Attenuation of Robust Glial Scar Formation after CNC Injury Can Facilitate Functional Recovery

Peripheral Nerve Research Laboratory
University of California, Irvine

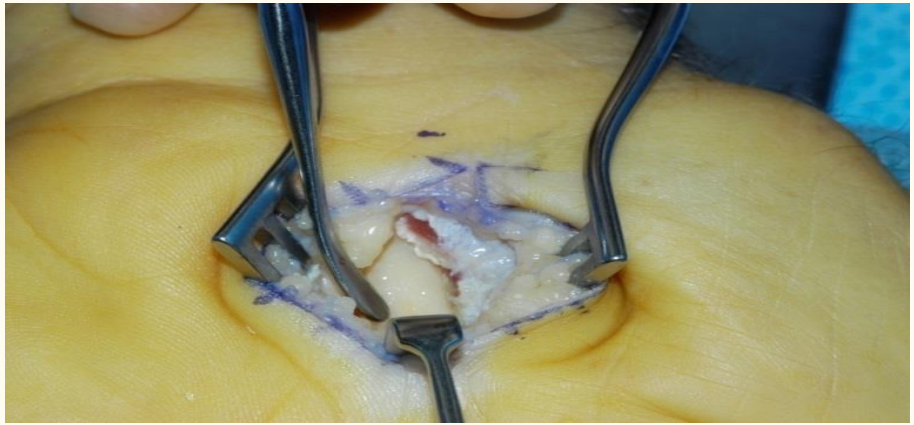
Minal Tapadia, Winnie Palispis, Diana Zhu, Michele Luu, James Jung, Tahseen Mozaffar, **Ranjan Gupta**

Disclosures

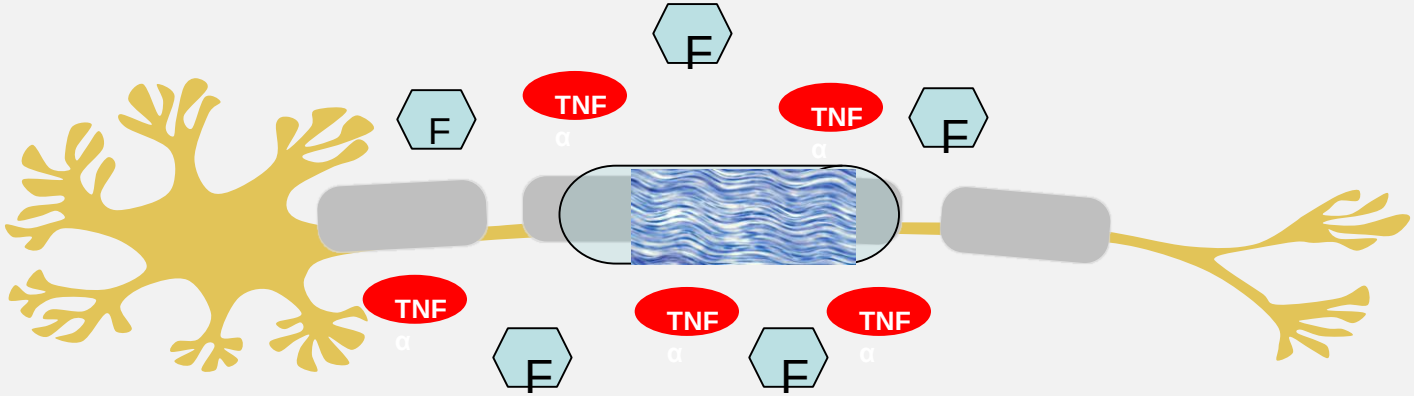
All presenters have **no** financial disclosures that would be a potential conflict of interest with this presentation.

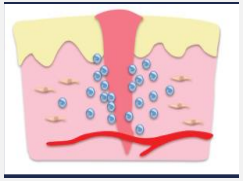
Surgical Management of Compressive Neuropathies

- Surgical decompression is often not completely effective in later-stage patients
- How can we optimize functional recovery in this patient population?

