Promising Treatments for SCI: 
What’s on The Horizon

Shawn Song, MD  
SCI Fellow  
University of Washington/VA Puget Sound  
Healthcare System

SCI: A Devastating Injury

- Epidemiology:  
  - Incidence of ~12,000 patients/year.  
  - ~265,000 people living with SCI in the US.

- Costs:  
  - Personal: Loss of independence.  
  - Societal: ~$20 billion/year for medical costs,  
    disability support, and lost productivity.

Case: Mr. MC

- 25 y/o M involved in motocross accident.  
  - No spontaneous movement of UE/LE's observed  
    by EMS.  
  - Immobilized, transported to HMC.  
  - Noted to be hypotensive in ED,  
    started on dopamine gtt.
Case: Mr. MC

- 25 y/o M involved in motocross accident.
  - CT reveals b/l C4-5 jumped facets, MRI shows increased T2 signal with punctate hemorrhage at level of C4-5.
  - ASIA exam reveals C4 AIS A level.
  - Taken to OR for C4-5 laminectomy, C3-C6 PSIF <24hrs after injury, admitted to neuro ICU post-op.

SCI Treatment: Current Strategy

- Manage acute medical complications:
  - Neurogenic shock.
  - Respiratory failure.
- Minimize secondary damage to spinal cord:
  - Maintain spinal perfusion.
  - Surgical decompression.
- Maximize function with rehabilitation.
- Manage chronic complications.

Clinical Targets

1. Rescue: Minimize 2nd damage
2. Reactivate: Enhance existing connections
Clinical Targets: 3 Rs

- **Rescue**: Minimize secondary damage.
  - Reduce intradural pressure: Durotomy?
  - Reduce inflammation: Induced hypothermia, ketogenic diet.
- **Reactivate**: Enhance existing connections.
  - Epidural stimulation.
- **Rewire**: Axonal regeneration.
  - Schwann cell transplantation, stem cells, matrix modification.

Intradural Pressure: Background

- Cord compression, hemorrhage, and swelling are associated with poor neurologic recovery.
- Standard surgical decompression does not relieve intradural pressure caused by cord edema and hemorrhage.
- Durotomy decompression improves functional outcomes in animal models.
Evidence for Durotomy

- Zhu et al. performed durotomy as well as removal of arachnoid adhesions and necrotic tissue in 30 patients with ASIA A SCI.
- **Results:**
  - All 30 patients were able to produce walking movements (43% were ambulatory with crutches, cane, or no assistive device).
  - Patients who underwent surgery between 4-14 days post-injury had the best functional recovery.

Hypothermia: Background

- **Theory:** Hypothermia leads to ↓ apoptosis, mitochondrial dysfunction, metabolic demand, cell membrane injury, inflammation.
- Therapeutic hypothermia is used successfully for brain protection following cardiac arrest.

Systemic Hypothermia

- **Evidence:**
  - Two recent small studies have shown improved rates of conversion from complete to incomplete injuries at 1 year after injury (43% conversion rate) following cooling in the acute period.

Local Hypothermia

• Hansebout et al. cooled the spinal cord of 20 patients with complete SCI to 6° C x 4 hrs within 8 hrs of injury.
• Cooling was achieved by direct application of an epidural cooling saddle during decompressive surgery.
• 13/20 patients converted to incomplete injuries > 1 year later (avg follow-up time was 5 yrs).

Neuroprotective Diet

• Animal studies have suggested improved neuroprotection and functional recovery with omega-3 polyunsaturated fatty acid supplementation and ketogenic diet.
• Ketogenic diet has been used successfully in patient with epilepsy.

Clinical Targets: 3 Rs

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Epidural Stimulation: Background

- The spinal cord of rats and cats can generate walking movements even in the absence of input from the brain.
  - Thought to be due to lumbosacral pattern generator circuitry.
- **Theory:** If similar spinal circuits exist in humans, stimulation of the cord may facilitate standing/stepping.

Epidural Stimulation: Evidence

- Harkema et al. implanted a lumbosacral epidural stimulator in 4 motor complete pts.
- Each received months of standing/walking training with weight-supported treadmill.
- All 4 patients were able to stand with full weight-bearing x several minutes and move muscles in their legs on command.

Clinical Targets: 3 Rs

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Glial Cell Transplantation: Background

- Glial cells such as Schwann cells provide support for axonal regeneration.
- Grafting Schwann cells at the site of SCI may support and encourage growth of new axons.

Glial Cell Transplantation: Evidence

- No human trials of efficacy yet.
- Phase I safety study using autologous Schwann cells has been initiated (Miami Project).
  - Population of complete thoracic-level SCI patients.
  - Autologous Schwann cells are injected directly into damaged spinal cord.
  - Outcome measures include neurologic function, level of disability, pain, and spasticity.

OEC Transplantation: Background

- Olfactory ensheathing cells (OECs) help the guidance and growth of newly generated olfactory receptor axons into the CNS throughout adult life.
- Grafted OECs have helped pet dogs that have suffered SCI regain some limb coordination.
OEC Transplantation: Evidence

• Tabakow et al. published a case study of one patient who underwent OEC transplantation.
• Patient: 38-y/o M with T9 complete injury, 21-months post-injury.
• Autologous sural nerve was used to bridge injured spinal cord section in combination with OECs.
• Patient improved to incomplete injury.

Stem Cells: Background

• Stem cells are capable of giving rise to a vast array of cell types.
• Stem cells might be able to bridge lesion sites and replace lost neurons or support cells.
• Risk of tumorigenicity, ethical concerns.

Stem Cells: Evidence

• One ongoing phase 1/2 trial of human neural stem cells in patients with SCI.
• 12 patients with chronic motor complete SCI have received stem cell transplants.
• To date, no safety concerns reported.
• Early results show sensory improvement below the level of injury in “some” patients.
Chondroitinase ABC: Background

• Chondroitinase ABC (ChABC) is a bacterial enzyme that digests sugar chains, which results in a matrix in the injured spinal cord that is more permissive for growth.
• Multiple studies have shown that ChABC results in functional recovery in animal models, including recovery of bladder function.

Chondritinase ABC: Evidence

• Lee et al. used peripheral nerve grafting in combination with ChABC to bridge the SCI lesion site in a rat model.
• Treated rats demonstrated recovery of bladder function, proving re-establishment of functional connections in the SC.
• No human trials to date.

Summary

• There is promising research in the areas of rescuing neural tissue from 2o damage, reactivating spared circuitry, and rewiring the spinal cord after injury.
• There is real hope that some of these interventions will translate into improved outcomes after SCI.