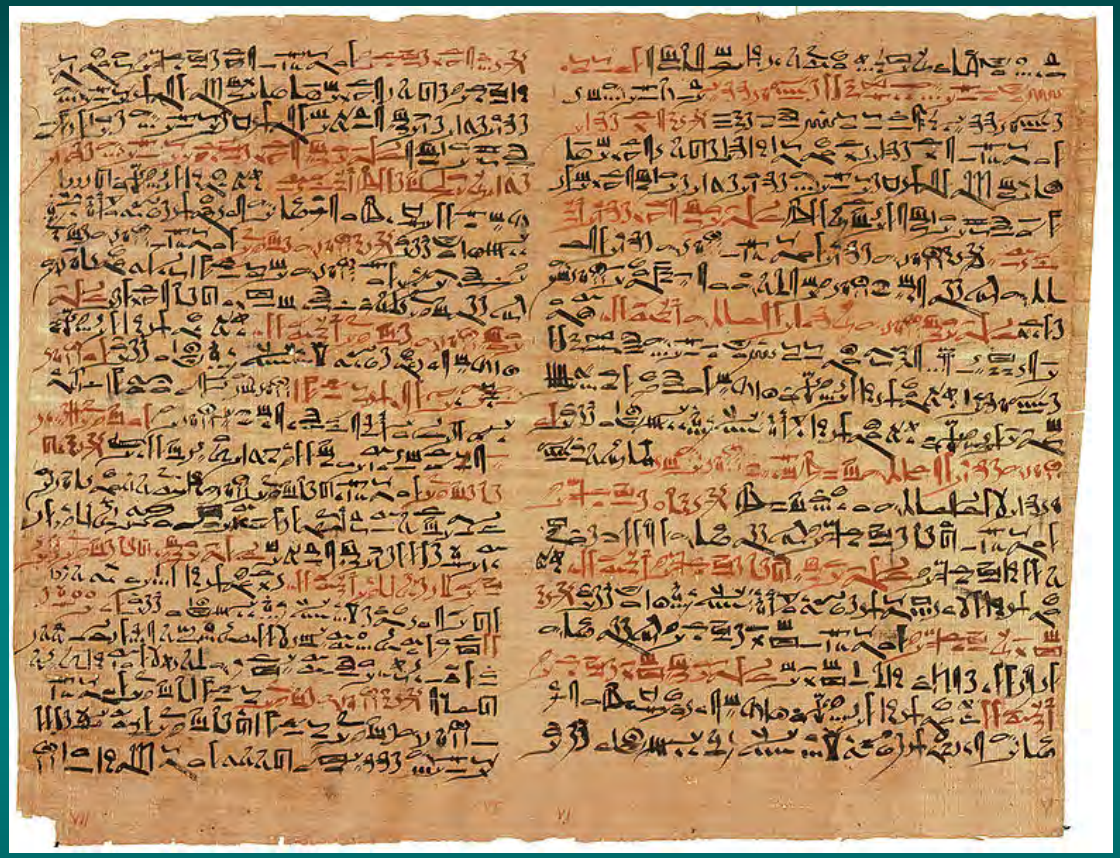
Repairing spinal cord nerves

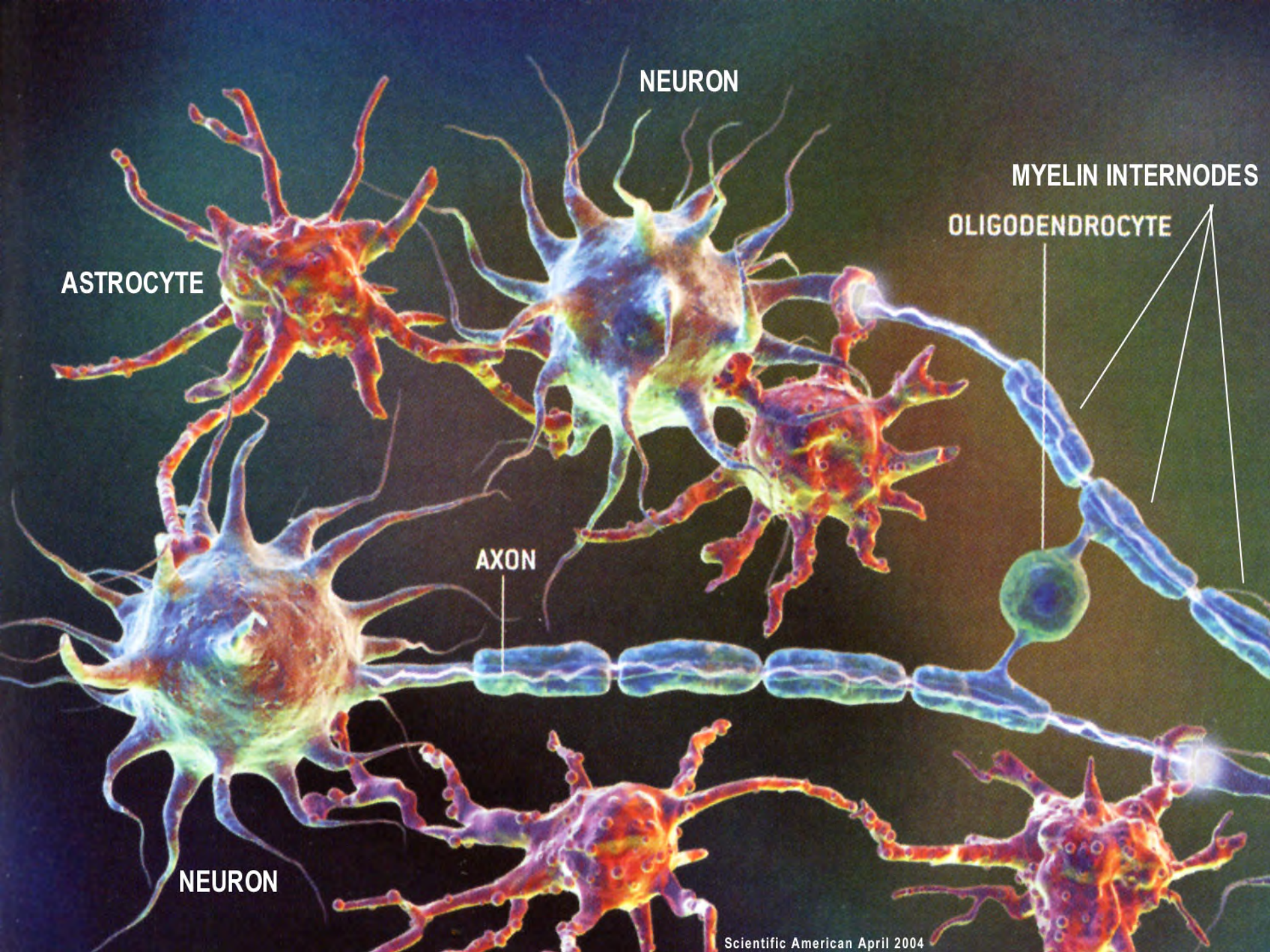
Ronald Schnaar
The Johns Hopkins School of Medicine

Traumatic spinal cord injury

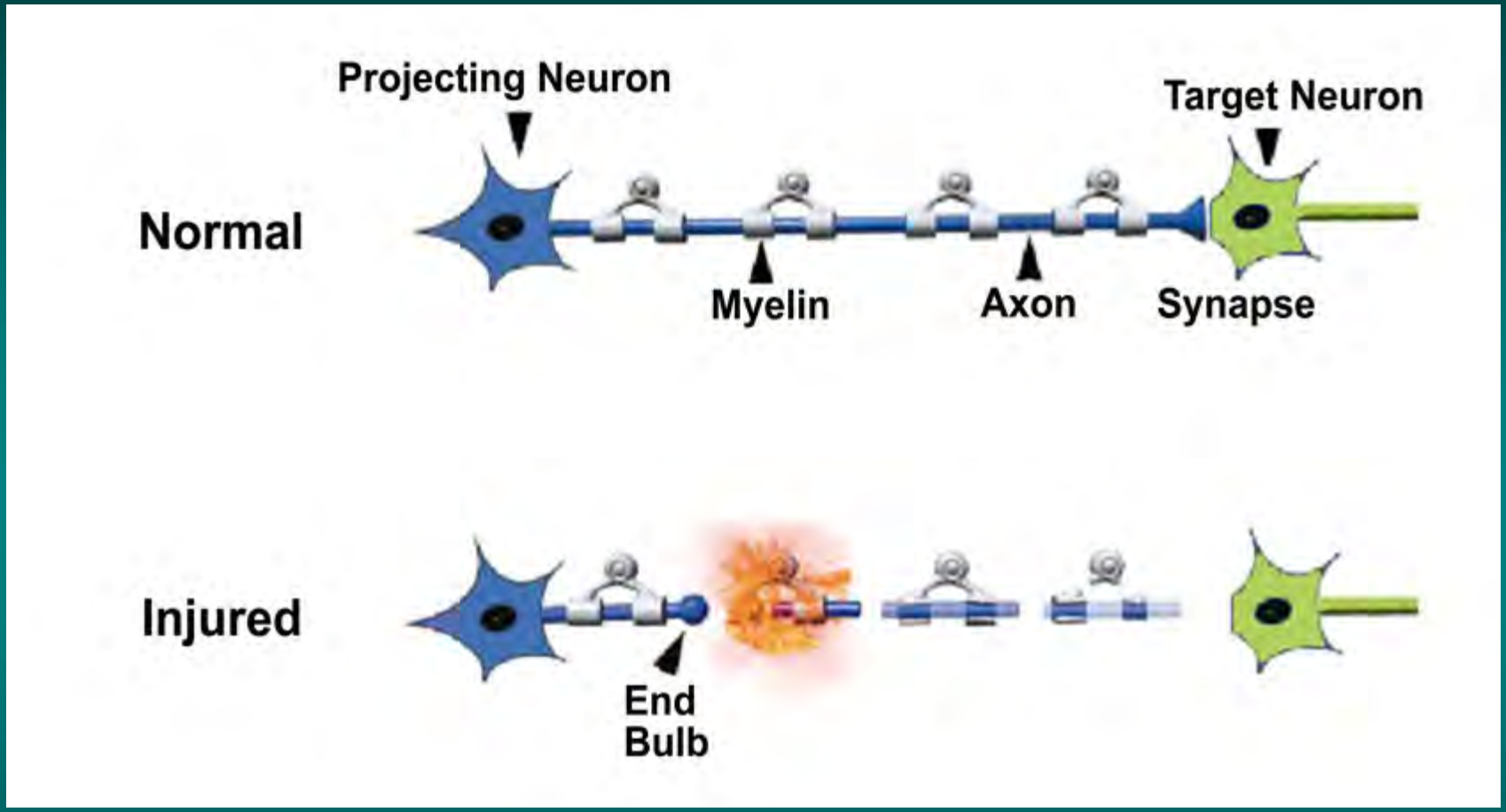


Edwin Smith Papyrus, Egypt, circa 1500 BC

Earliest medical text on battlefield trauma, in which spinal cord injury was deemed: “An ailment not to be treated”


NEURON
MYELIN INTERNODES
OLIGODENDROCYTE
ASTROCYTE
AXON
NEURON
Scientific American April 2004

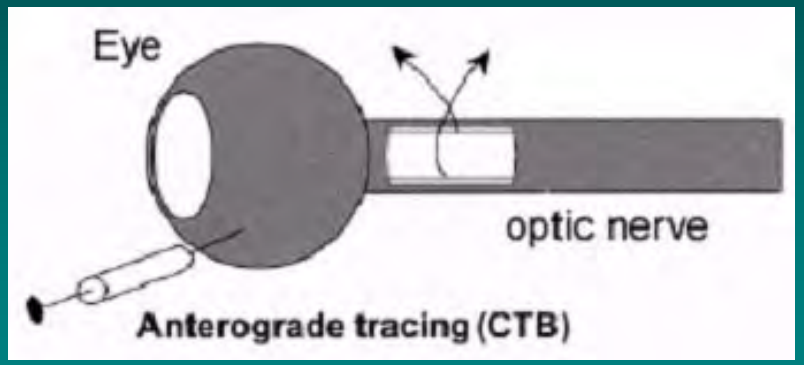
Axon transection in traumatic nerve injury



Modified from Brittis and Flanagan, Neuron (2001) 30, 11

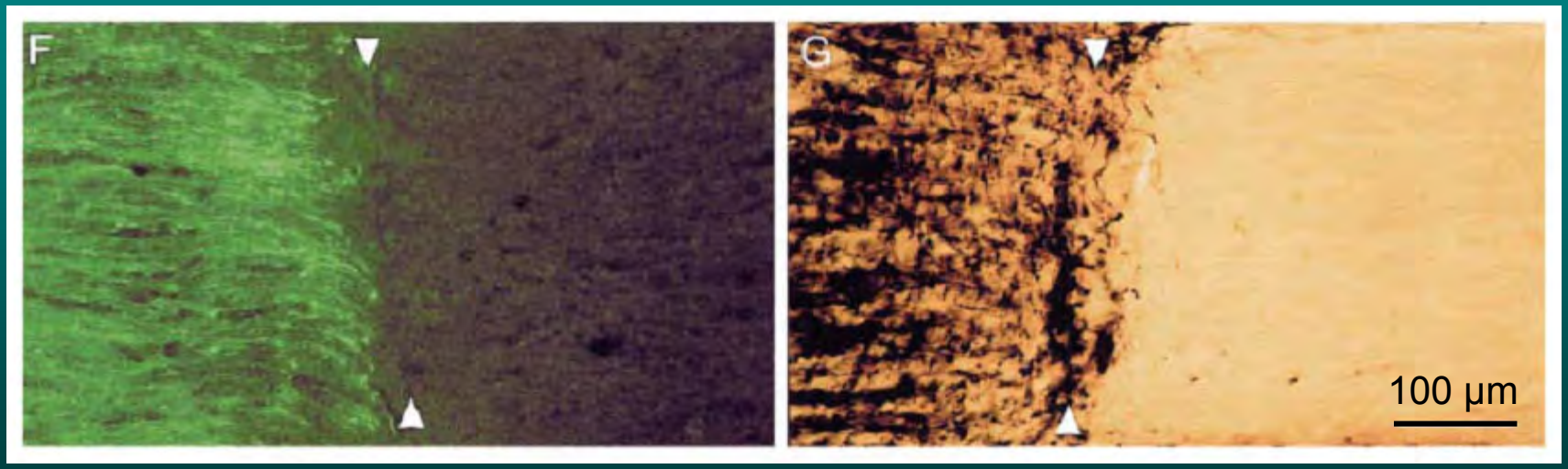
Even after a microcrush injury, nerve axons fail to regenerate after injury

optic nerve microcrush:



