Treatments for Acute Spinal Cord Injury

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Spinal Cord and Brain Injury Research Center
University of Kentucky
FDA Approved Drugs for Acute SCI
Progress to date

• NIH funding
  • ~$142 million/yr (486 active awards)
• State/Private foundations
  • ~$30 million/yr
• >5000 papers on SCI treatments in rodents
  • Most replication studies failed
• 140 clinical trials on Acute SCI
• No FDA-approved drugs for Acute SCI
Insanity: Doing the same thing over and over again and expecting different results.

Albert Einstein
“SUCCESS IS THE ABILITY TO GO FROM ONE FAILURE TO ANOTHER WITH NO LOSS OF ENTHUSIASM.”

WINSTON CHURCHILL
“FAILURE IS SIMPLY THE OPPORTUNITY TO BEGIN AGAIN, THIS TIME MORE INTELLIGENTLY.”

HENRY FORD
Why have we been unsuccessful in developing a drug for acute SCI?

• Problems with pre-clinical studies?
  • Reproducibility, Statistics, Bias
• Our animal models are inadequate?
• Complexity of SCI? Wrong targets?
  • Single target insufficient?
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Amgen attempted to reproduce findings in 53 ‘landmark’ cancer papers. **Six findings were replicated (11%)**

Begley and Ellis, Nature 2012
Why Most Published Research Findings Are False

John P. A. Ioannidis

Power failure: why small sample size undermines the reliability of neuroscience

Katherine S. Button, John P. A. Ioannidis, Claire Mokrysz, Brian A. Nosek, Jonathan Flint, Emma S. J. Robinson and Marcus R. Munafò

Nature Reviews Neuroscience, 2013

The fickle P value generates irreproducible results

Lewis G Halsey, Douglas Curran-Everett, Sarah L Vowler & Gordon B Drummond

Nature Methods, 2015
Which finding would get published?
A 2 populations, different sample sizes

Lactate (mmol L\(^{-1}\))

\[
P = 0.066 \quad P = 0.044
\]

Low    High    Low    High

B Difference between means and 90% confidence limits

Difference in lactate (mmol L\(^{-1}\))

Samples of 20    Samples of 40

Actual difference
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Spinal Cord Injury Models

Infinite Horizons Impactor (Scheff et al., 2003, J Neurotrauma)

15 min post-injury

Joachim (Sanders) et al, PLOS One 2010
Time course of degeneration following 5 min compression injury to cat spinal cord

- Cross section of the normal spinal cord
- 3 to 5 minutes after SCI
- 15 to 30 minutes after SCI
- Several weeks after SCI

Courtesy of Doug Anderson via Ed Hall
Spinal Cord Injury Models

Animal Model
• Controlled injury, targeted
• Dorsal impact
• Pre-injury anesthesia
• Pre-injury decompression
• Reproducible injury severity (Mild to moderate) in most studies

Human Subjects
• Uncontrolled, often multi-trauma
• Dorsal and Ventral impact
• No anesthesia
• Post-injury decompression
• Wide range of injury severities in most clinical trials

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What is a spinal cord injury?
What causes secondary neurodegeneration? What should we target?

Mechanisms of Injury

Primary Injury
1 - Loss of Neurons/Axons
2 - Demyelination

Secondary Injury
1 - Loss of Neurons/Axons
2 - Demyelination
3 - Inflammation
4 - Reactive Oxidative Damage and the Astrocytic Glial Scar
5 - Cyst Formation

Activated Astrocytes
Infiltrating Lymphocytes
Activated Monocytes
Phagocytic Monocytes
Neurons

Salewski, Emrani, Fehlings 2013 DOI: 10.5772/55054
What causes secondary neurodegeneration? What should we target?

Primary Injury → Spinal Cord

(Initiation of secondary injury process)

↑ Ca²⁺, ROS, Cytokines → ↑ Calpain, Caspase-3

Calpain inhibitor, Caspase-3 inhibitor → Apoptosis (Neurodegeneration)

Injury → Ca²⁺ Influx → Mitochondrial Ca²⁺ uptake → mtNOS activation → O₂⁻, NO → ONOO⁻ → Penicillamine, PN scavenger

•OH, •NO₂, •CO₃ → Tempol, PN scavenger

Cell membrane oxidative damage → Inhibition of Ca²⁺ ATPase → Phenelzine, CHO scavenger → ↓ in ATP & Ca²⁺ buffering

Ca²⁺ release → Calpain activation → NEURODEGENERATION

Ray, Hogan, Banik, Brain Res Rev 2003

Bains, Hall BBA 2012
Either there is a destruction of axis cylinders directly consequent to the impact, or else, owing to the impact, there is an edematous and hemorrhagic outpouring into the cord tissue, by which its pressure and chemical activity inhibits temporarily all conduction function, or destroys permanently the “spinal cord.”  

