

Biophysical Stimuli Induce Demyelination via an Integrin Dependent Mechanism

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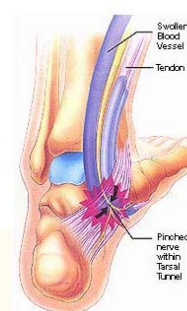
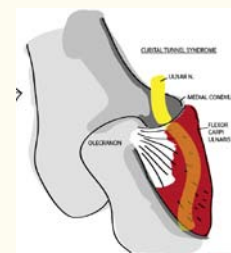
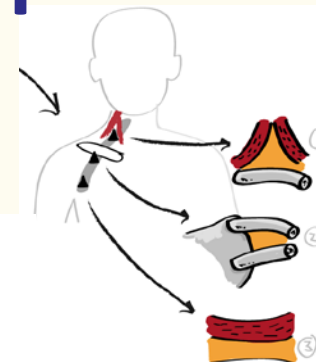
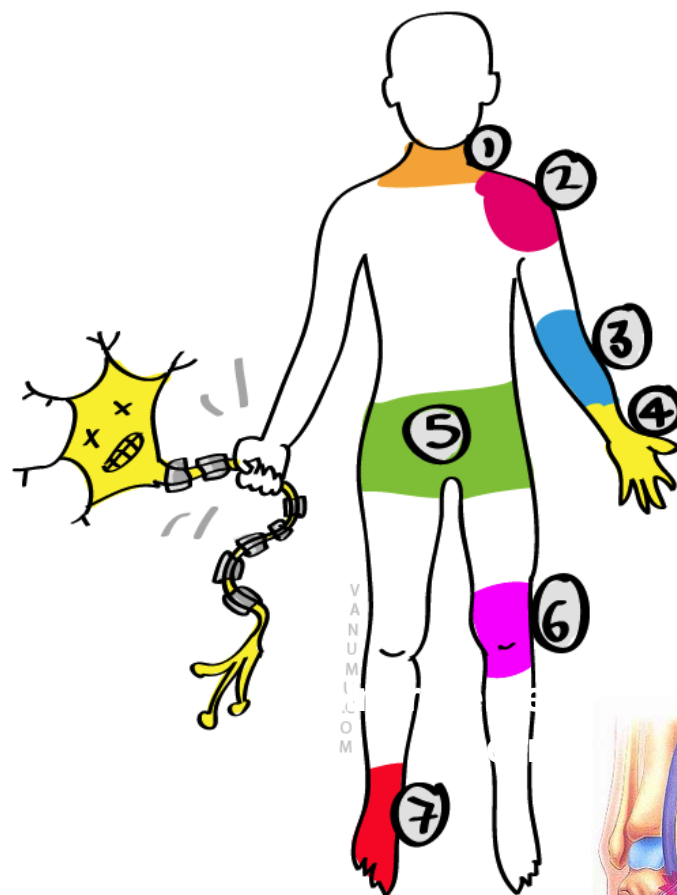
UC Irvine Peripheral Nerve Lab

Disclosures:

The Gupta Lab has been continuously funded by the NINDS/NIH for the past 10 years on Nerve Injuries

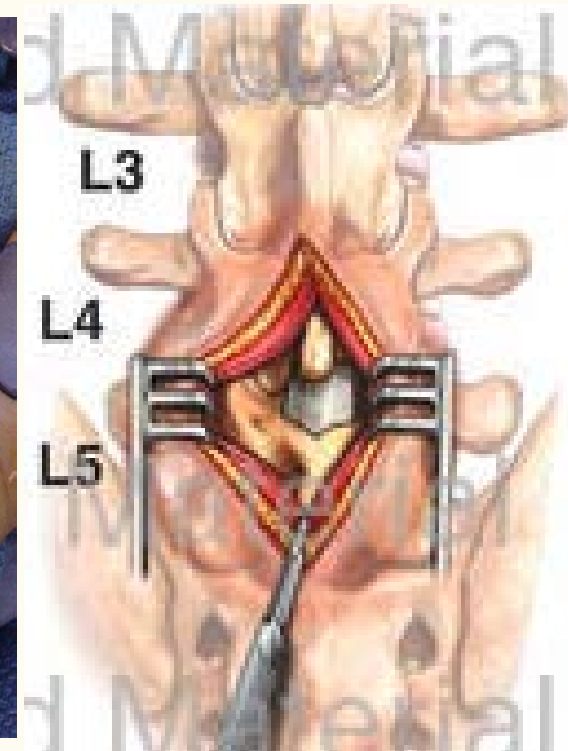
Chronic nerve compression (CNC) Injury

- Thoracic outlet, Spinal Nerve Root Stenosis, Cubital Tunnel syndrome, Tarsal tunnel syndrome
- Caused by chronic mechanical insult to the peripheral nerve
- Presenting symptoms:
 - Pain
 - Tingling
 - Weakness

