A BioMEMS Implant to Treat Spinal Cord Injuries

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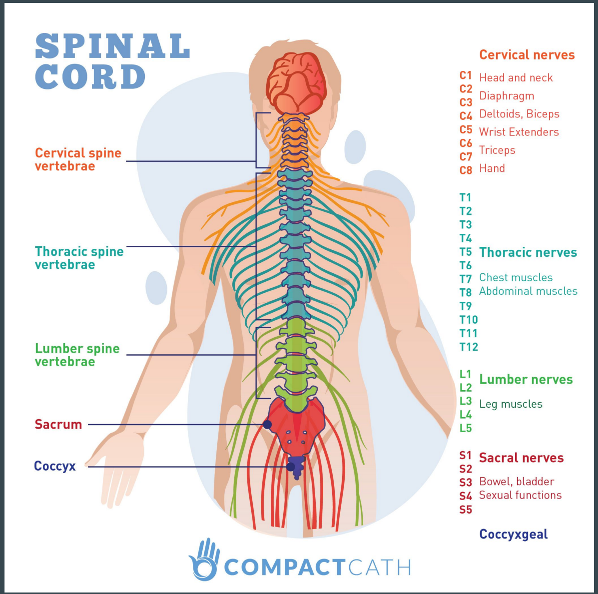
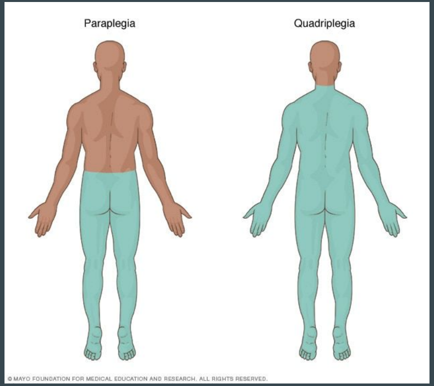
Background

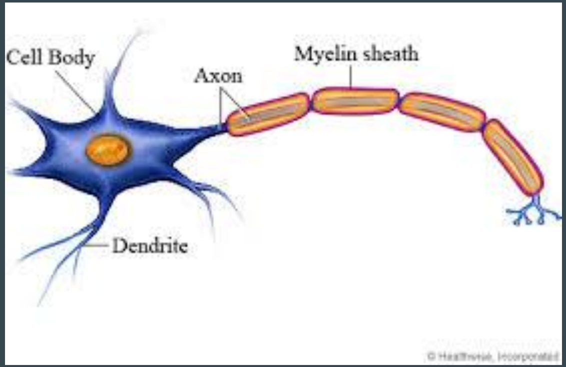
- The spinal cord consists of nerves that transmit information between the brain and the rest of the body
- 17,000 SCIs occur each year in the US
- Common causes include motor vehicle accidents, violence, sports, and falls
- 50% of SCIs are complete, meaning that the patient has lost all motor and sensory function below the injury site





Background

- Response to injury: PNS vs. CNS
  - Wallerian Degeneration (Schwann cells vs. oligodendrocytes)
  - Regeneration-Associated Genes (RAGs)
  - Impact on recovery
- Potential for PNS -> CNS transplantation
  - Schwann cells shown to perform well in new environment