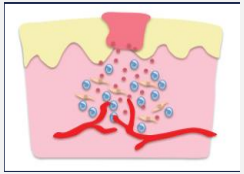


CNC Injury as Chronic Wound Healing

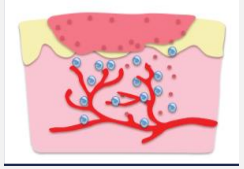




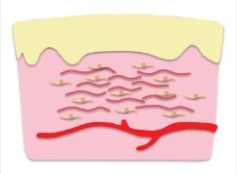
Inflammation



Proliferation



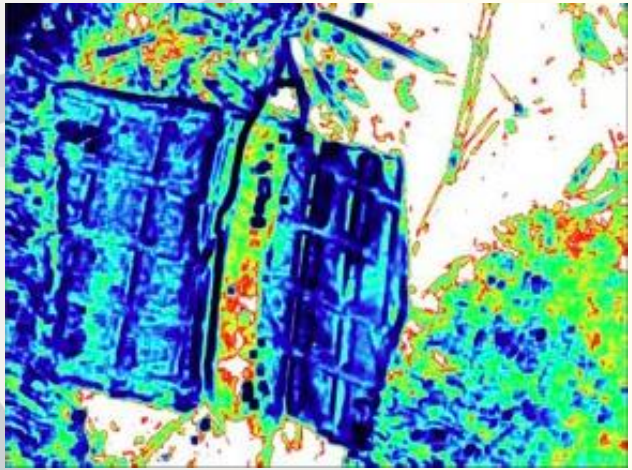
Angiogenesis



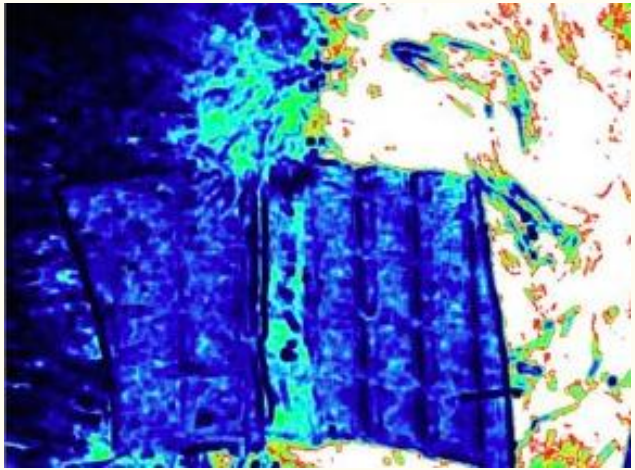
Remodeling

Hahn, P et al. January, 2012. *Neural Wound Healing: Why Surgery May Not Be Enough for Carpal Tunnel Syndrome.* ASPN, Las Vegas, Nevada.

CNC Injury and Altered Revascularization



Early Decompression

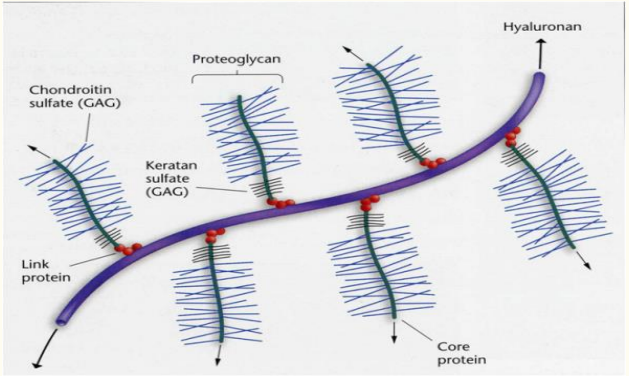


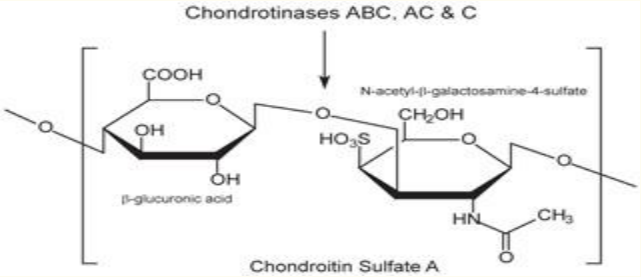
Late Decompression

Jung et al. Early but not late surgical decompression restores neurovascular blood flow and ischemic parameters in an in vivo animal model of chronic nerve compression injury. *J Bone Joint Surg*, 96(11):897-906 (2014).