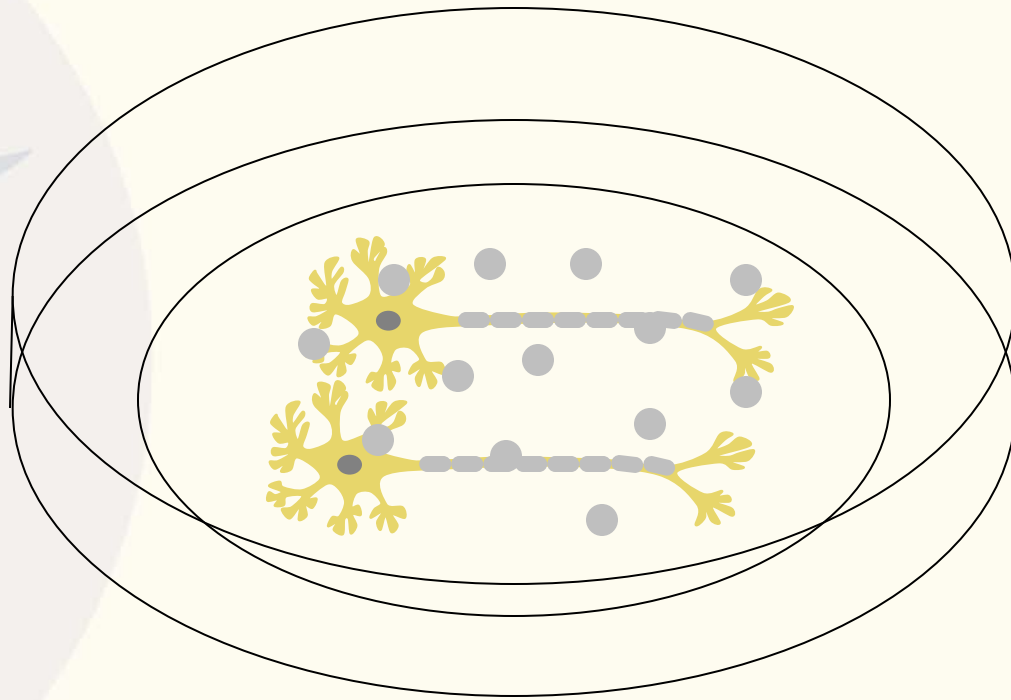


Treatment of CNC Injury

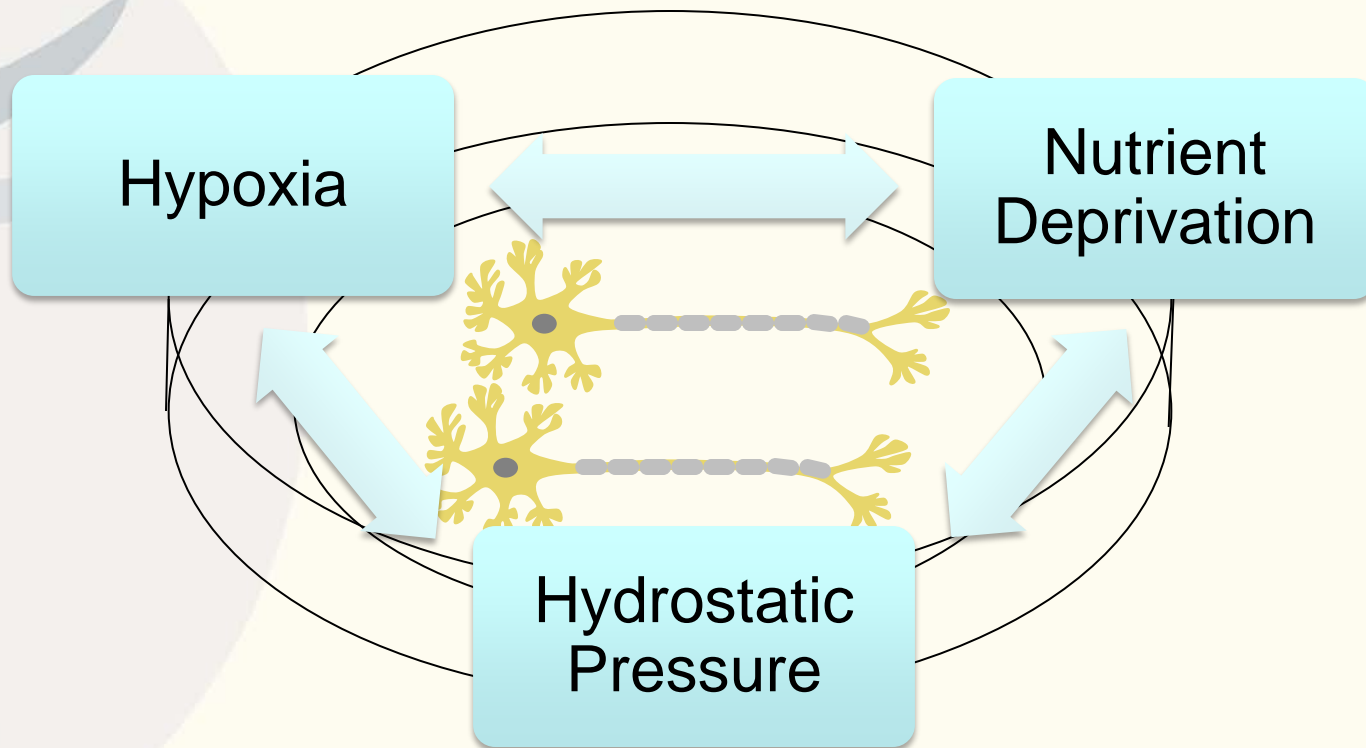
- Steroid Injections
- NSAIDS, rest, physical therapy
- Surgery
- Limited effectiveness of non-surgical management and surgical treatment in later stages of disease
- Limited understanding about the molecular pathogenesis