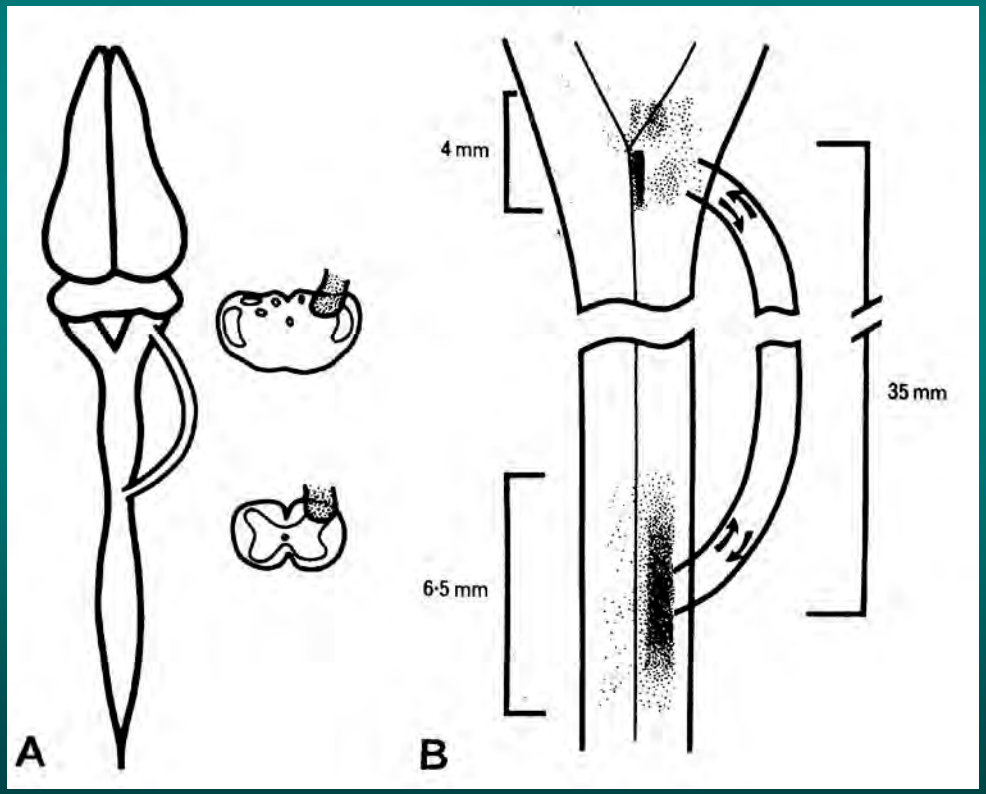
Axon retraction
24 h post-injury

Regeneration failure
2 wks post-injury



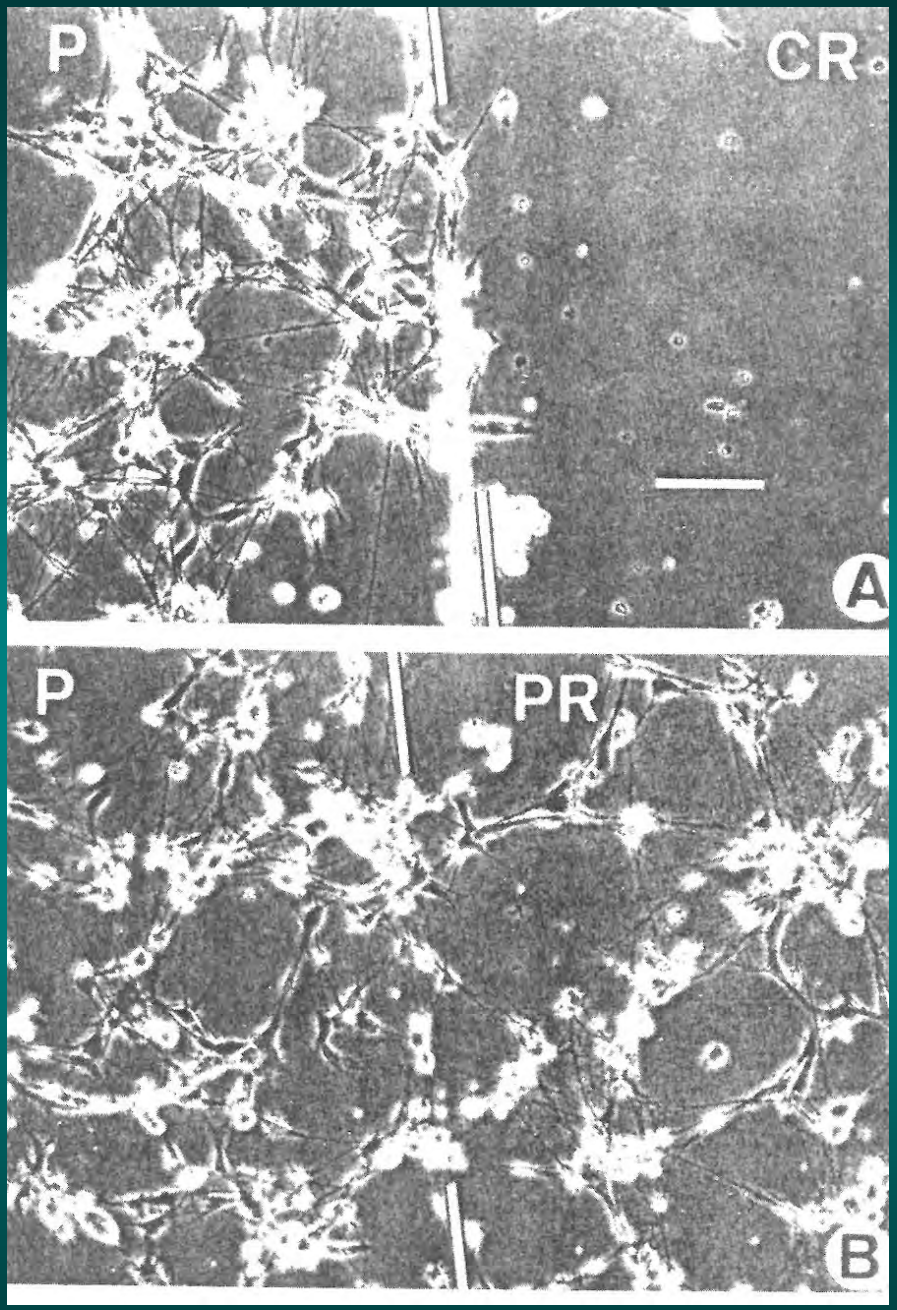
Selles-Navarro, et al. (2001) Exp. Neurol. 167, 282-289

- The peripheral nervous system (PNS) is more permissive for axon regeneration than the central nervous system (CNS).
- When PNS nerve sheath is grafted into a CNS injury, some CNS axons regenerate through the graft



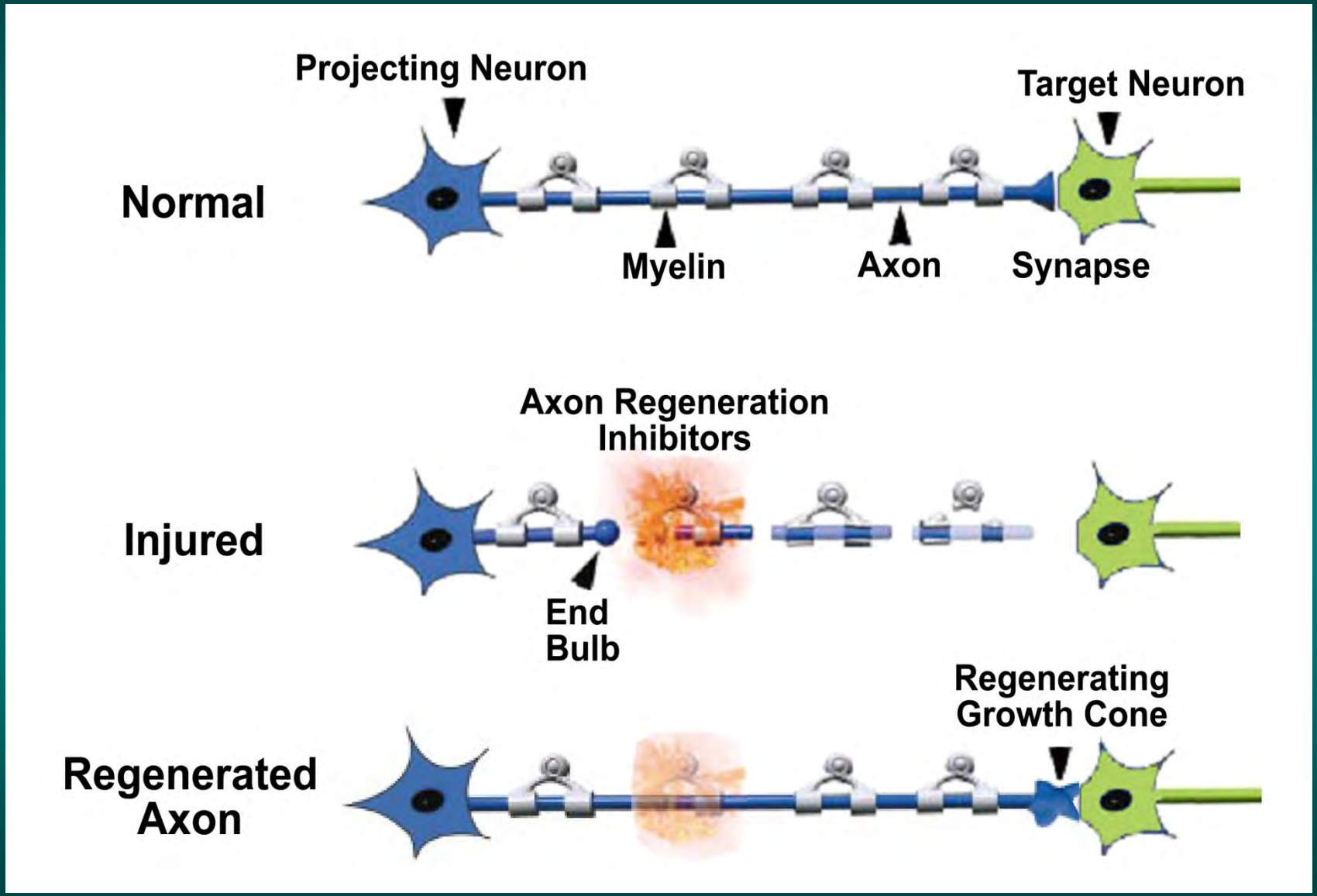
Adult Rat CNS axon regeneration
David & Aguayo (1981) *Science* **214**, 931-933

In vitro, superior cervical ganglion neurites extend on a surface coated without myelin (P) or on PNS myelin (PR), but not on a surface coated with CNS myelin (CR)



Caroni & Schwab (1988) *J Cell Biol* **106**, 1281-1288

Axon transection in traumatic nerve injury



Modified from Brittis and Flanagan, Neuron (2001) 30, 11

Multiple axon regeneration inhibitors (ARI's) accumulate at the site of a CNS injury

- Myelin-associated glycoprotein (MAG)
  - on residual myelin
- Nogo
  - on residual myelin
- OMgp
  - on residual myelin
- Chondroitin sulfate proteoglycan (CSPG)
  - on residual myelin and the astroglial scar

Blocking one or more ARI may enhance axon regeneration after spinal cord and other CNS injuries