SCI and Scar Formation

- Glial scar forms by astrocytes/fibroblasts
  - CSPGs (chondroitin sulfate)
  - HSPGs (heparan sulfate)
  - Keratan sulfate proteoglycans
- Schwann cell-rich ECM domains
  - Collagen IV
  - Laminin
  - Fibronectin



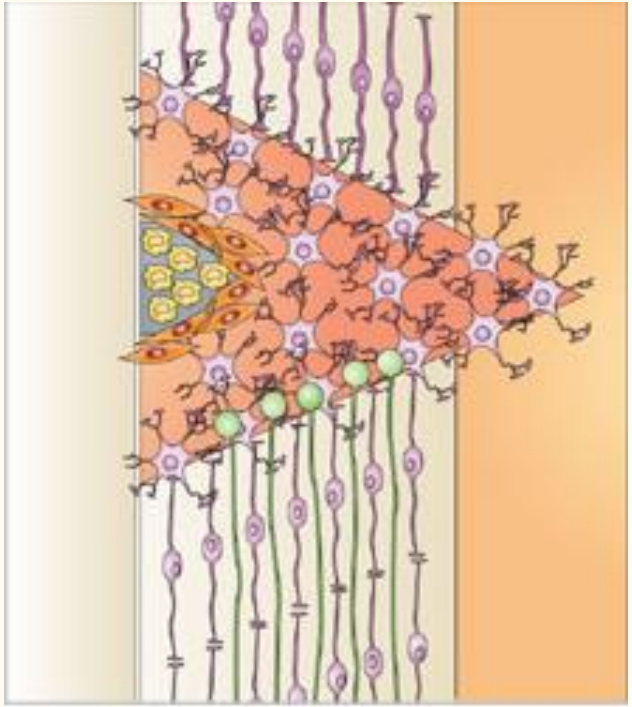


Buss et al. Growth-modulating molecules are associated with invading Schwann cells and not astrocytes in human traumatic spinal cord injury. *Brain* 130:940-53 (2007).

SCI and Glial Scar Formation

Reactive astrogliosis by CSPGs has consequences

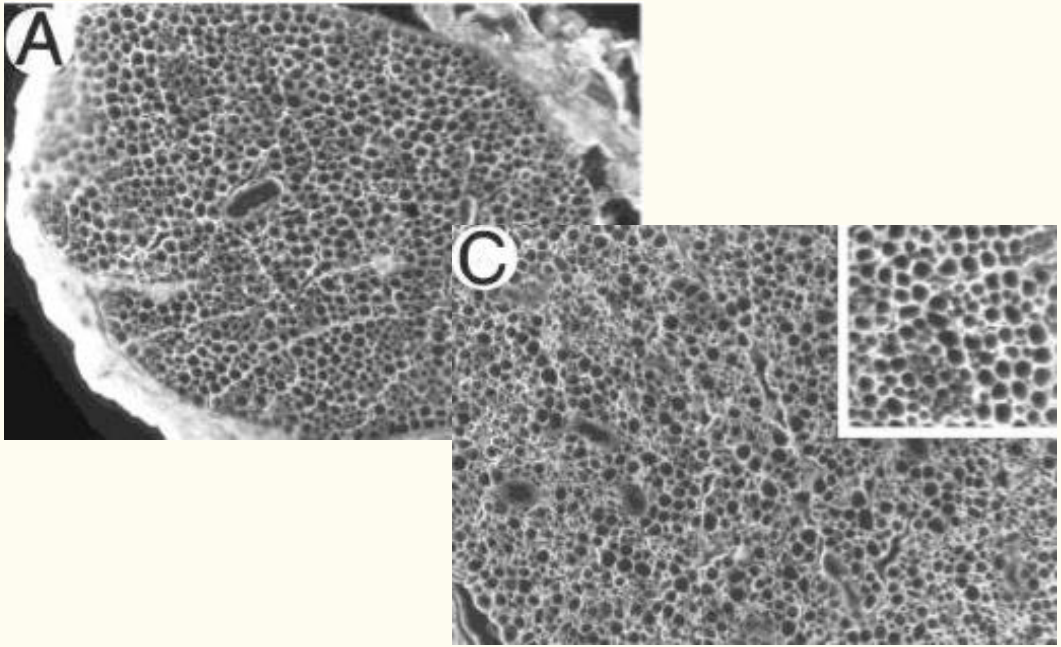
- Impedes axonal regeneration
- Altered revascularization
- Impaired OPG process outgrowth, differentiation, myelination
- Transduction of extracellular signalling