...direct injury to the axis cylinder by the impact is beyond our reach, at that we should better confine our attention to the amelioration of the heightened intramedullary pressure.
Allen  1911, 1914

Dog spinal cord 6h after 540 gm-cm impact

A median longitudinal incision of at least 1 cm is made completely through the cord, following which there is a goodly outpouring of blood and serum from the cord substance. *(Full depth myelotomy)*
The typical distribution of intraparenchymal hemorrhage in the acutely contused spinal cord.

Mautes, Noble et al., *Phys Ther* 2000
Arterial supply to the spinal cord

http://stroke.ahajournals.org/content/strokeaha/45/10/e203.full.pdf
Freeman and Wright, 1953

- also examined dogs (adult female) 340-500 gcf
  - Paired based on size, one injury alone, 2nd injury plus myelotomy
**TABLE 5**

*Recovery measured by the inclined-plane technique in the full-depth myelotomy study*

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<th>Post Op Week</th>
<th>Myelotomy: Full Depth</th>
<th>Control</th>
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<tbody>
<tr>
<td>1</td>
<td>29.5 ± 4.4</td>
<td>28.2 ± 3.4</td>
</tr>
<tr>
<td>2</td>
<td>36.8 ± 9.2</td>
<td>28.1 ± 3.7</td>
</tr>
<tr>
<td>3</td>
<td>40.2 ± 9.7</td>
<td>30.5 ± 3.7</td>
</tr>
<tr>
<td>4</td>
<td>41.9 ± 9.1</td>
<td>31.3 ± 3.9</td>
</tr>
<tr>
<td>5</td>
<td>47.5 ± 4.3</td>
<td>31.7 ± 3.5</td>
</tr>
<tr>
<td>6</td>
<td>47.5 ± 4.4</td>
<td>33.5 ± 3.4</td>
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</tr>
<tr>
<td>8</td>
<td>47.7 ± 4.4</td>
<td>33.6 ± 3.2</td>
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Rivlin, Tator. Effect of vasodilators and myelotomy on recovery after acute spinal cord injury in rats. *J Neurosurg.* **1979** Mar;50(3):349-52. (half-depth myelotomy was not as effective)
Myelotomy 24h post-injury improves locomotor function and tissue sparing

Yang et al., *Spinal Cord* 2013
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Glibenclamide reduces hemorrhage and lesion size, and improves function after SCI

Simard JM et al., J Clin Invest. 2007
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Pressure monitoring

- Measurement of intracranial pressure (ICP) is a **cornerstone of care for treatment of TBI**.
- Also mean arterial pressure (MAP) and cerebral perfusion pressure (CPP) = MAP - ICP
- Treatment aims to optimize CPP, results in reduction in mortality and morbidity
- Intraspinal pressure (ISP) is not monitored following SCI
  - Thought that anatomy of spinal cord allows for substantial swelling
Relationship between monitored physiological parameters and neurological outcome.

A

B

Improvement (% of patients)

1 or > AIS grade improvement

2 or > AIS grades improvement

C

D

Improvement (% of patients)

Saadoun, Papadopoulos et al. J Neurol Neurosurg Psychiatry, 2016
Elevated ISP in rats following SCI

Khaing, Hofstetter et al., J Neurotrauma, 2017
The dura causes spinal cord compression after SCI (Laminectomy does not reduce ISP)

http://vanat.cvm.umn.edu/neurLab2/pages/MeningesDrawing.html

Sadoon, Papadopolous et al., *Br J Neurosurg.* 2016
Durotomy and dural allograft following SCI

200 kdyn, C5

Smith et al., Journal of Bone and Joint Surgery, 2010
Contusion + Durotomy + Dural Allograft

Lesion Volume (mm$^3$)

Also improved functional outcomes (grip strength)
Durotomy improves outcomes in human SCI

Phang, Papadopoulos et al., *J Neurotrauma*, 2015
Review

• Vascular damage and swelling/edema were the first targets of experimental treatments for acute SCI (Allen 1911-14).
  • The older literature is important.
  • Early SCI treatments were based on TBI treatments
    • Hypothermia, methylprednisolone, myelotomy
• Removal of blood (hematomas) and monitoring ICP are standard of care for TBI.
• ISP management may be beneficial in SCI, along with treatments to target hemorrhage (myelotomy, glibenclamide, durotomy)
• SCI is, at least in part, a vascular disorder
Why have we been unsuccessful in developing a drug for acute SCI?

• Problems with pre-clinical studies?
  • Reproducibility, Statistics, Bias
  • Could be improved—larger n’s, replication, multi-center preclinical trials

• Our animal models are inadequate?
  • Animal models are good, but not perfect.

• Complexity of SCI? Wrong targets?
  • Single target insufficient?
  • Treat ‘obvious’ targets, then deal with complexities