AXON REGENERATION INHIBITORS
A working model with therapeutic opportunities

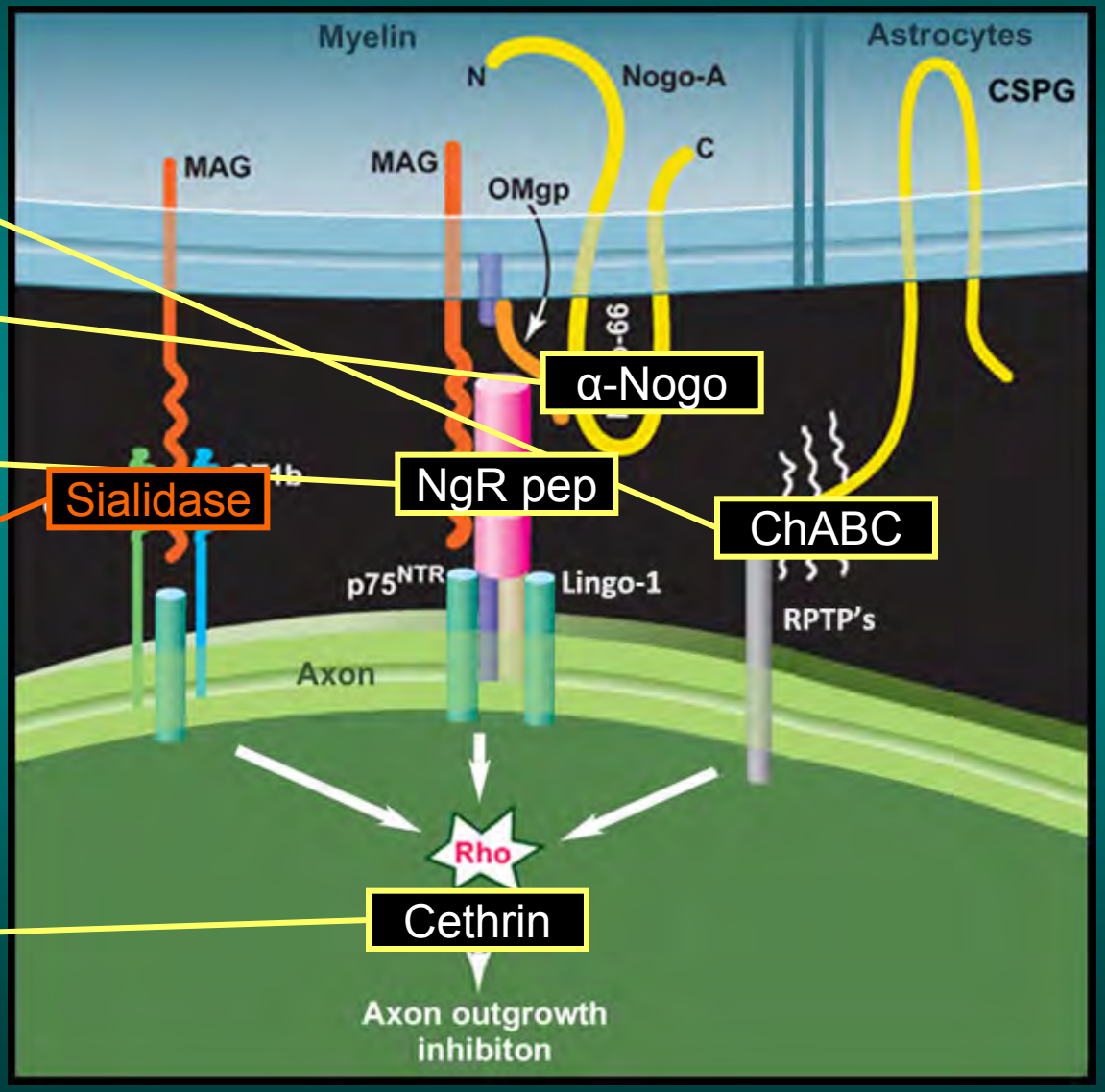
Chondroitinase ABC, Acorda

Anti-Nogo antibody, Novartis

Nogo receptor fragments Biogen IDEC

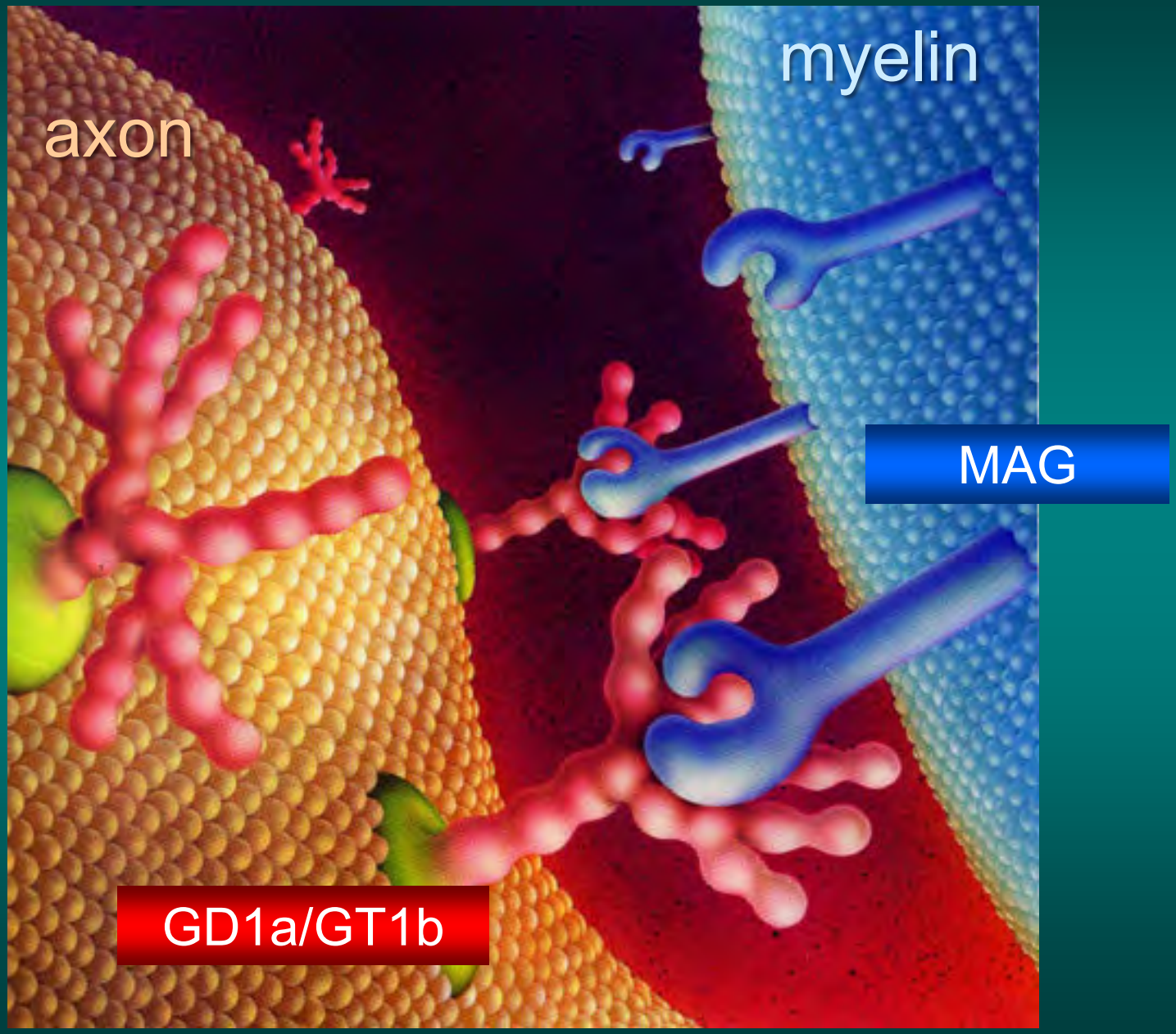
Johns Hopkins

Cethrin, BioAxone



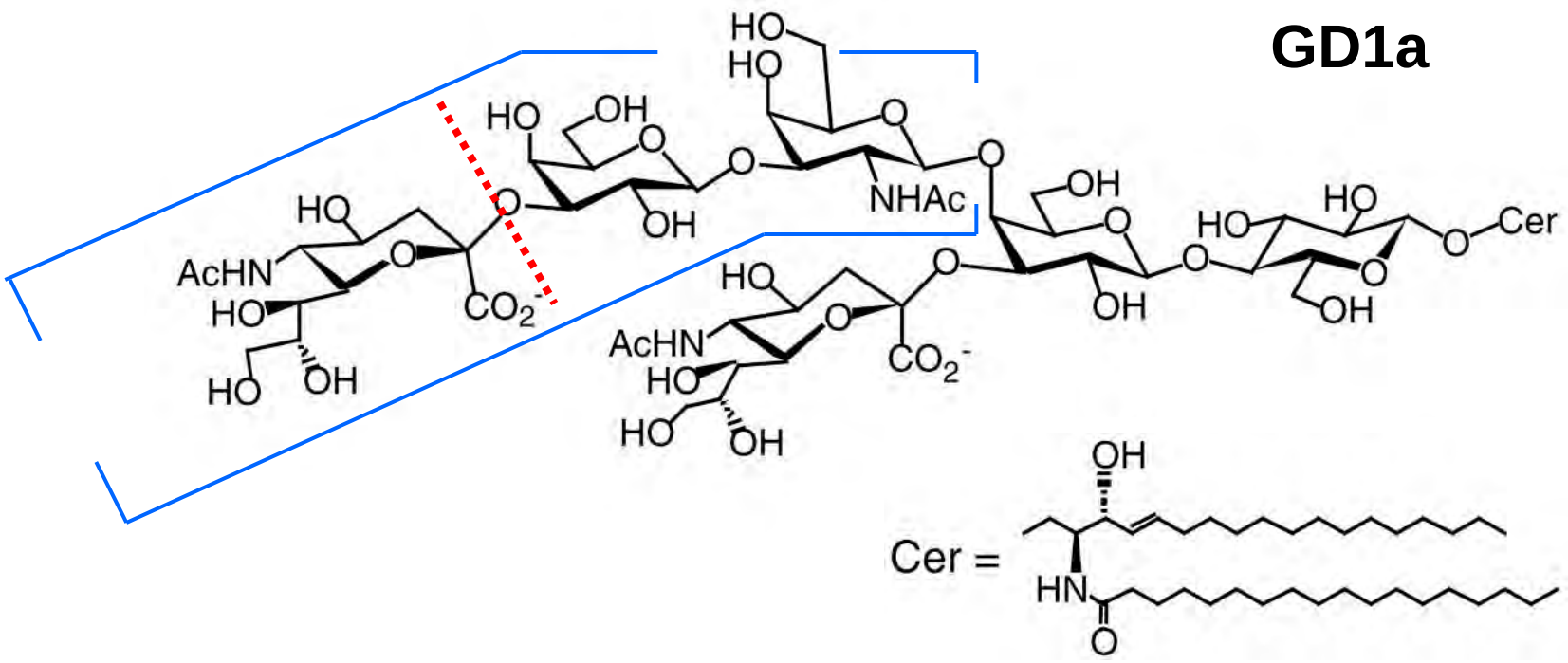
Modified from Woolf & Bloechlinger, Science (2002) 297, 1132

MAG on myelin engaging its receptors on axons



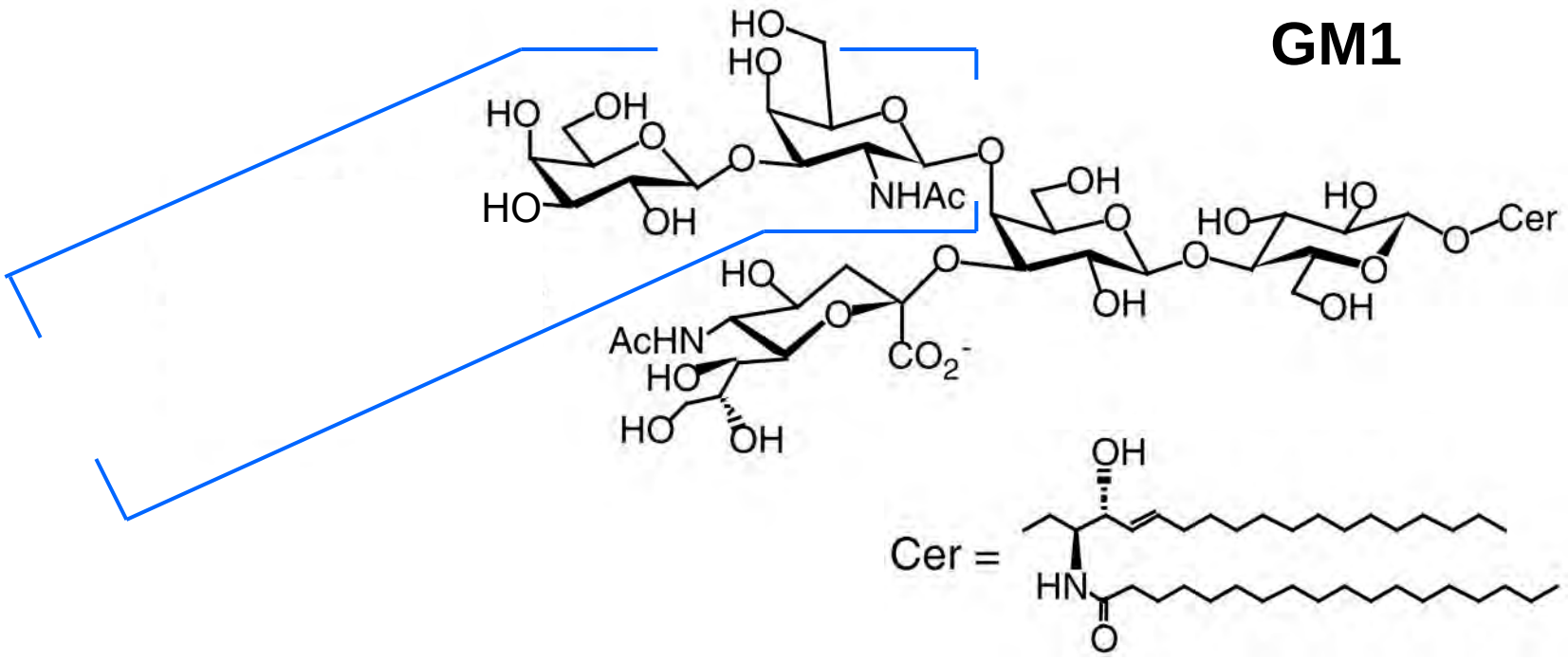
Modified from Sharon and Lis (1993) Scientific American

MAG receptor GD1a on axons



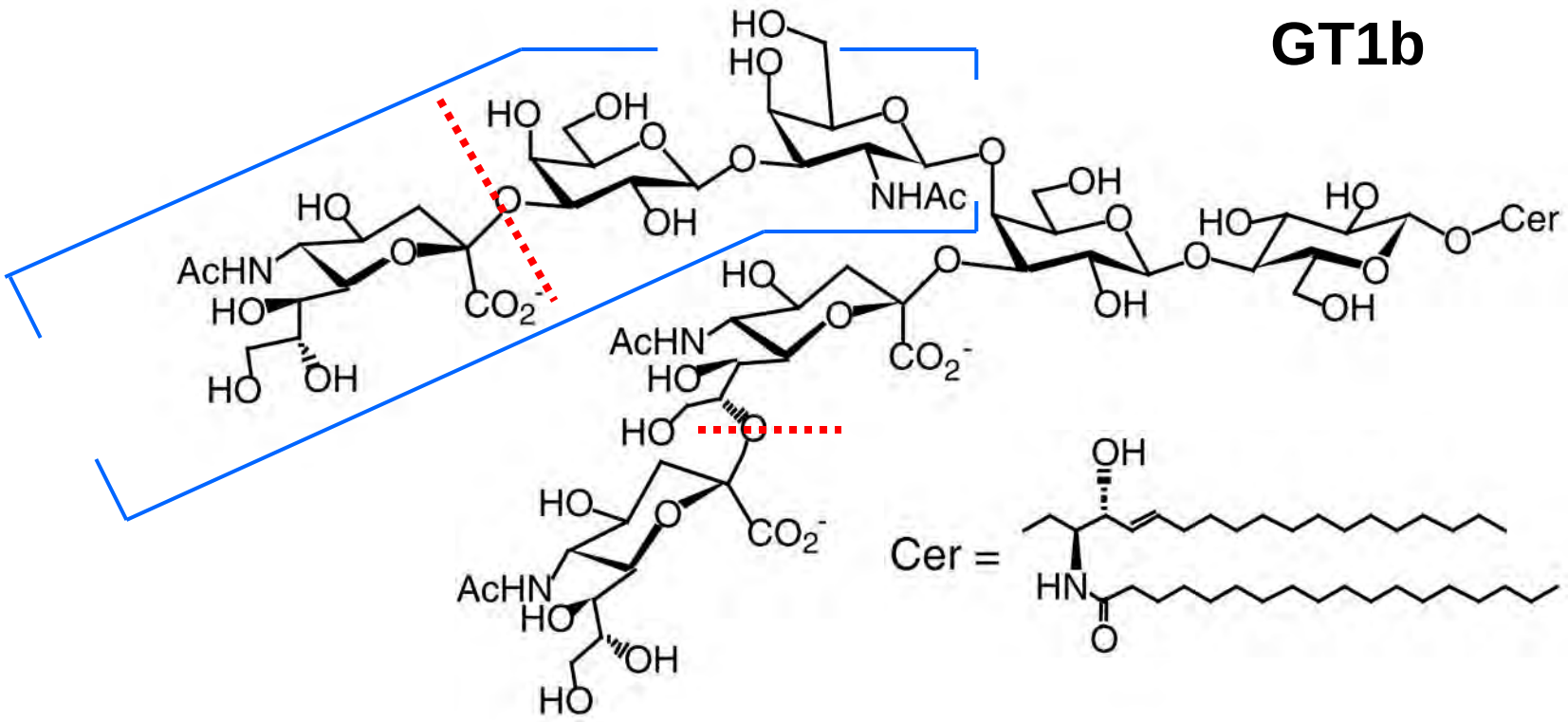
NeuAc α3 Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer