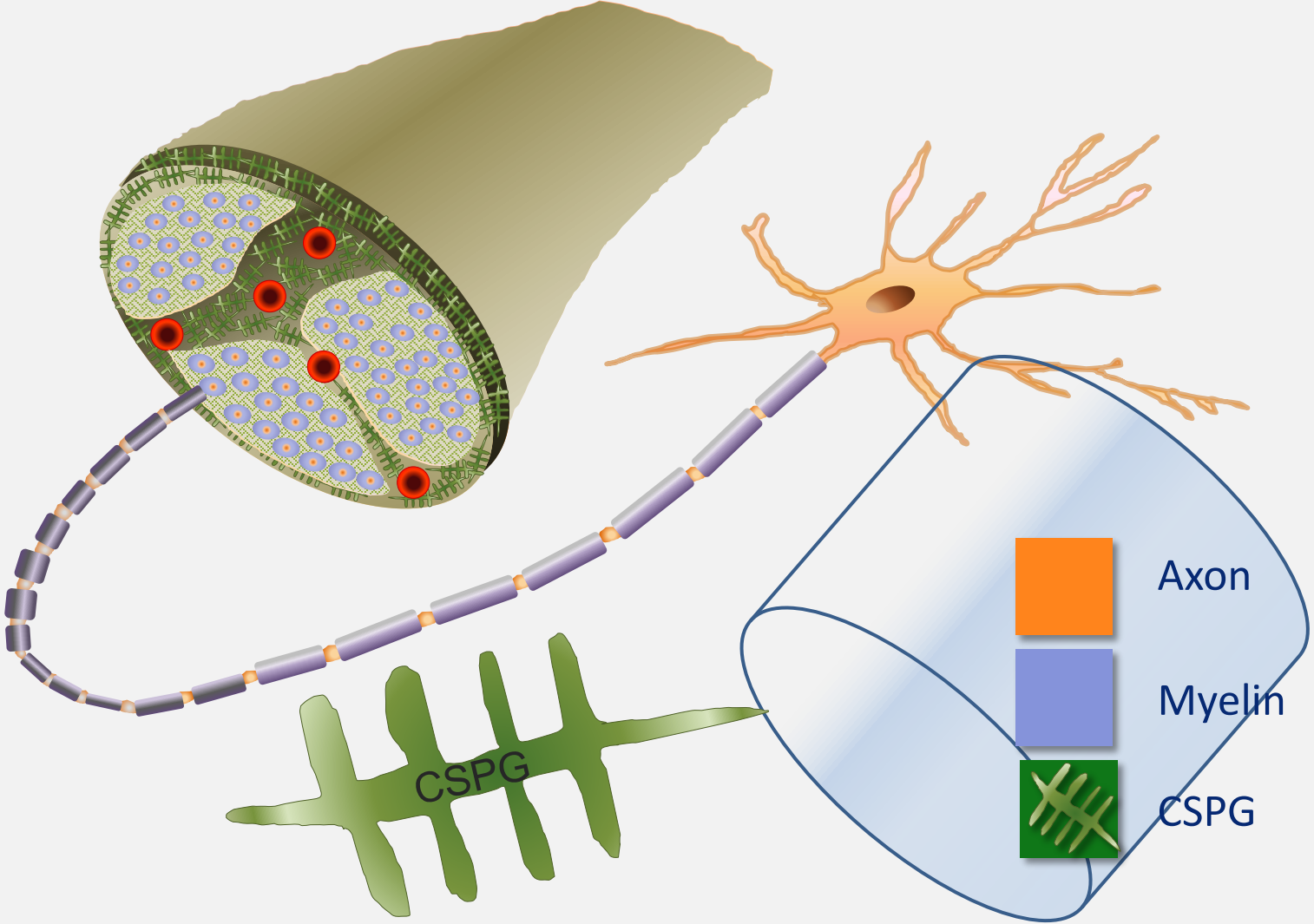
Silver and Miller. Regeneration beyond the glial scar. *Nat Rev Neuroscience* 5:146-156 (2004).