Neural Stem Cells

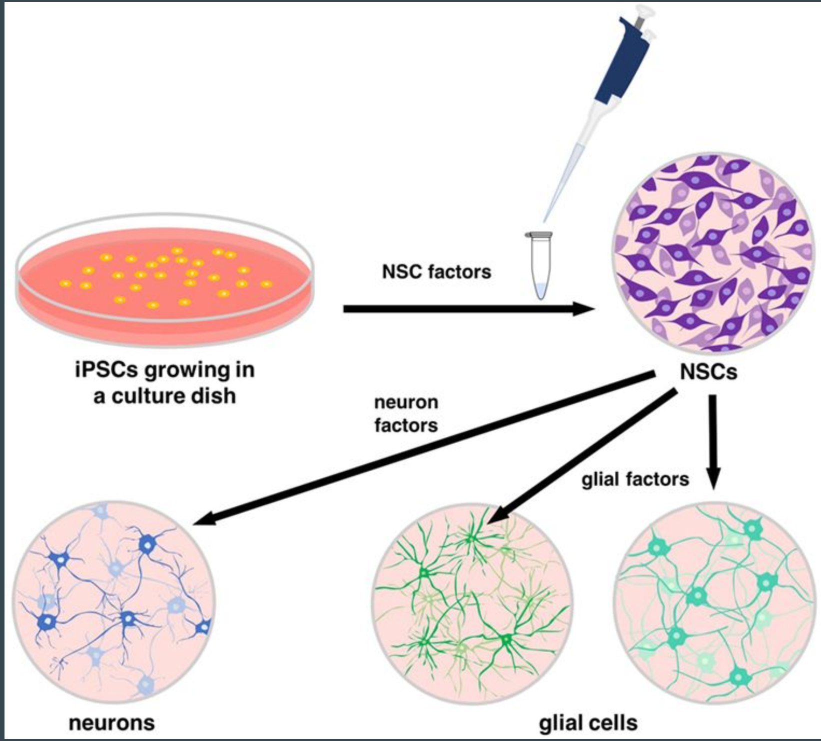
Neural stem cells (NSCs) and Schwann cells (SCs) enhance axonal regeneration

NSC's can be made from any other cell in the body

Problems during studies:

-Survival of stem cells after transplantation

-Encouraging the transplanted cells to make connections with the patient's neurons



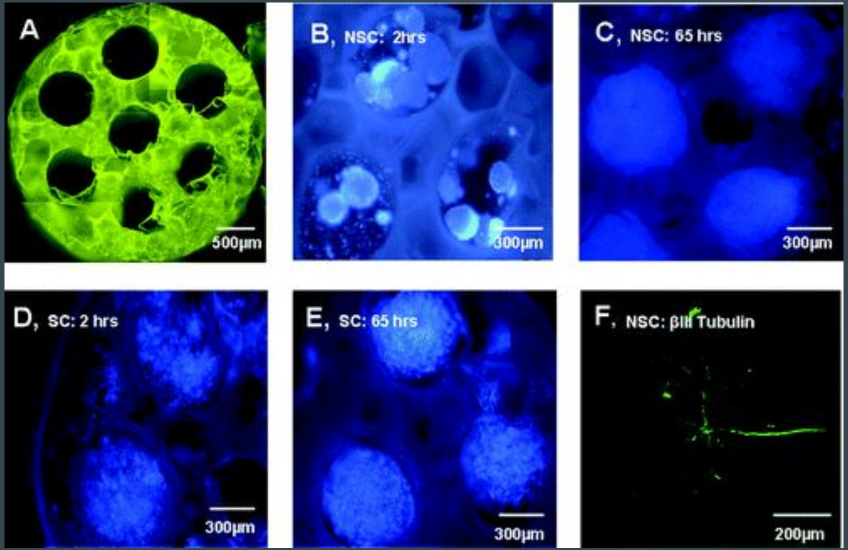
Biodegradable Polymer Scaffold

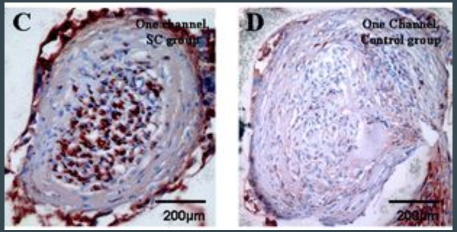
Helps guide axonal regeneration and bridge gaps at the injury site

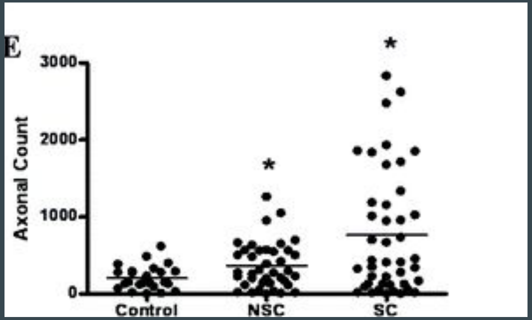
PLGA: biocompatible polymer that loses structural support at 8 wks, degrades at 24 wks