Sialidase cleaves the terminal sialic acid from GD1a



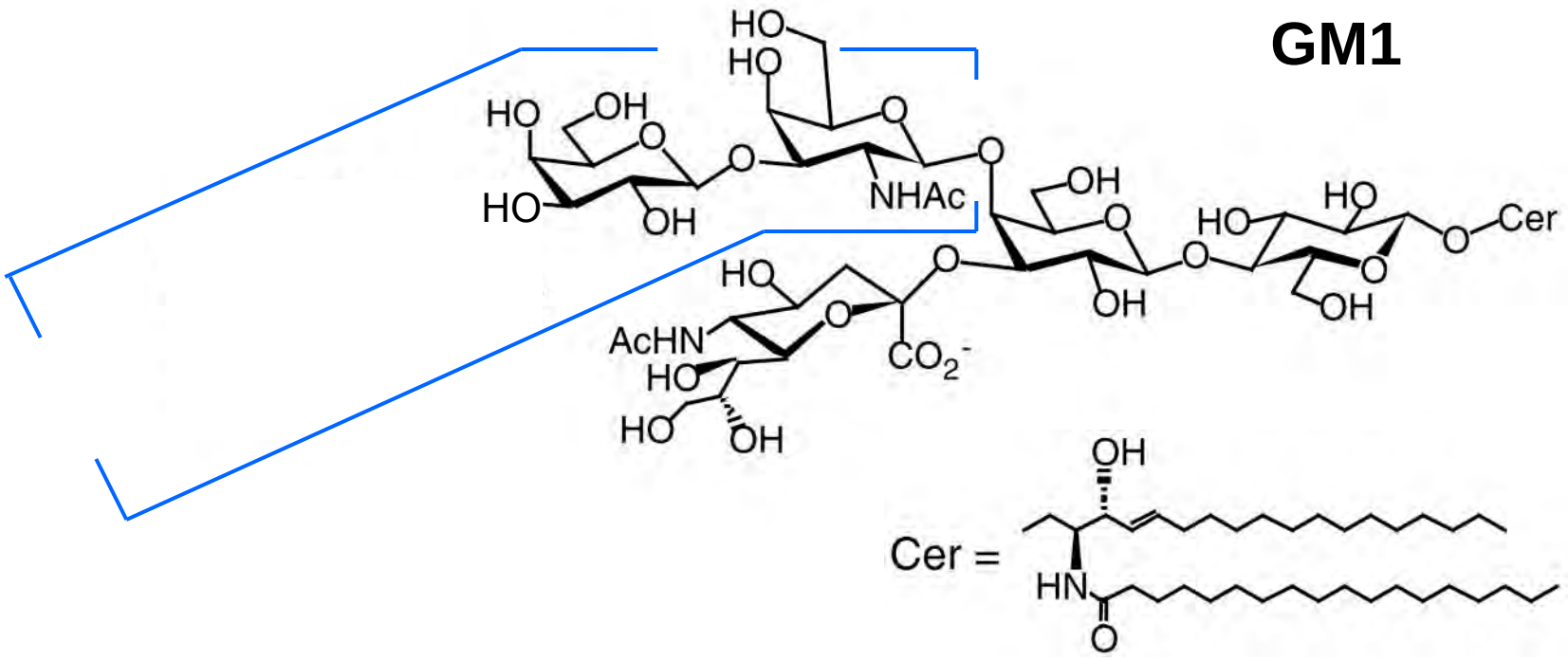
Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer

MAG receptor GT1b on axons



NeuAc α3 Gal β3 GalNAc β4 (NeuAc α8 NeuAc α3) Gal β4 Glc β Cer

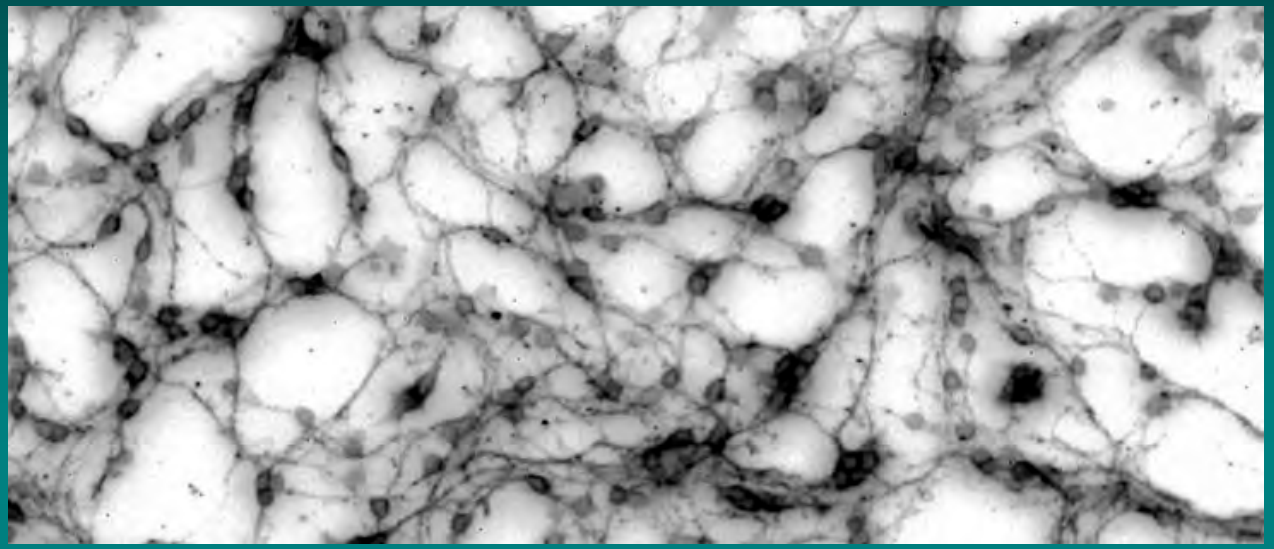
Sialidase cleaves the terminal sialic acid from GD1a



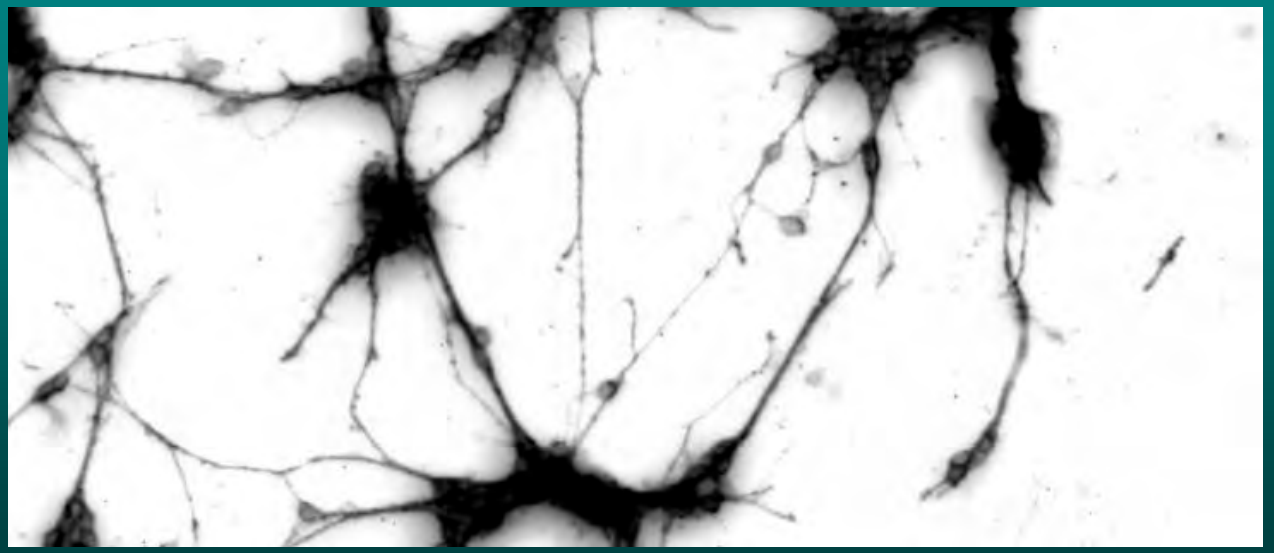
Gal β3 GalNAc β4 (NeuAc α3) Gal β4 Glc β Cer

MAG inhibits axon outgrowth from nerve cells *in vitro*

Control surface

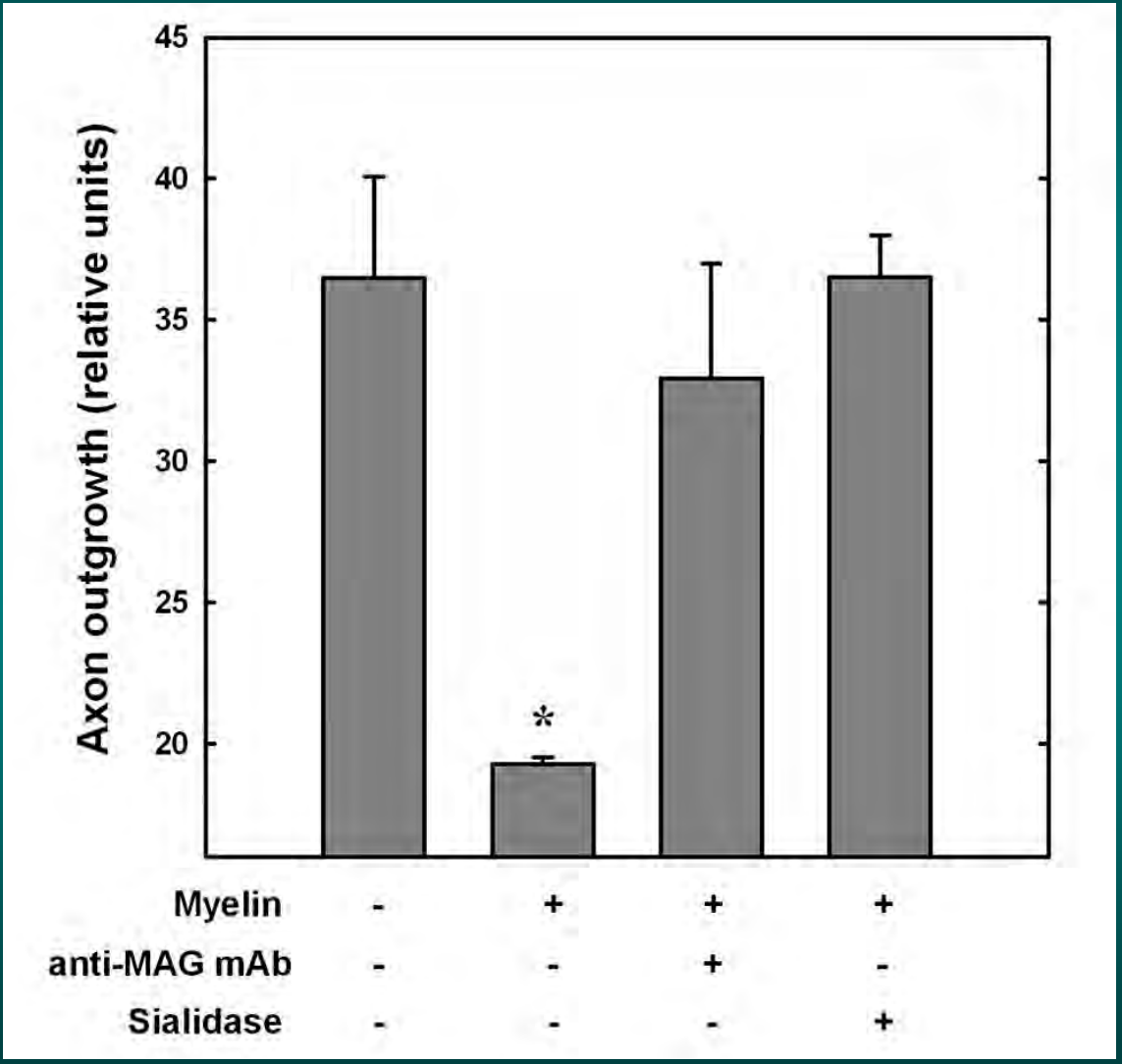


Myelin-derived MAG



Vyas et al. (2005) J. Biol. Chem. 180, 16301

Myelin-derived MAG inhibition of axon outgrowth is reversed by anti-MAG antibody and by sialidase



Vyas et al. (2005) J. Biol. Chem. 180, 16301

SIALIDASE PRECLINICAL STUDIES

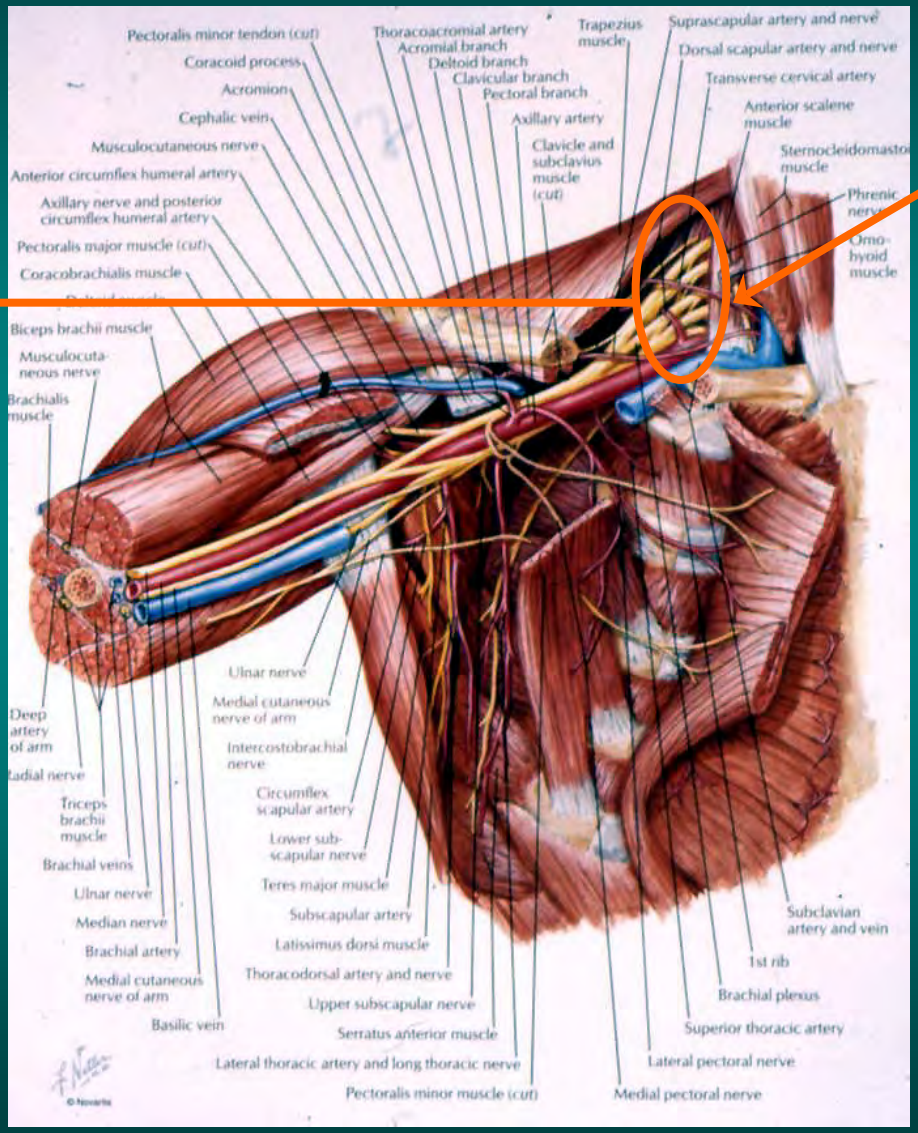
- Brachial Plexus injury
- Contusion SCI