CSPGs in Peripheral Nerve

Peripheral nerves upregulate CSPGs after crush and transection injuries



Zuo et al. Chondroitin sulfate proteoglycan with neurite inhibiting activity is up-regulated following peripheral nerve Injury. J. Neurobiol 34(1): 41-54 (1998).


CSPG
Axon
Myelin
CSPG

Hypotheses

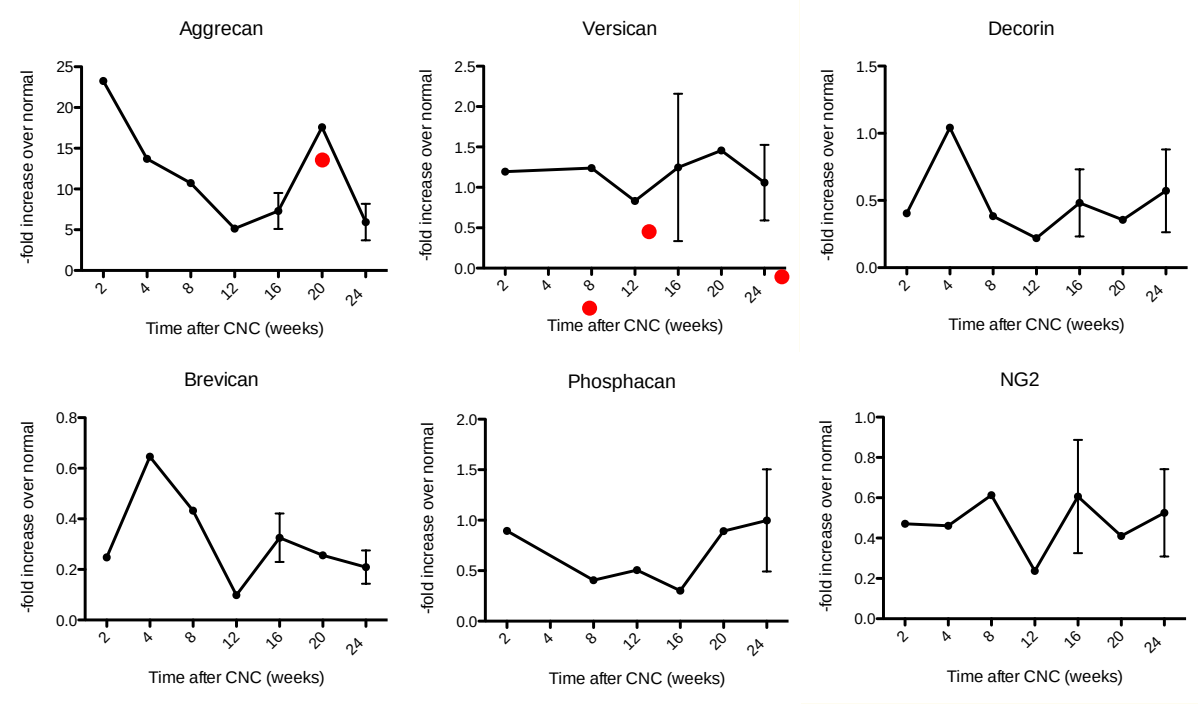
1. CNC injury upregulates ECM proteins and proteoglycans

2. Chondroitinase delivery may attenuate scar formation and improve functional outcomes by improving remyelination and blood flow

Murine Model

Gupta et al. Chronic nerve compression alters Schwann cell myelin architecture in a murine model. Muscle & Nerve 45(2):231-241 (2012).