Counted number of axons 1 month after transplant

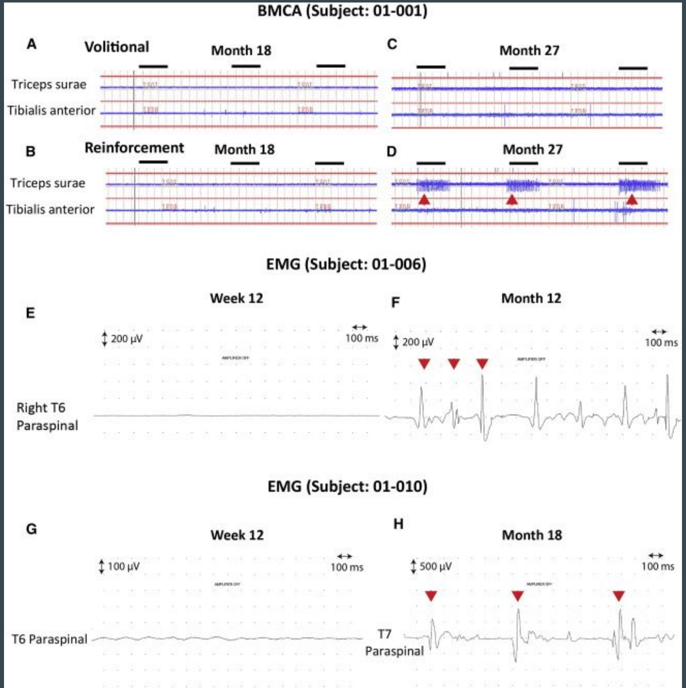
Schwann cells supported more regeneration



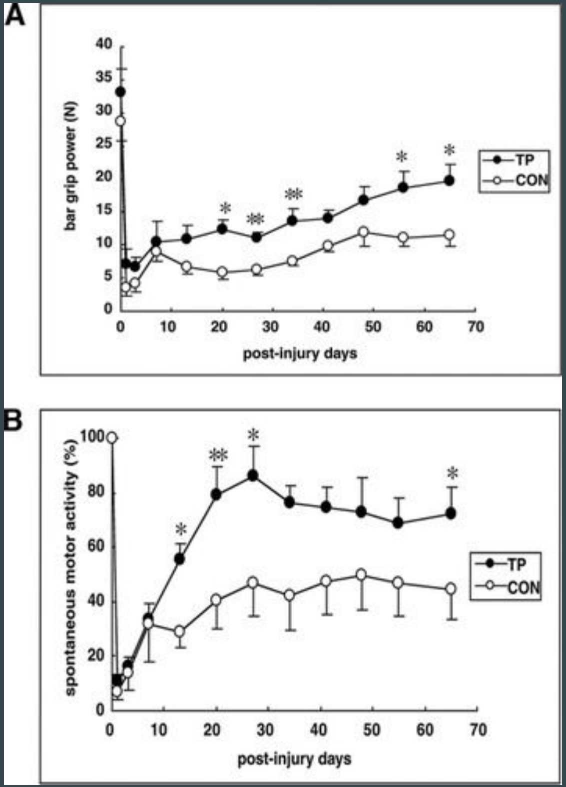




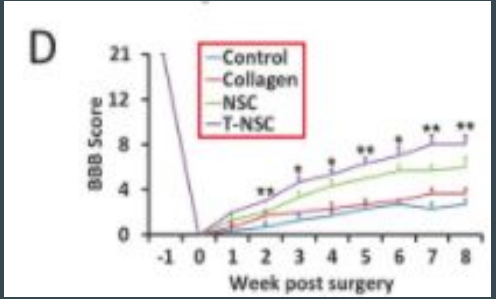
Olson 2009



Curtis, 2018



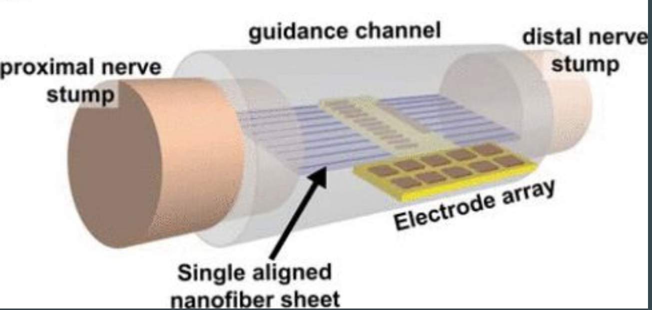
Iwanami, 2005



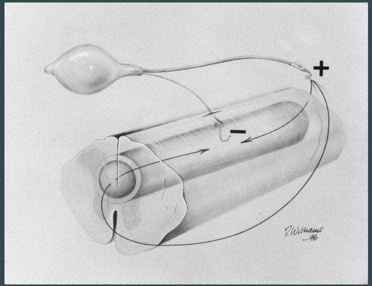
Li, 2016

Electrode Array

Implanted electrodes allow for creation of electric field
Goal 1: Influence and direct neuronal growth
Goal 2: Allow for migration of neural cells / growth factors towards crucial growth plates
Secondary Goal: Strengthen nerve signalling through longer term pulses