SIALIDASE PRECLINICAL STUDIES

- Brachial Plexus injury
- Contusion SCI

BRACHIAL PLEXUS

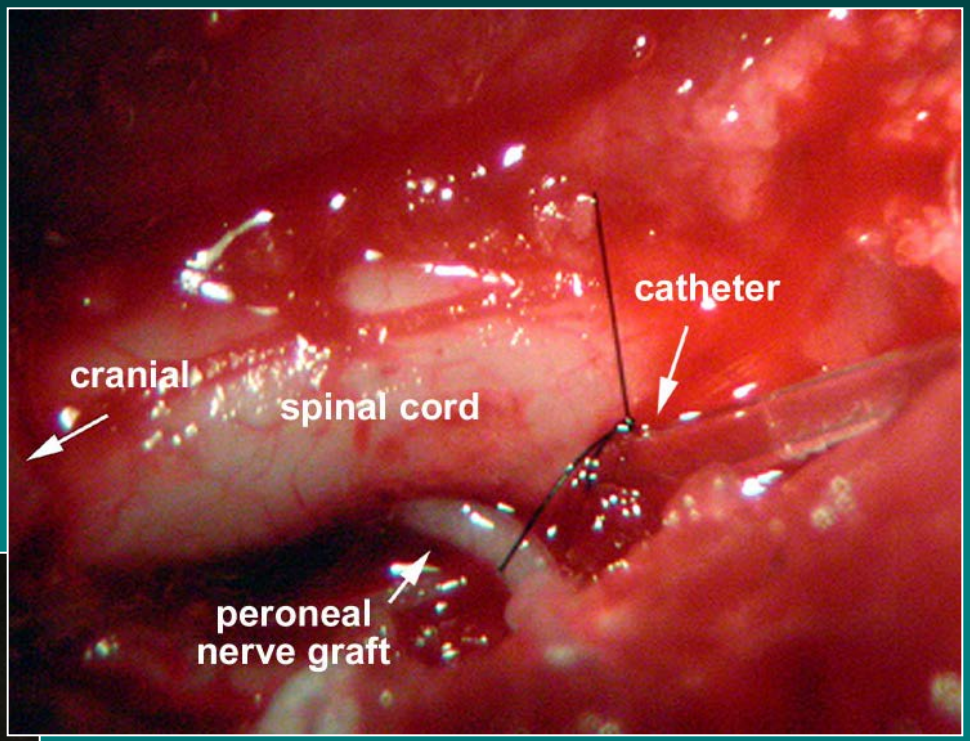
brachial plexus nerves

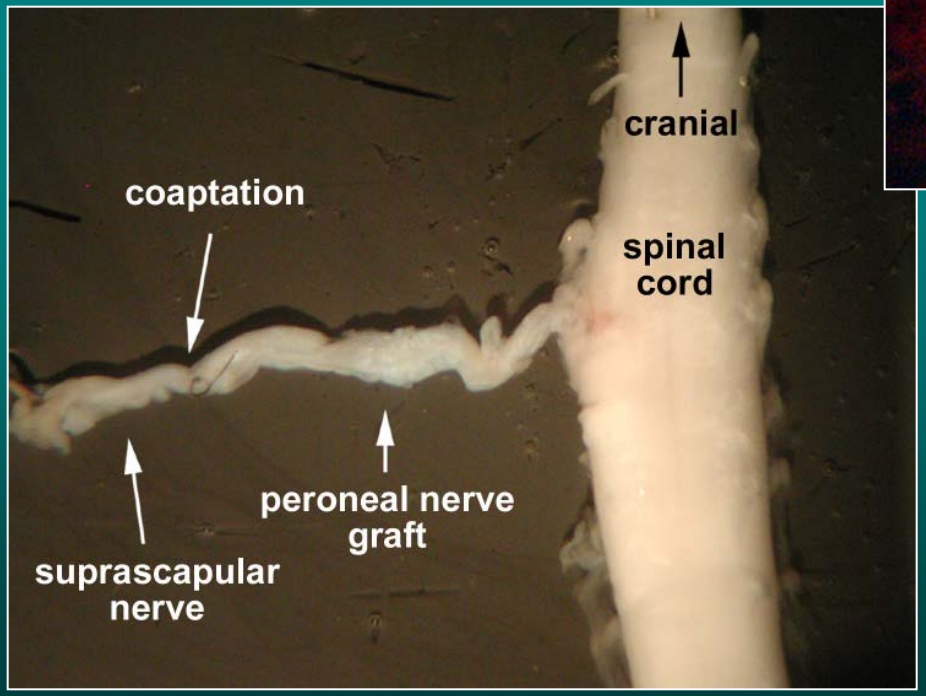


spinal cord

BRACHIAL PLEXUS INJURY & REPAIR MODEL

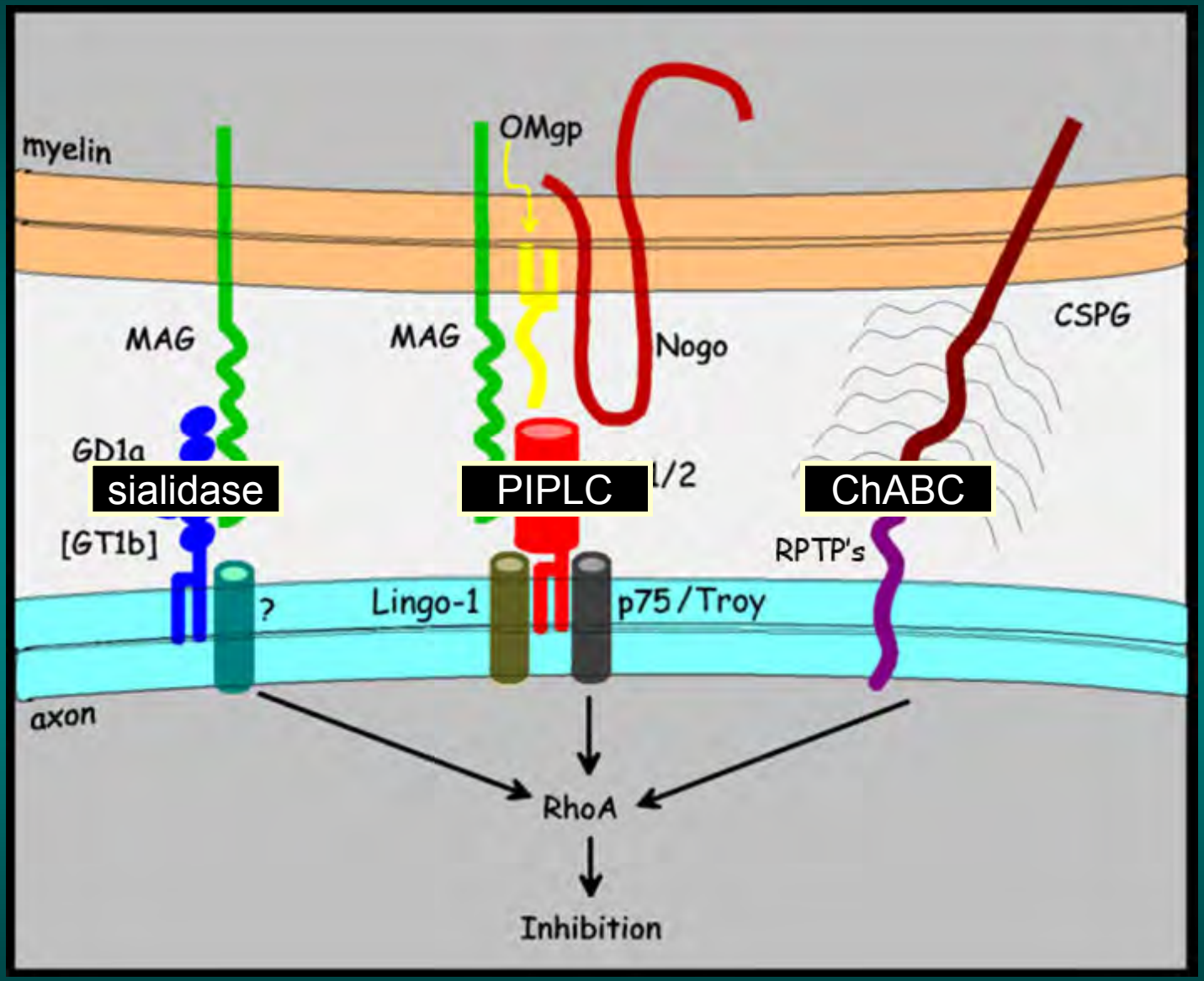
- Cut C8 ventral and dorsal roots
- Insert peroneal nerve graft into cord
- Deliver hydrolases to the site of injury
- After 4 wks cut graft 7 mm from cord
- Immerse cut end in Fluororuby dye
- After 3 d Fix, section, count retrograde labeled spinal neurons





Yang, LJY, et al. (2006) Proc. Natl. Acad. Sci. USA 103, 11057

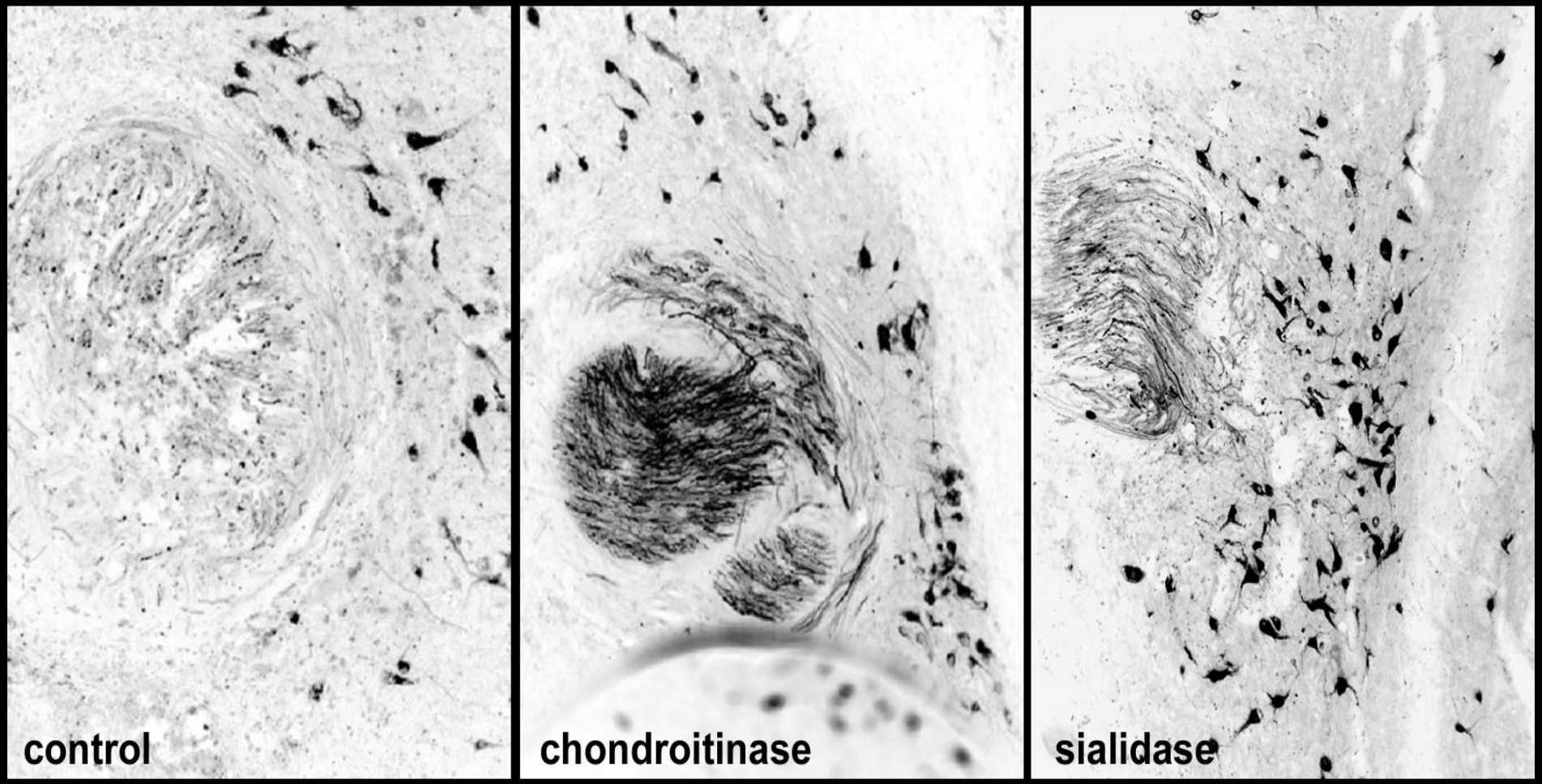
Axon regeneration inhibitors: reversal by bacterial hydrolases



Modified from Woolf & Bloechlinger, Science (2002) 297, 1132

BRACHIAL PLEXUS RESULTS

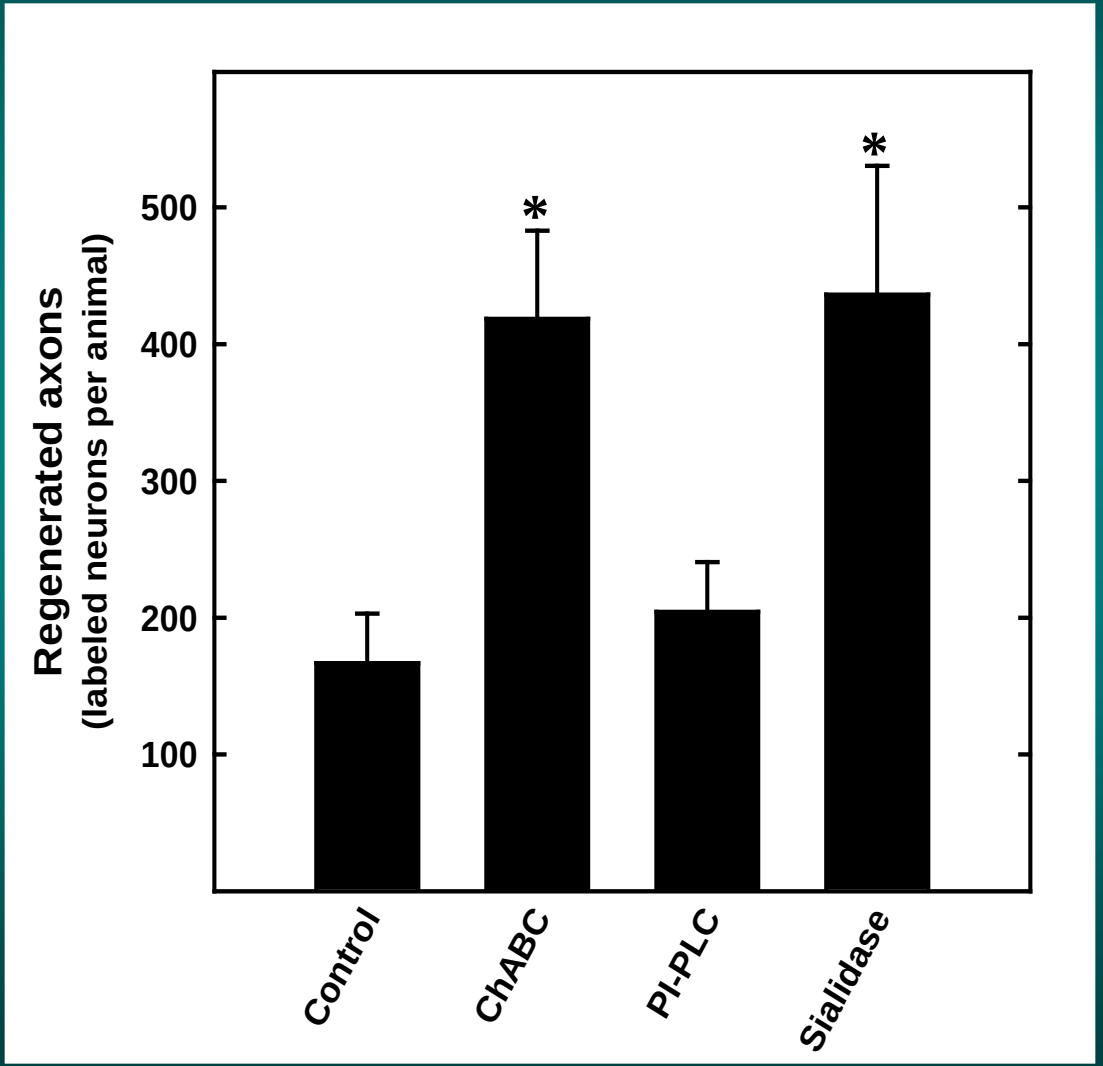
Sialidase and chondroitinase (but not PIPLC) enhance spinal axon regeneration