Differential CSPG mRNA Expression Profiles after CNC Injury



Aggrecan Upregulation in Early and Late CNC Injury

N	C	N	C
-	-	+	+

4 months (EARLY)
40.9-fold upregulation

6 months (LATE)
17.8-fold upregulation

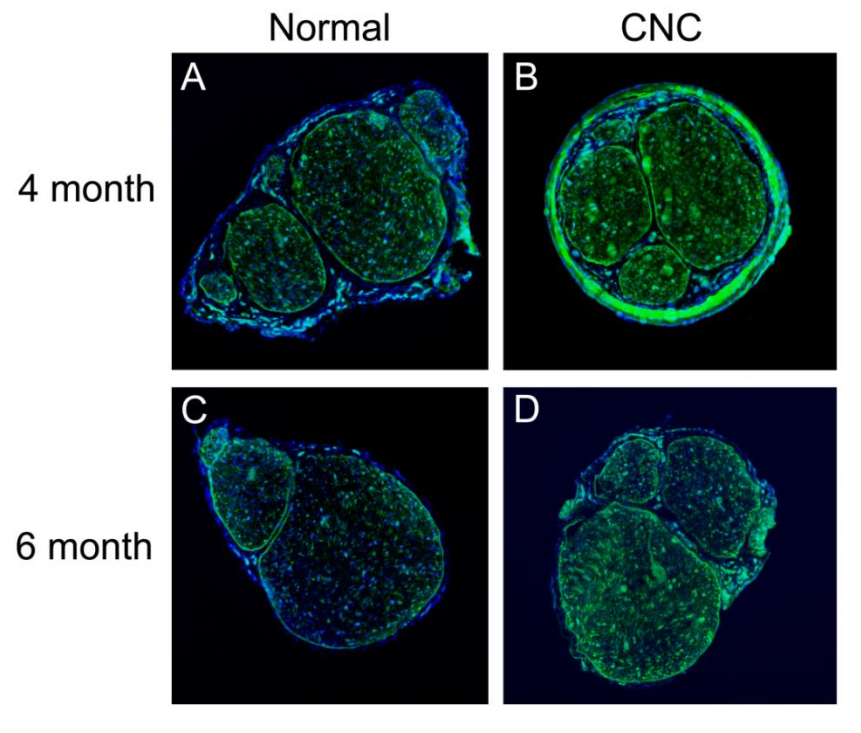
260 kDa