In vitro model of CNC injury

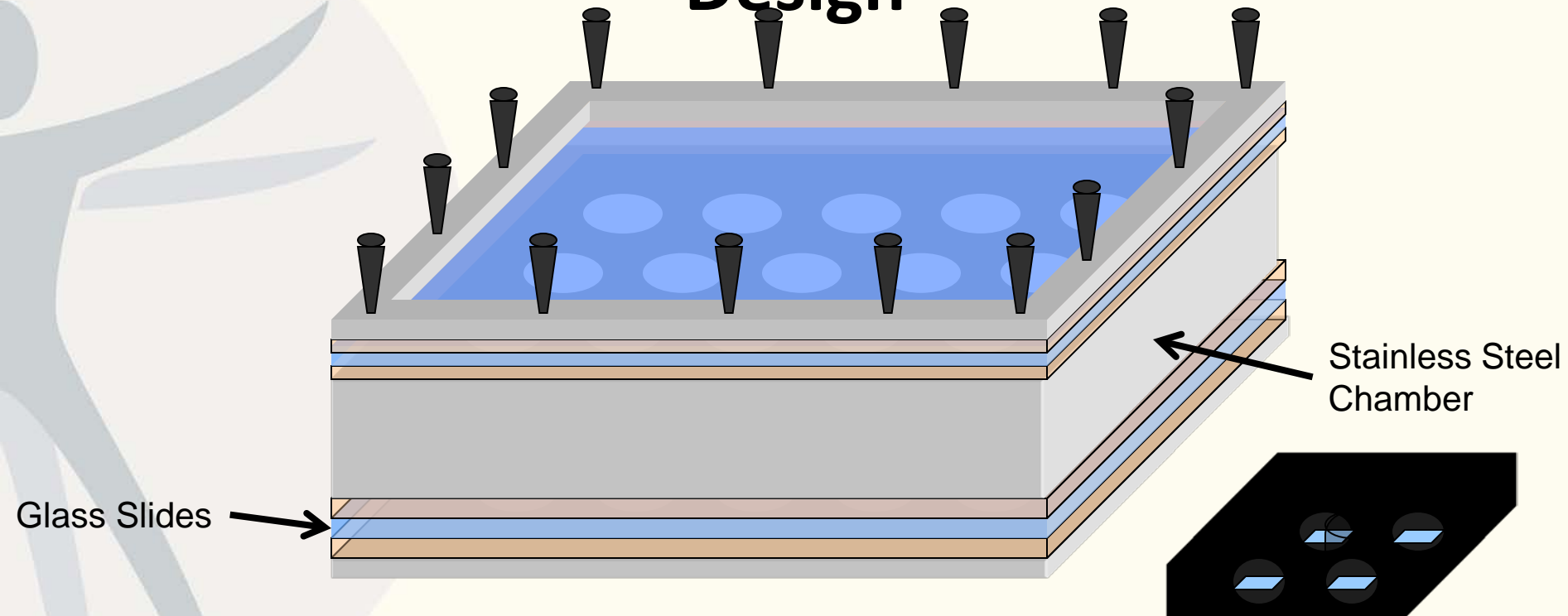


In vitro model: biophysical stimuli