Yang, LJY, et al. (2006) Proc. Natl. Acad. Sci. USA 103, 11057

BRACHIAL PLEXUS RESULTS

Sialidase and chondroitinase (but not PIPLC) enhance spinal axon regeneration



Yang, LJY, et al. (2006) Proc. Natl. Acad. Sci. USA 103, 11057

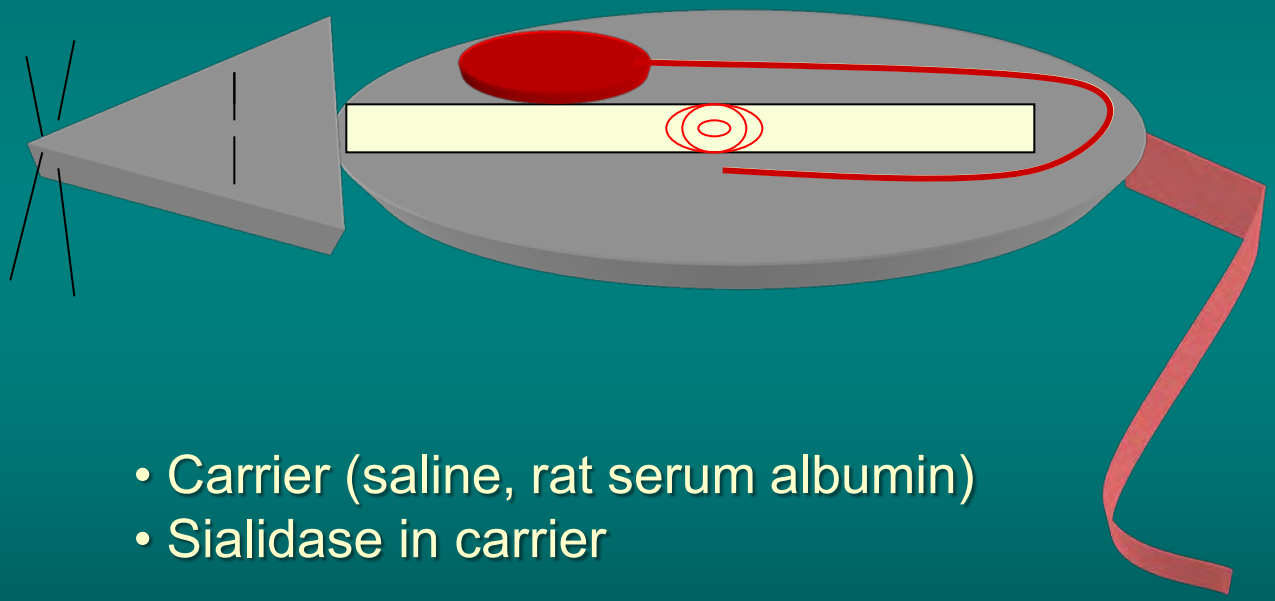
SIALIDASE PRECLINICAL STUDIES

- Brachial Plexus injury
- Contusion SCI

SIALIDASE PRECLINICAL STUDIES

- Brachial Plexus injury
- Contusion SCI

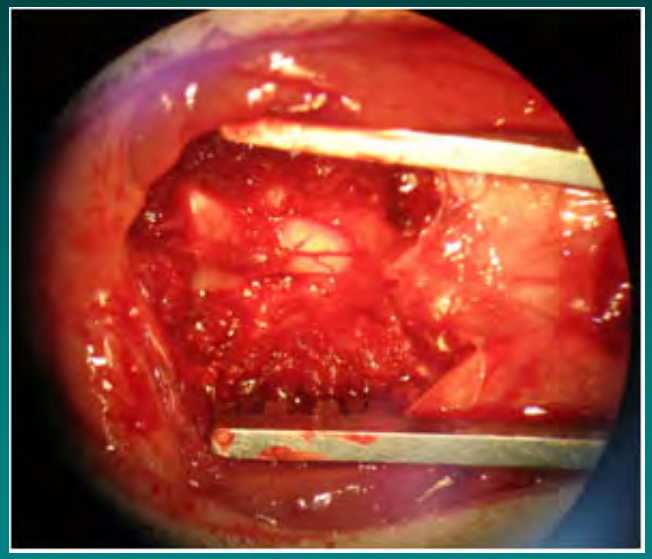
Intrathecal sialidase delivery to treat spinal cord contusion injury in the rat

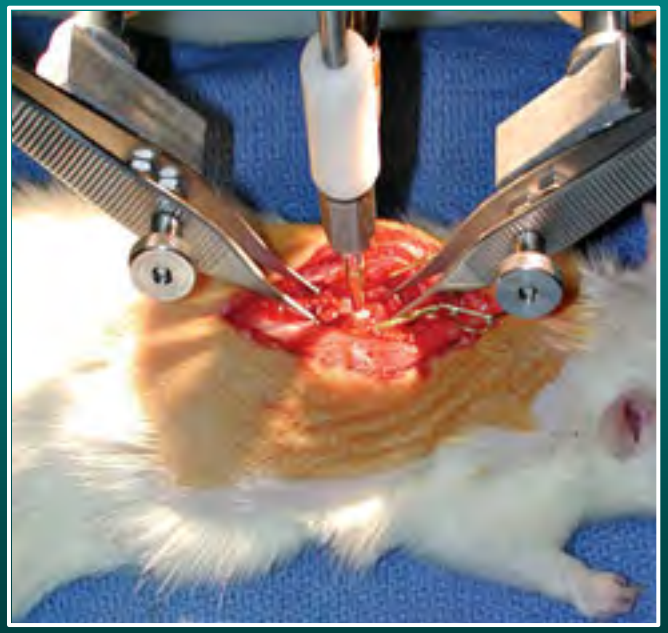


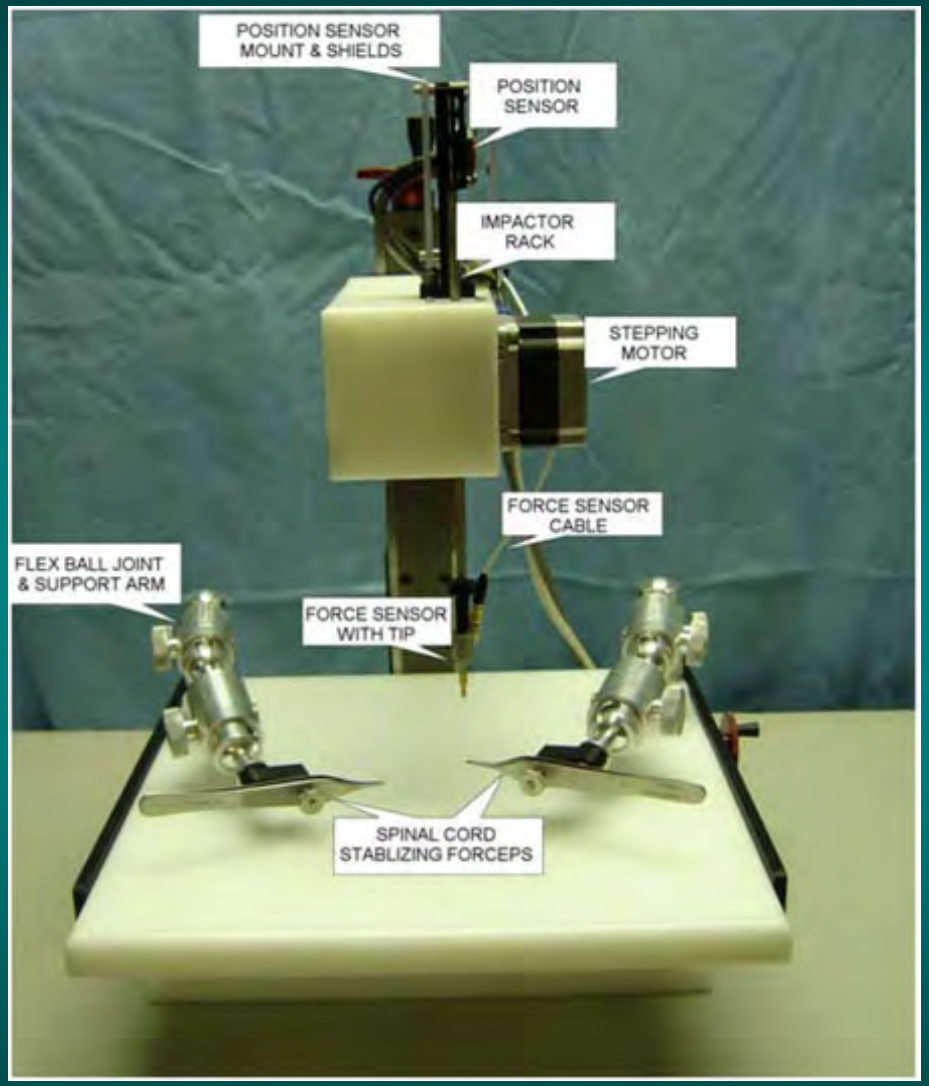
- Carrier (saline, rat serum albumin)
- Sialidase in carrier

Recombinant *V. cholerae* sialidase plasmid kindly provided by G. Taylor, St. Andrews, UK
2 U/ml delivered intrathecally – 50 µl initial dose then 0.4 µl/h for 14 days via osmotic pump

Spinal cord contusion injury model

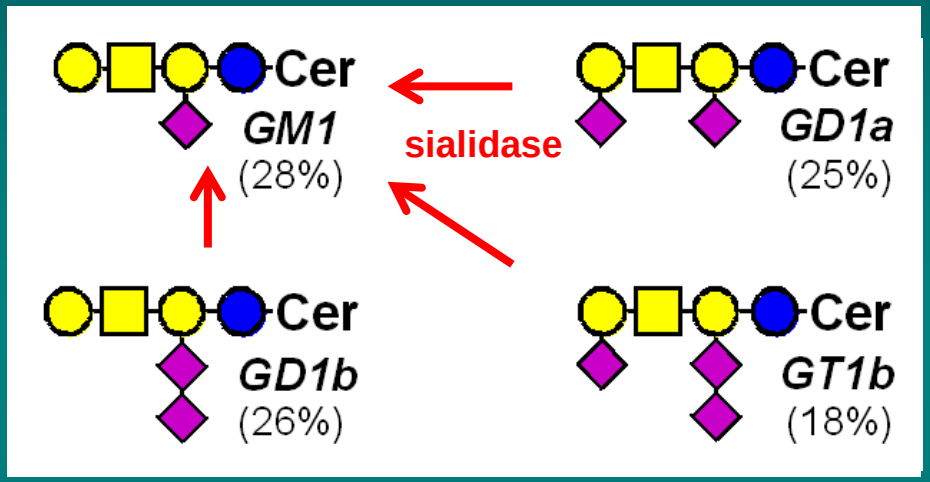


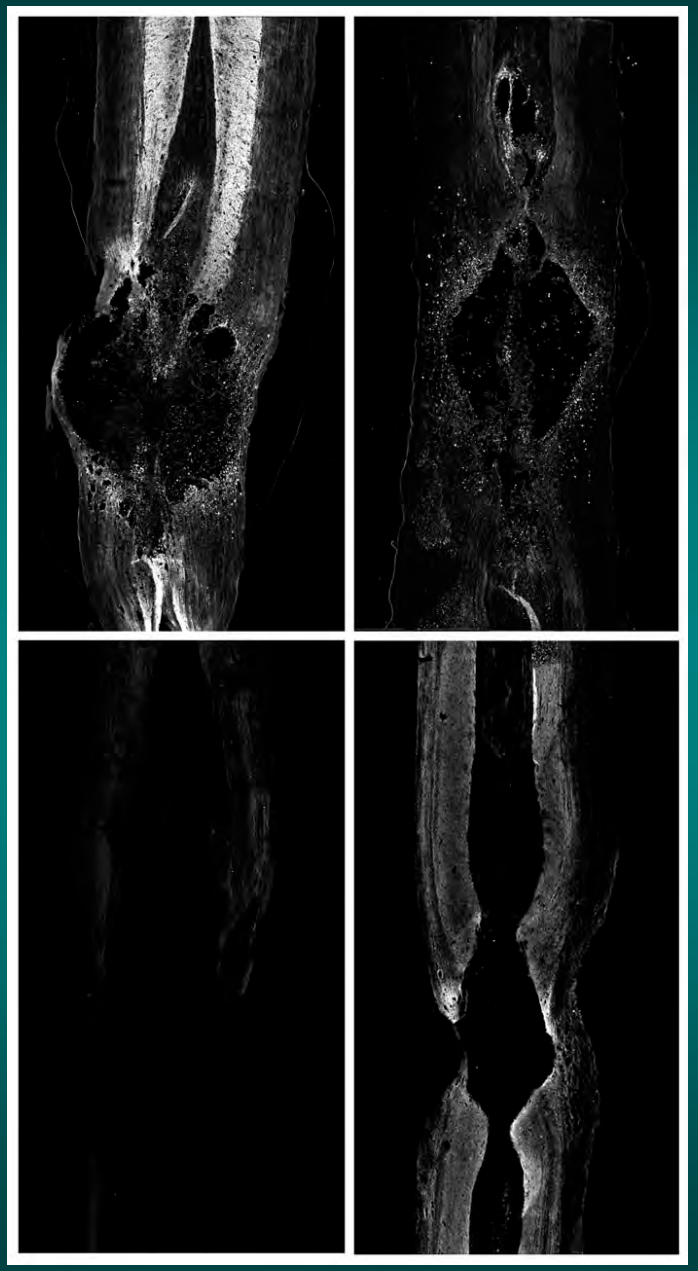




Infinite Horizons Impactor, Precision Scientific & Instr.
Scheff, et al. (2003) J. Neurotrauma 20, 179

