 0.02</td>
<td>1.11 ± 0.03</td>
<td>1.18 ± 0.03</td>
<td>1.08 ± 0.02</td>
<td>2.964; .0381</td>
</tr>
<tr>
<td>GLX/Ins</td>
<td>1.48 ± 0.04</td>
<td>1.46 ± 0.07</td>
<td>1.49 ± 0.04</td>
<td>1.26 ± 0.05</td>
<td>4.712; .0051</td>
</tr>
</tbody>
</table>
Raphe Nuclei Stimulation Targeting Neuropathic Pain after SCI

Laboratory of Dr. Ian Hentall

**Pain**
- Cytokines
- Vestibular
- Hypothermia
- Unconsciousness
- CO2, blood pressure

**raphe nucleus**

- Serotonin Neuropeptides (TRH, substance P, galanin)
- Pain inhibition
- Motor facilitation

**Cyclic AMP**
- Expression of neurotrophic genes
- Disinhibition of remyelination
- Modulation of inflammation

**Rehabilitation**

**Deep Brain Stimulation**
- FDA approved clinical applications
- Parkinson's Disease or Essential Tremor
- ≈300 in PAG for drug-refractory pain

**Previous findings: moderate T8 contusion**
- NRM stimulation lasted 1-7 days and started 2hrs after injury

**MOTOR**
- BBB, gridwalk, footprint
  - Most variables improved, some ∝ stim. duration
  - Best start 2d post-SCI
  - Least effective start 56d post-SCI

**HISTOLOGY**
- Preservation of myelinated fibers
- Increased 5HT terminals with longer stim

**PAIN**
- mechanical allodynia
  - Forepaws normalized

**cAMP SIGNALING**
- All around recovery of injury-induced decline in cAMP, phospho-PKA and phospho-CREB

**Current human trial**
**Treatment of Pain and Autonomic Dysreflexia in SCI with DBS**
- 8 patients with >T6 SCI and chronic neuropathic pain
- Collaboration with:
  - Jonathan R. Jagid, M.D (Miami Project to Cure Paralysis)
  - Eva Widerstrom-Noga, Ph.D. (Miami Project to Cure Paralysis)
  - Alberto Martinez-Arizala, M.D. (Miami VA)
CNS Injury Research

- Neuroprotection/Pathophysiology
  - Can we protect?
- Transplantation/Regeneration
  - Can we repair?
- Rehabilitation
  - Can we retrain?
- Quality of Life
  - Can we improve life?
- Clinical Trials
  - Can we improve functional outcome?
- Education/Training
  - Can we train the next generation of scientists?
Combination Therapies

- Neuroprotection (Hypothermia, Pharmacotherapy)
- Promoting endogenous reparative processes
- Develop novel bridging strategies
- Innovative cellular transplants
- Targeting growth/inhibitory factors
- Improving axonal function
- NeuroRehabilitation—retraining/enabling the injured CNS
- Brain/Machine Interface - Neuroprosthesis
Closing Remarks

- As a scientific community we have accomplished many things regarding the pathophysiology and treatment of SCI.
- Indeed, these are exciting times in the field with many disciplines coming together to help target the complicated problem of SCI.
- Therapeutic hypothermia and temperature management appears to be a safe and effective strategy for SCI.
- However, we still have many hurdles to clear before “Cures” are fully realized.
Factors Influencing the Continued Successful Progress in the Treatment of SCI

- Reproducibility/replication of preclinical findings.
- Cross-fertilization between different research areas.
- Ethical and safety considerations of new trials.
- Emphasis on patients needs (quality of life).
- Role of rehabilitation and biotechnology.
- Better strategies for dealing with patient heterogeneity.
- Funding of large multicenter clinical trials/0.8% of NIH budget for SCI.
- Interaction between academia and industry.
- Precise data collection, analysis and distribution.
- Continued emphasis on multi-organ dysfunction after SCI.
The Miami Project Faculty 2014

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Rehabilitation Medicine
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Thank You