Flat “sieve” electrode design

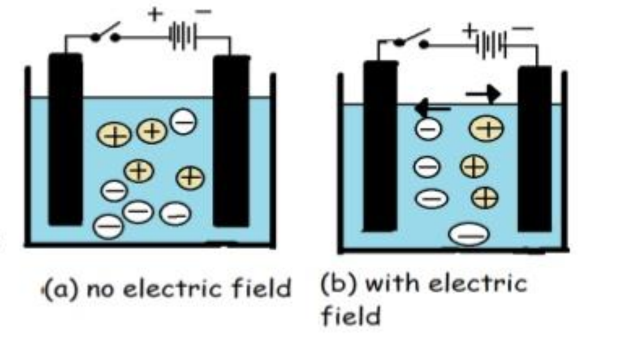


Earlier, simpler 2-end electrode

I. P. Clements, V. J. Mukhatyar, A. Srinivasan, J. T. Bentley, D. S. Andreasen and R. V. Bellamkonda, "Regenerative Scaffold Electrodes for Peripheral Nerve Interfacing," in *IEEE Transactions on Neural Systems and Rehabilitation Engineering*, vol. 21, no. 4, pp. 554-566, July 2013.

Electric Fields

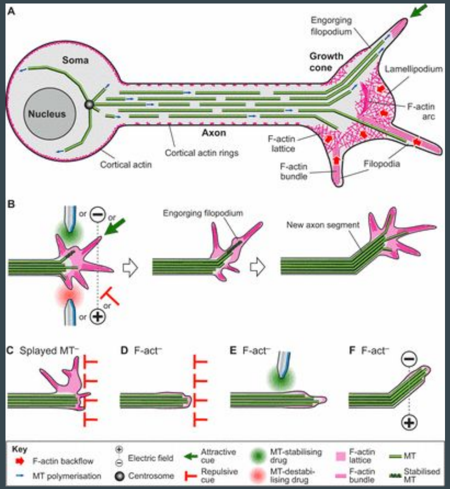
- Natural electric fields coincide with crucial periods of CNS development
  - Electrophoresis of materials
- Cathode (+) and Anode (-)
- Axons tend to grow towards cathodes (+)
- Electric activity induces axon growth ("guidance effect")
  - Elevates cytoplasmic Ca, cAMP - induces attraction



Patel N, Poo MM. Orientation of neurite growth by extracellular electric fields. J. Neurosci. 1982;2(4):483–496.

Natural Neural Regeneration

- Endogenous (natural) electric fields induce axon growth
- CNS injury leads to loss of neurons - needed for new synapses
- Transplantation of oligodendrocytes + Schwann cells (equivalents)
  - Restore axon function + insulation
- Axons in affected area grow laterally to regain function
  - Schwann cells form actin protein to degrade isolated sections of axon
  - Allows for healthy part of the axon to grow back and reconnect to its former target



Andreas Prokop, Robin Beaven, Yue Qu, Natalia Sánchez-Soriano. Using fly genetics to dissect the cytoskeletal machinery of neurons during axonal growth and maintenance. Journal of Cell Science 2013 126: 2331-2341; doi: 10.1242/jcs.126912

Artificial Stimulation and Neuroregeneration

1) Introduce transplanted Schwann cells to expose healthy axons

2) Induce both transplanted and natural neurons to grow their axons

Neural Stem Cell Migration (NSCs)

- Differentiate into neuron / glial cells - establish physiological connections
- Provide trophic support
- Enhance basal regeneration
- Effective directional migration is key to maximizing NSC effectiveness