GAPDH

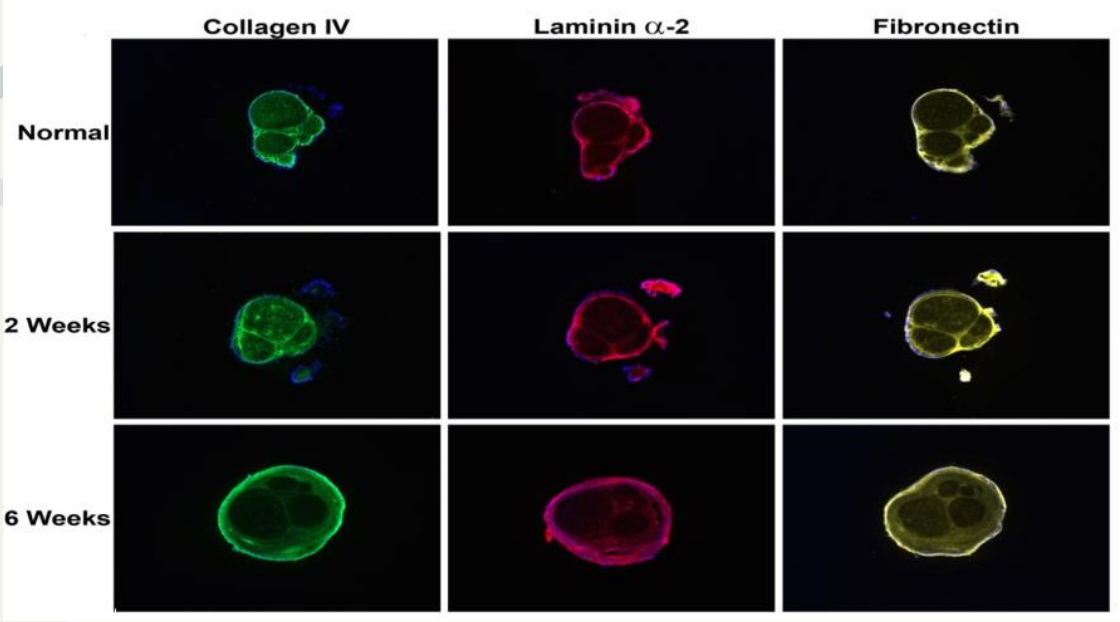
260 kDa

GAPDH

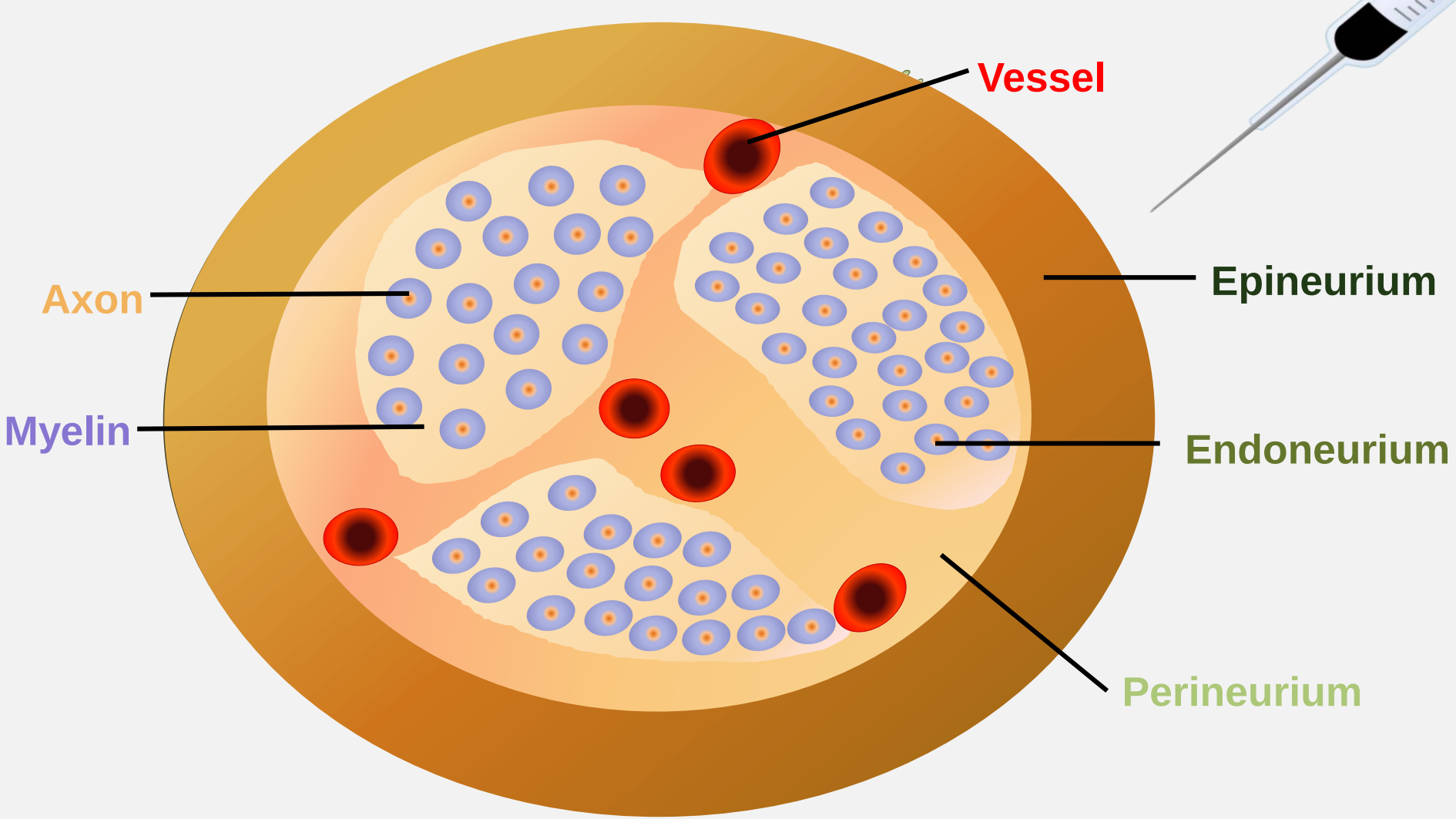
Aggrecan Upregulation in Early and Late CNC Injury



ECM Remodeling



Collagen IV, laminin, and fibronectin are upregulated in epineurium at later timepoints