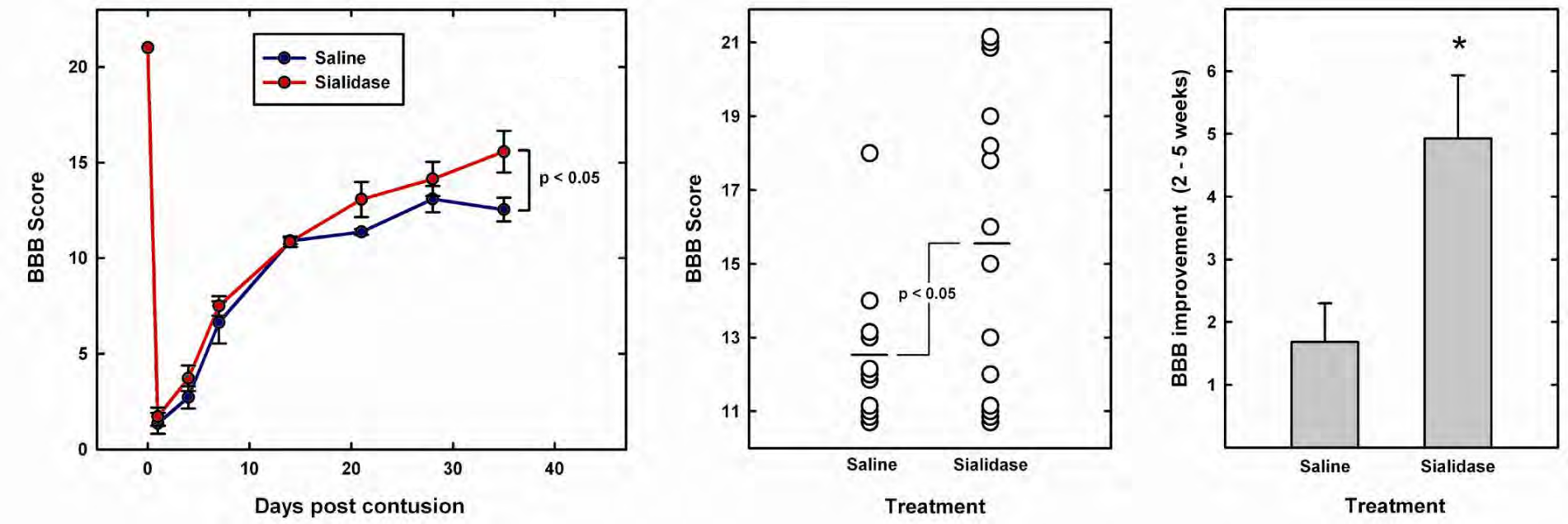
Sialidase efficacy on spinal tissue *in vivo*





Mountney et al. (2010) *Proc Natl Acad Sci USA* **107**, 11561

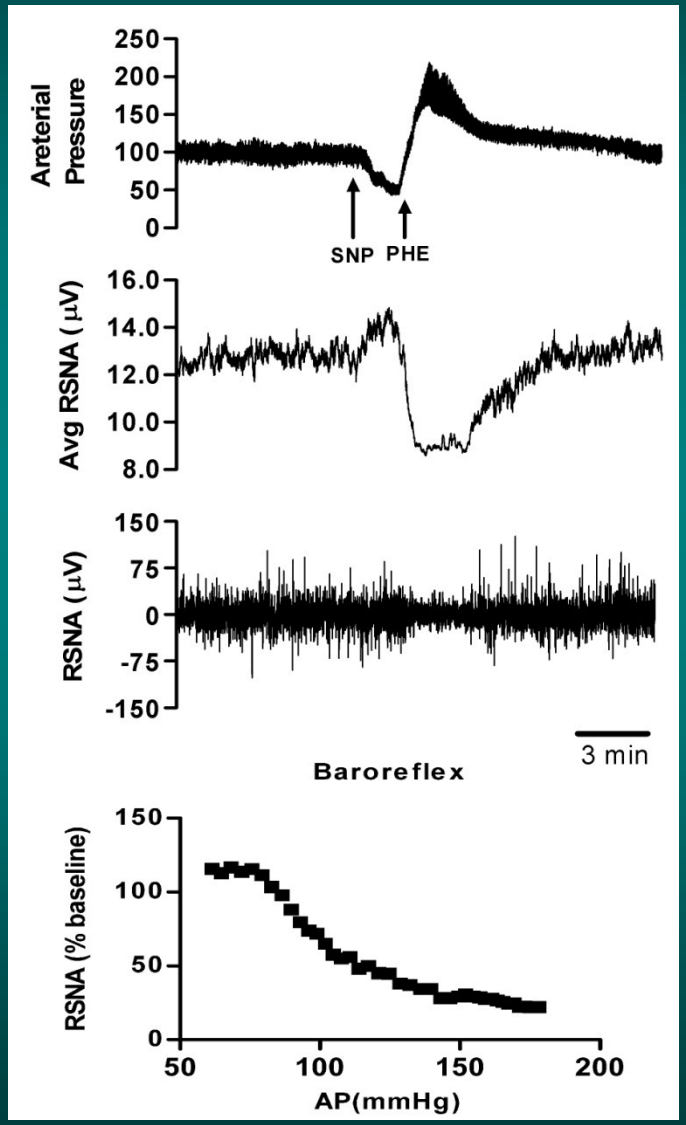
Sialidase promotes motor behavioral recovery after spinal cord contusion injury



Mountney et al. (2010) *Proc Natl Acad Sci USA* **107**, 11561

Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury

Baroreceptor reflex



Arterial pressure is lowered and raised with drugs

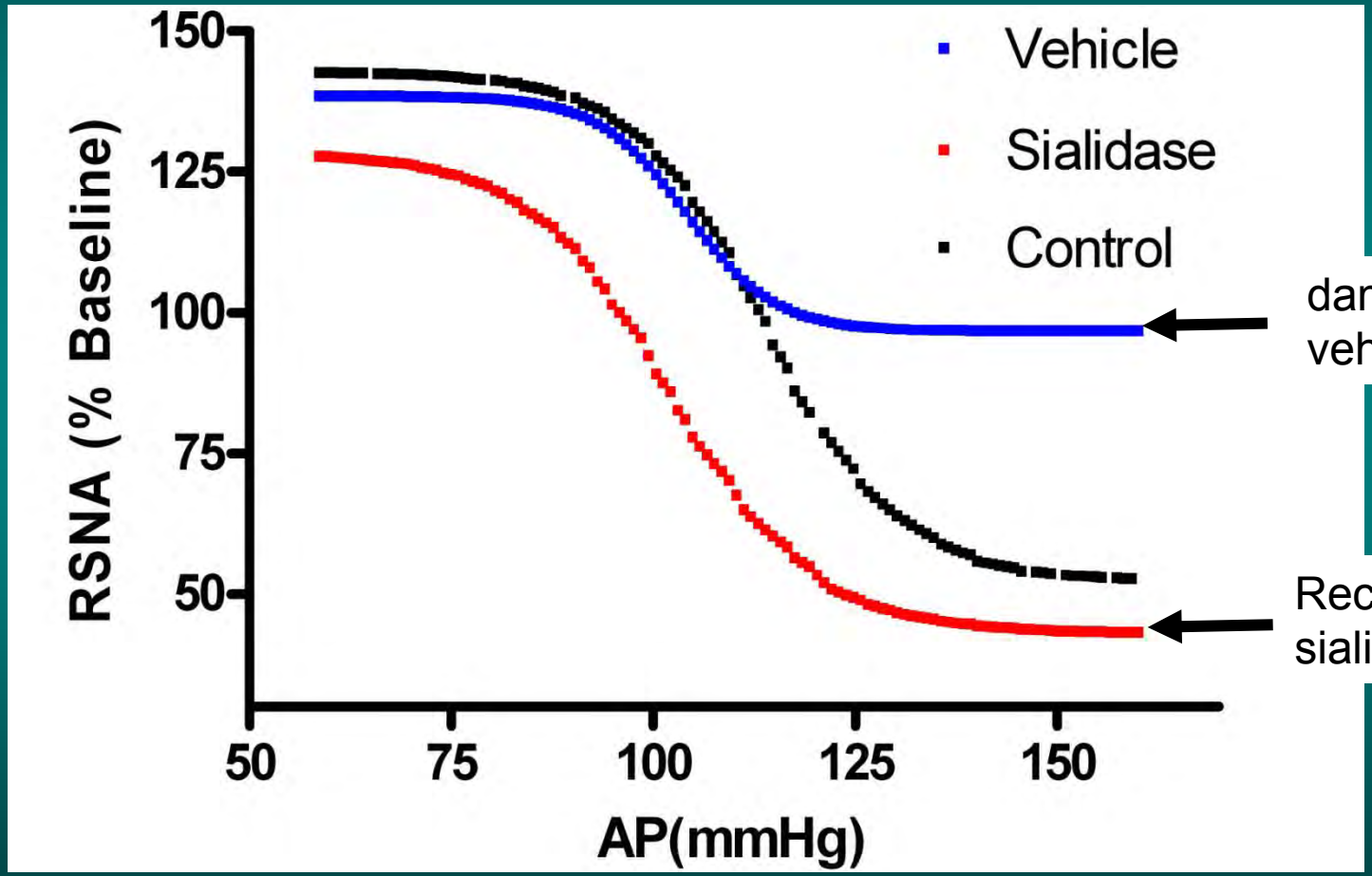
Renal sympathetic nerve activity (RSNA) changes reciprocally.

Normal relationship between blood pressure and RSNA

Mountney et al. (2010) *Proc Natl Acad Sci USA* **107**, 11561

Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury

Exemplary results

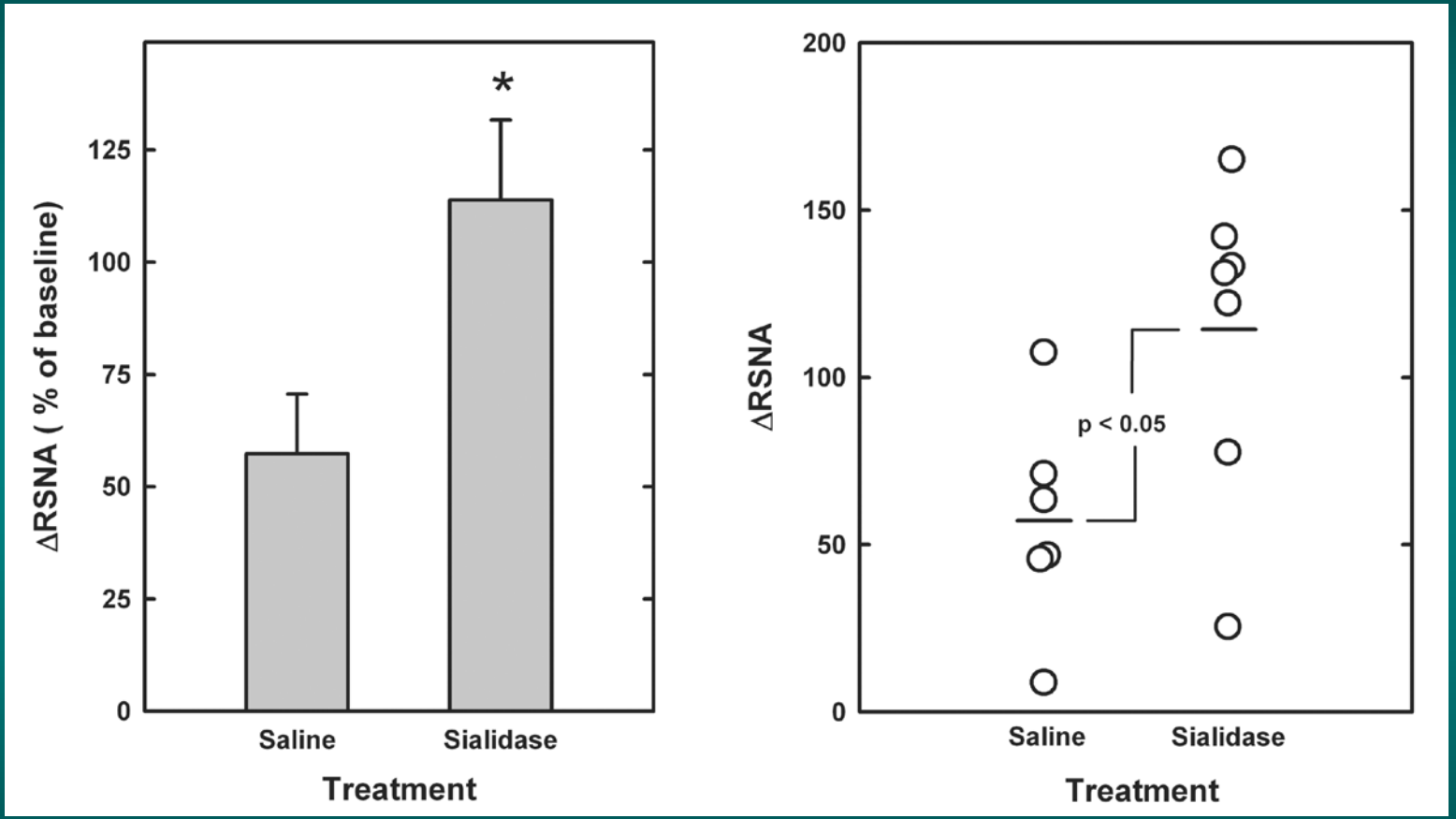


damped reflex in SCI vehicle-treated rats

Recovered reflex in SCI sialidase-treated rats

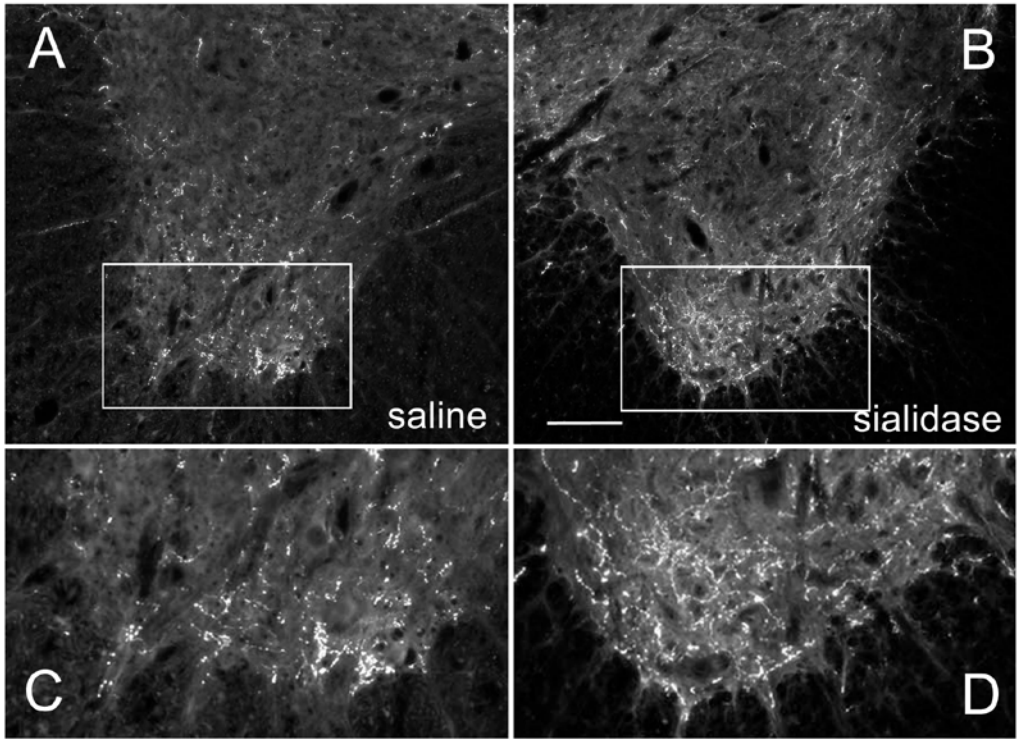
Zahner and Schramm, unpublished

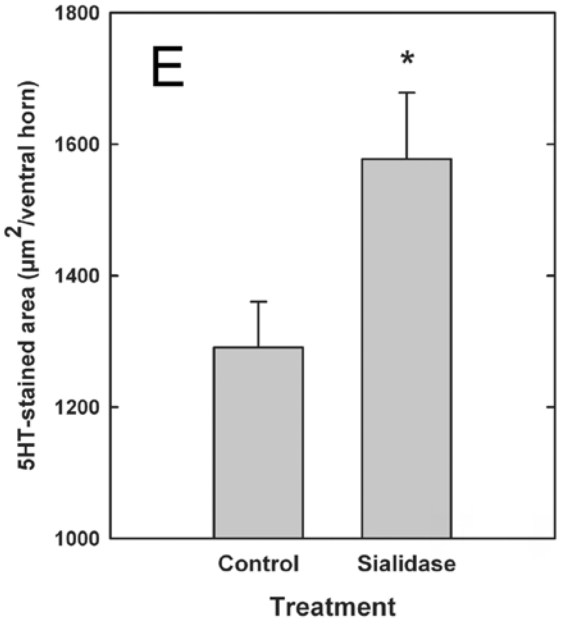
Sialidase promotes cardiovascular reflex recovery after spinal cord contusion injury