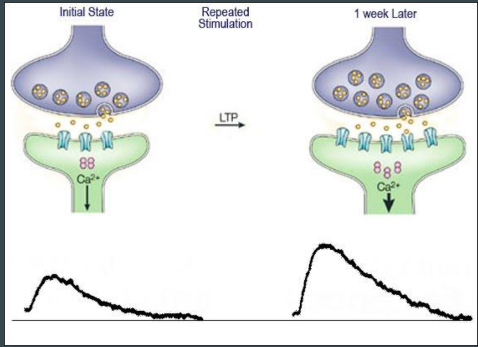
Yao, L., Li, Y. The Role of Direct Current Electric Field-Guided Stem Cell Migration in Neural Regeneration. *Stem Cell Rev and Rep* 12, 365–375 (2016).
https://doi-org.ezp3.lib.umn.edu/10.1007/s12015-016-9654-8

Long-Term Potentiation (LTP)

Increase in synaptic response following electrical stimuli

Stimulus generally high frequency, low duration (100Hz, < 1s)

Potential to strengthen existing connections with pulsed current



Sandkühler, J., & Gruber-Schoffnegger, D. (2012). Hyperalgesia by synaptic long-term potentiation (LTP): An update. *Current Opinion in Pharmacology, 12*(1), 18-27.

Proposal

We propose a hybrid biomems device that aims to promote axonal regeneration in individuals with spinal cord injuries

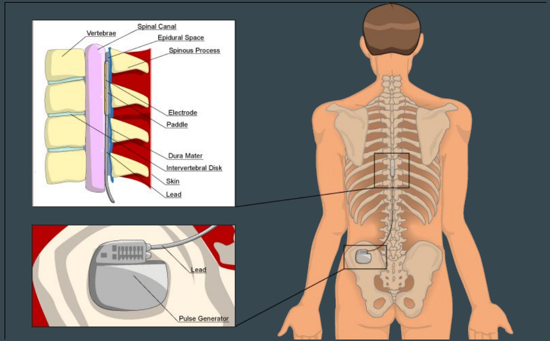
Previous and ongoing studies have been done on the restoration of functions in those with spinal cord injuries, but have limitations

Using neural stem cells can help regrow the damaged spinal cord, while electrical stimulation can strengthen these connections

Biodegradable scaffold using NSCs combined with a permanent electrode array

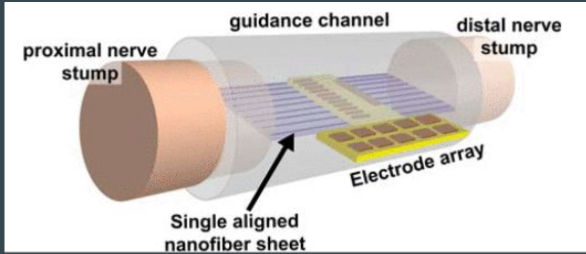
Courtine

Harkema



More detail about our specific design

- Thin-film electrode array organized within a thin-film aligned nanofiber scaffold
- Electrode design:
  - Electrically mediated guidance and regeneration of spinal axons
  - Constrain transected nerve axons to regenerate through channels, within electrode range
- Scaffold design:
  - Infused with neural stem cells
  - Scaffolding substrates within a guidance channel direct axon growth, influence morphology of the regenerated nerve
- Low-profile nerve interface design minimally obstructing the cross-sectional nerve area



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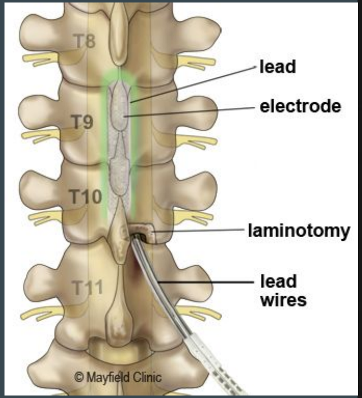
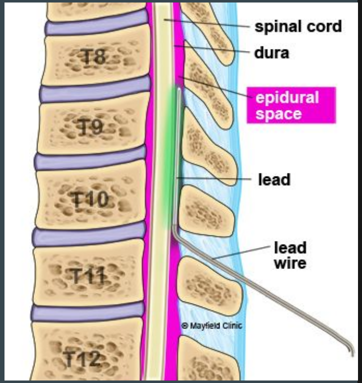
Fabrication + Design Considerations