Vessel
Axon
Epineurium
Myelin
Endoneurium
Perineurium

Scar attenuates after administration of chondroitinase ABC

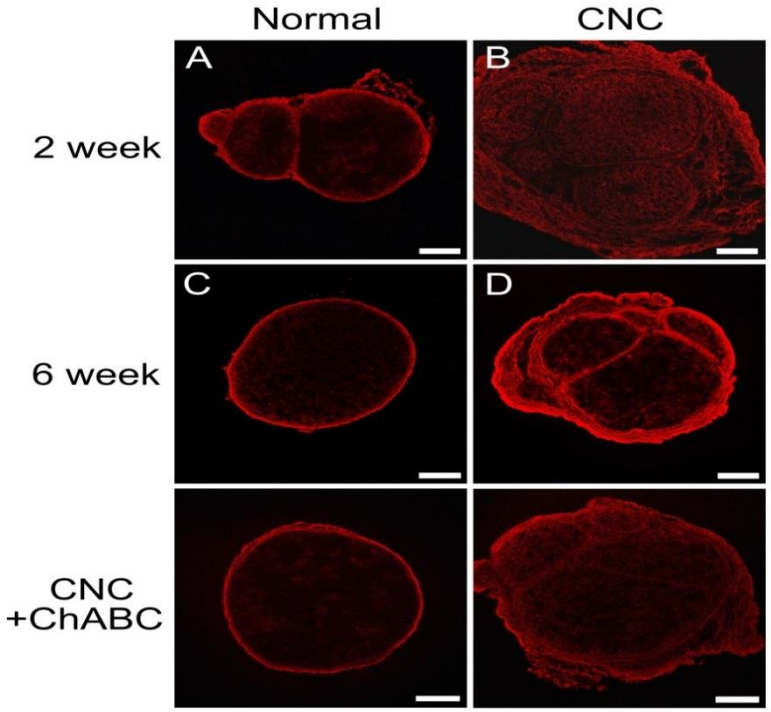
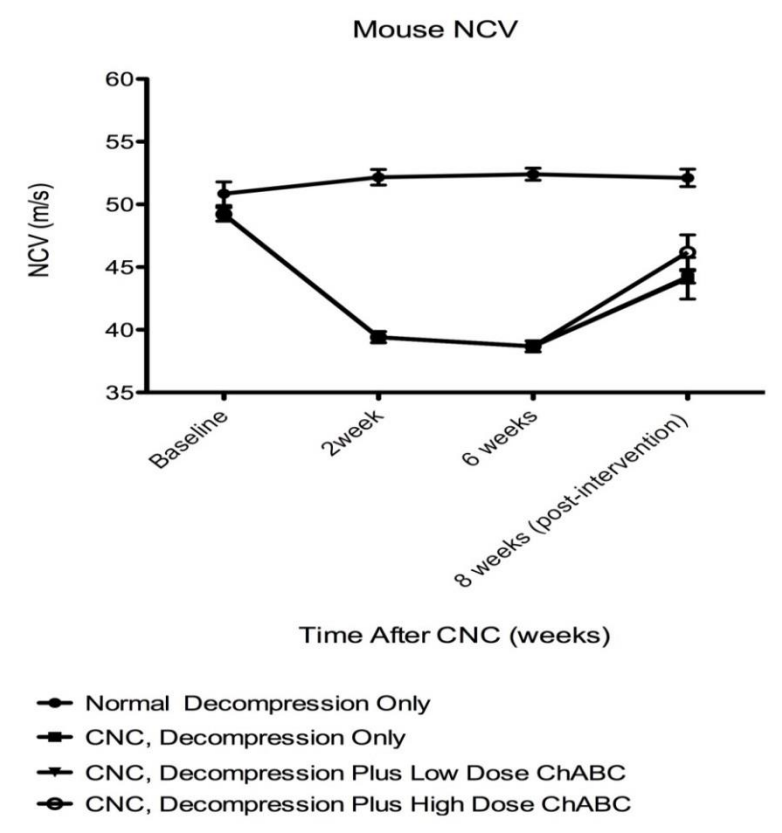


Figure 2. (A-B) Immunohistochemistry demonstrating no change in decorin levels in compressed nerves at 2 weeks, with (C-D) marked upregulation at 6 weeks and (E-F) attenuated decorin scar after administration of chondroitinase.

Functional improvement occurs after chondroitinase ABC administration



Conclusions

- CNC injury in peripheral nerve induces scar formation comprised of ECM proteins and proteoglycans

- Chondroitinase attenuates proteoglycan scar formation in the peripheral nerve, and improves functional outcomes

Thank you

UC Irvine Peripheral Nerve Research Lab

Funding

NIH-NINDS 2R01NS049203-06A1

Jared Su
Michelle Luu
Diana Zhu
Dr. Minal Tapadia
Dr. Winnie Palispis
Dr. Weiping Wang
Dr. Tahseen Mozaffar
Dr. Ranjan Gupta