Mountney et al. (2010) *Proc Natl Acad Sci USA* **107**, 11561

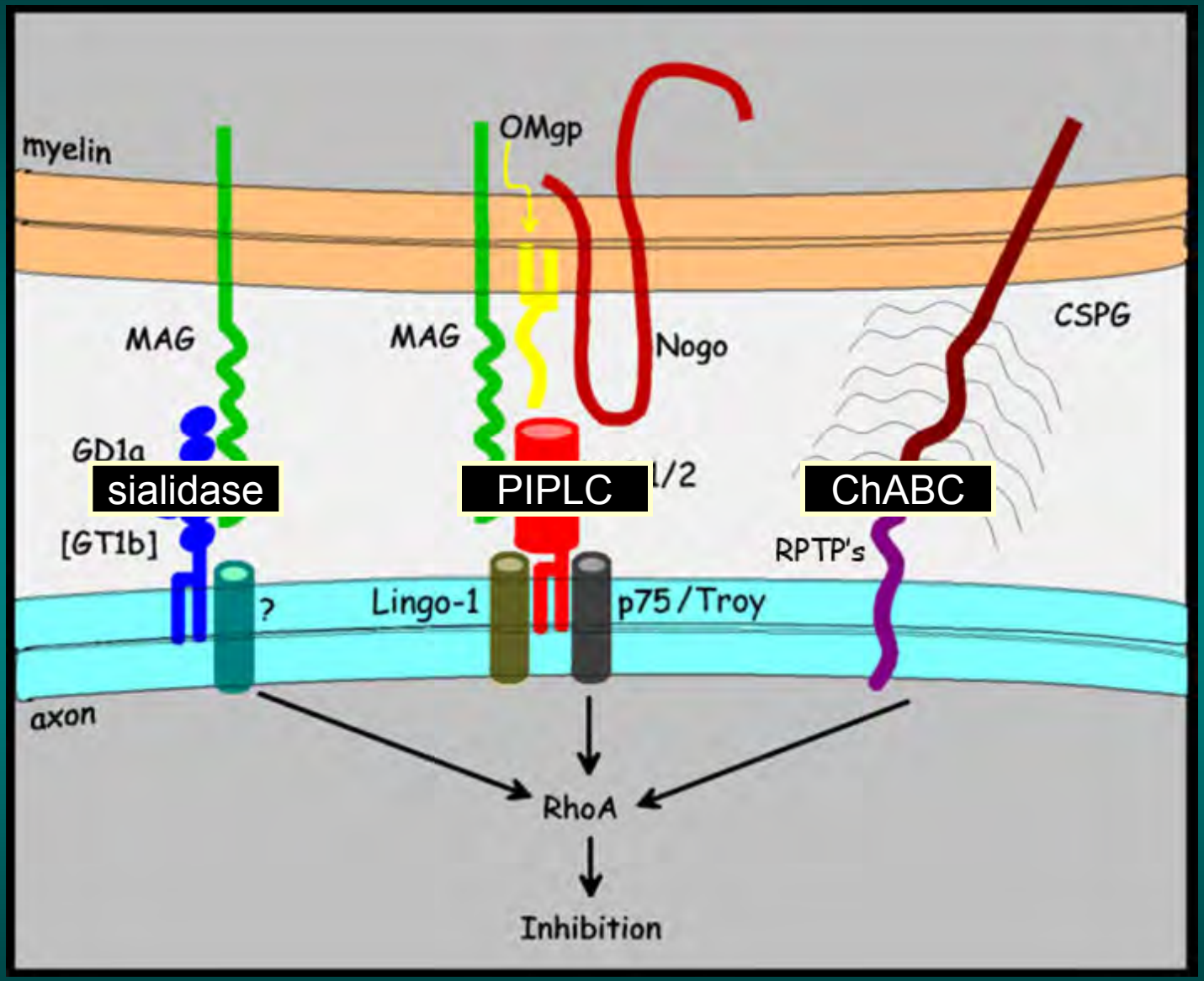
Sialidase increases axon sprouting caudal to a contusion injury





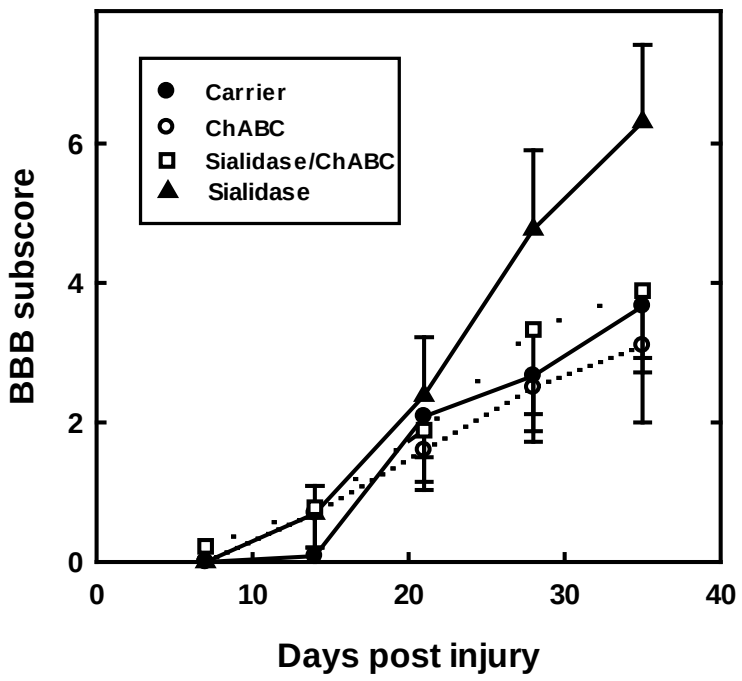
Mountney et al. (2010)
Proc Natl Acad Sci USA **107**, 11561

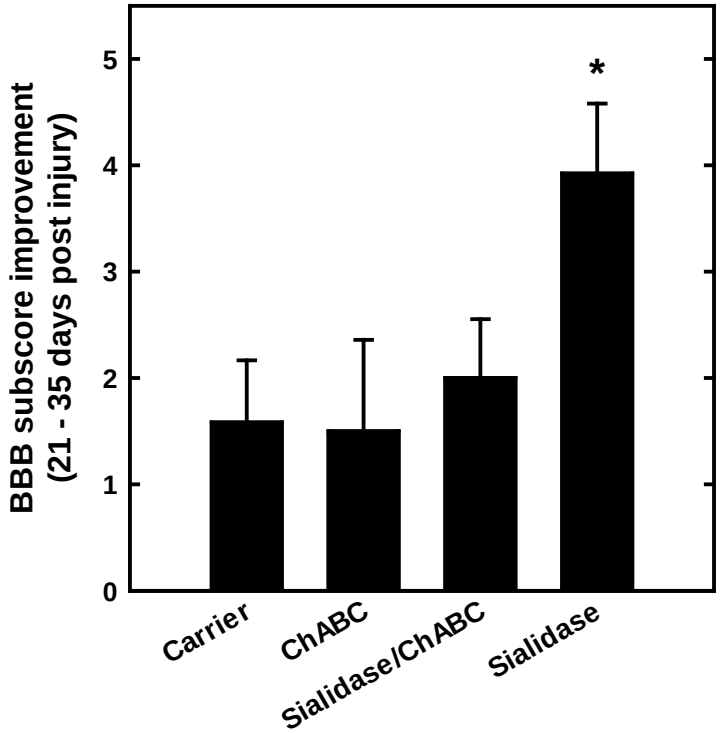
Axon regeneration inhibitors: reversal by bacterial hydrolases



Modified from Woolf & Bloechlinger, Science (2002) 297, 1132

Sialidase alone enhances recovery of hindlimb mechanics after contusion spinal cord injury

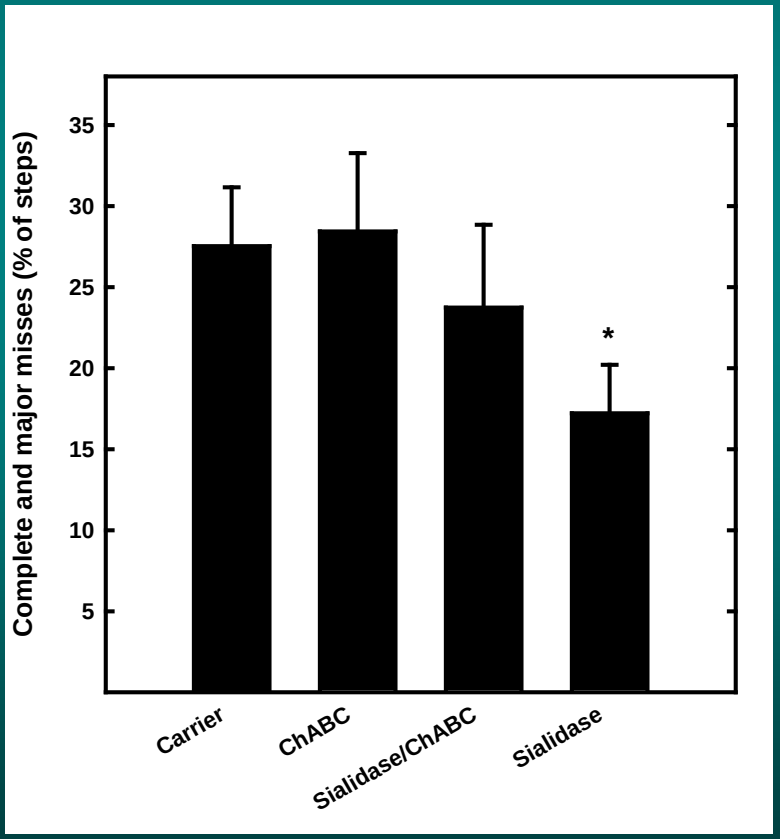




Mountney et al. (2013) *J Neurotrauma* **30**, 181

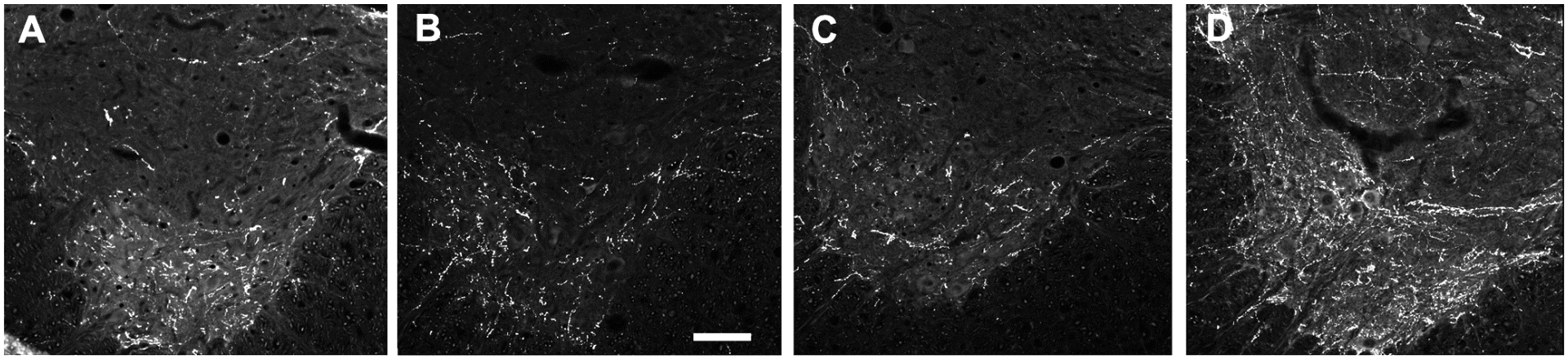
Sialidase alone enhances grid walking

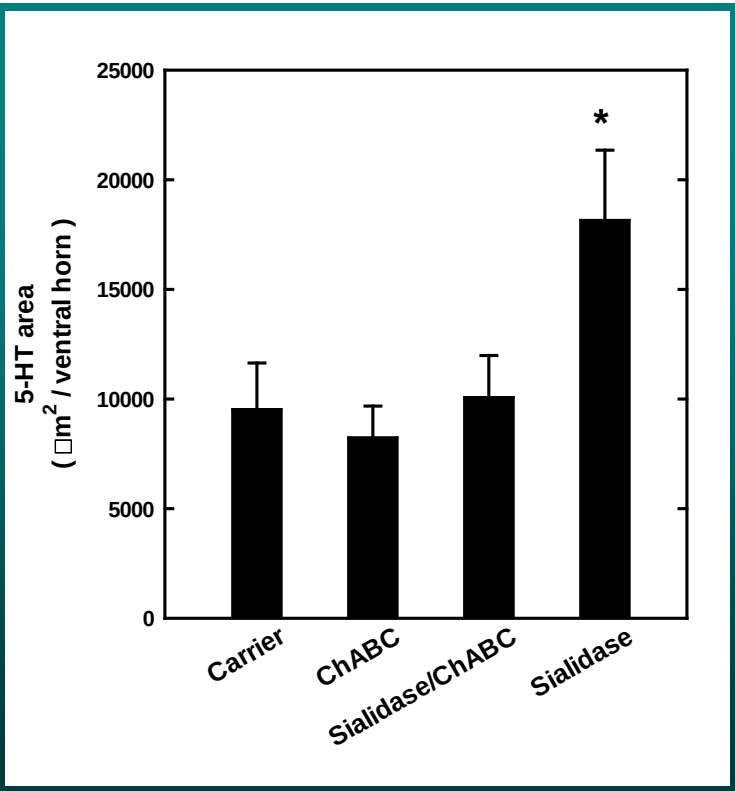
Mountney et al. (2013) *J Neurotrauma* **30**, 181



Sialidase alone enhances axon sprouting below the lesion (5-HT)

Carrier ChABC ChABC/sialidase sialidase





Mountney et al. (2013)
J Neurotrauma **30**, 181

- Spinal cord injury is no longer “untreatable”. Rehabilitation, electrical stimulation, and drug treatments are in use or on the horizon.
- Reversal of axon regeneration inhibitors may provide rationally-designed therapies to enhance recovery after traumatic spinal cord injury.

Collaborators

Schnaar Lab

- Jeff Aston
- Ileana Lorenzini
- Andrea Mountney
- Chris Riley
- Elizabeth Sturgill
- Katarina Vajn
- Lynda Yang

Neurology

- Andres Hurtado
- Martin Oudega

Biomedical Engineering

- Lawrence Schramm
- Matthew Zahner

Thanks to Garry Taylor (St. Andrews) for providing the sialidase plasmid, and to John McDonald and The International Center for Spinal Cord Injury Research (Kennedy Krieger Institute, Baltimore) for logistical support.