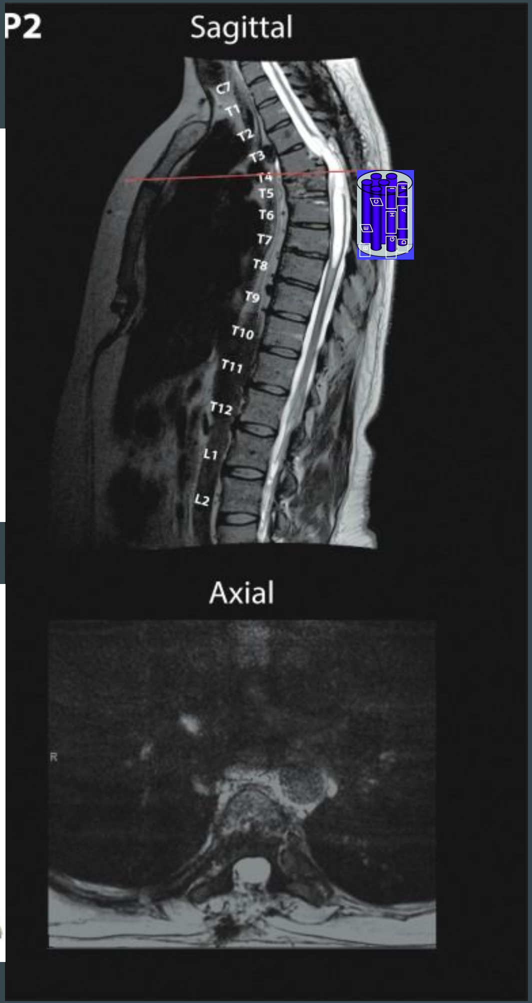
Scaffold:
- Fabricated from PLGA by an injection molding–solvent evaporation process
- Cylinder with several µm-scale internal channels

Electrodes:
- Insulating coating to prevent toxic byproduct buildup
- Appropriate EF strength ~ 5 - 10 mV/mm
- Frequency / PW
- Battery capacity / rechargeability affects long-term delivery of field

Implantation:
- Epidural space via laminotomy
- Pulse generator implanted in the back
- Begin stimulation after 2 weeks of healing



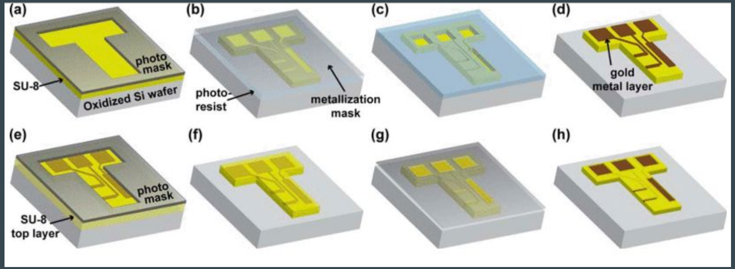




Darrow 2019

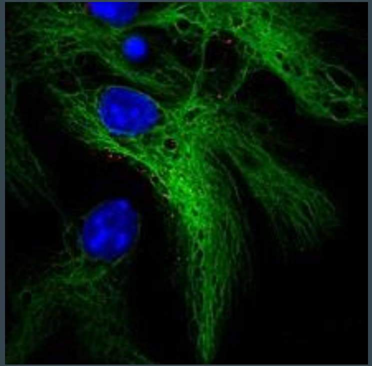
Materials

- Microelectrodes
- Wafer and photoresist material
- Nanofiber scaffolding sheets (PLGA)
- Harvested NSCs
- Semipermeable polysulfone tube (guidance channel)
- UV adhesive (medical grade)



Biocompatibility:

- Coated microelectrodes
- Biocompatible material for tube
- Biodegradable material for nanofiber scaffold



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Nerve Regeneration Test Process

- Animal studies and human studies
  - Biomarkers to gauge effectiveness
  - Evaluate use for treatment in different forms of SCIs
    - Contusion / abrasion
    - Partial
    - Transection

Future Steps

- Treatment aimed at combating inhibitory environment in CNS
- Treatment shifting to gene therapy / protein expression
  - Targeting RAGs or Myelin-Associated Inhibitors (MAIs)
    - Upregulate regeneration genes, downregulate growth-inhibiting genes
  - Treatment affecting intrinsic growth capacity of CNS neurons
    - Potential for replacing growth cone proteins