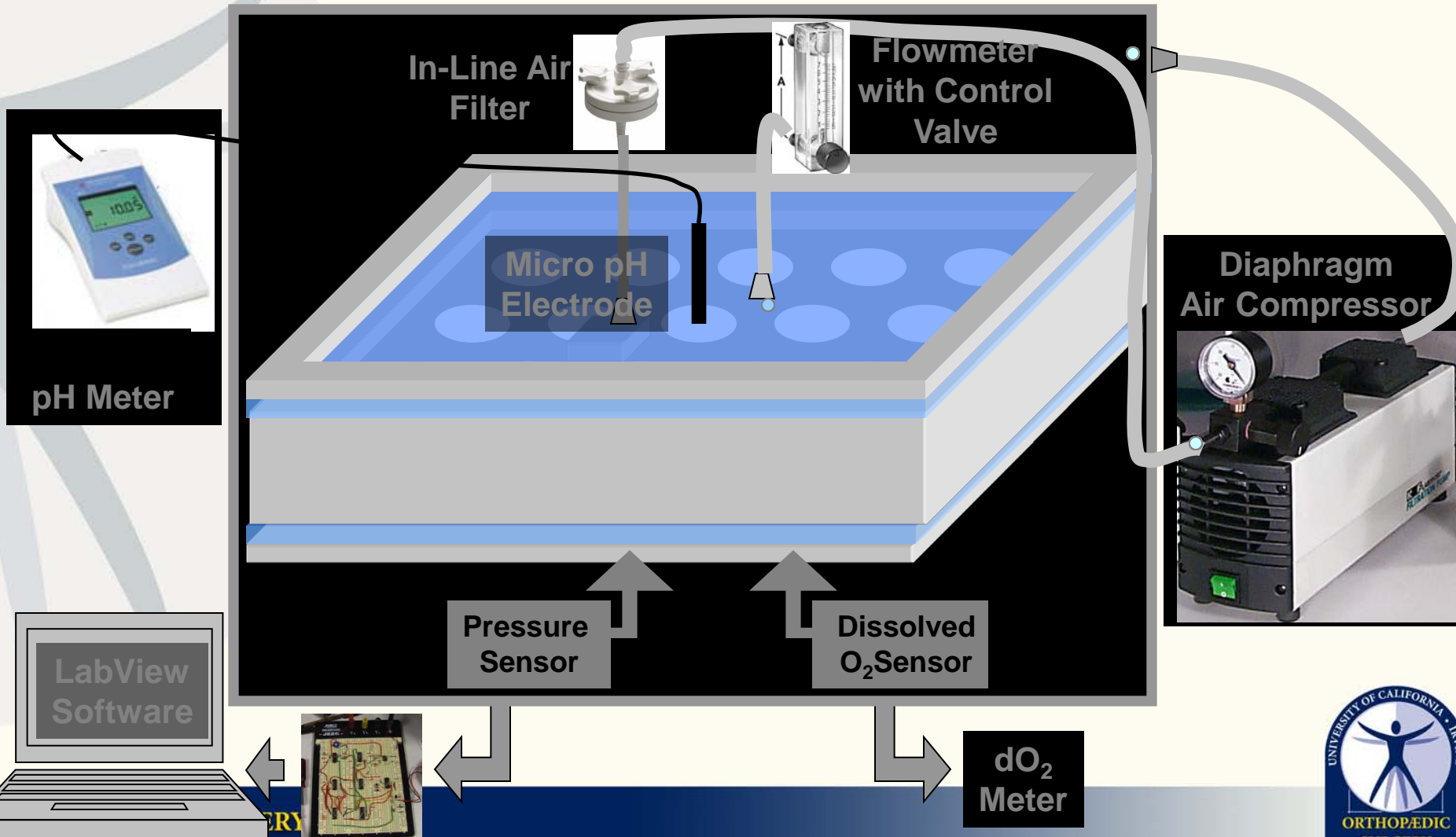
Friebos L and Gupta R. *Journal of Neurotrauma* 2009

Hydrostatic Compression Chamber Design

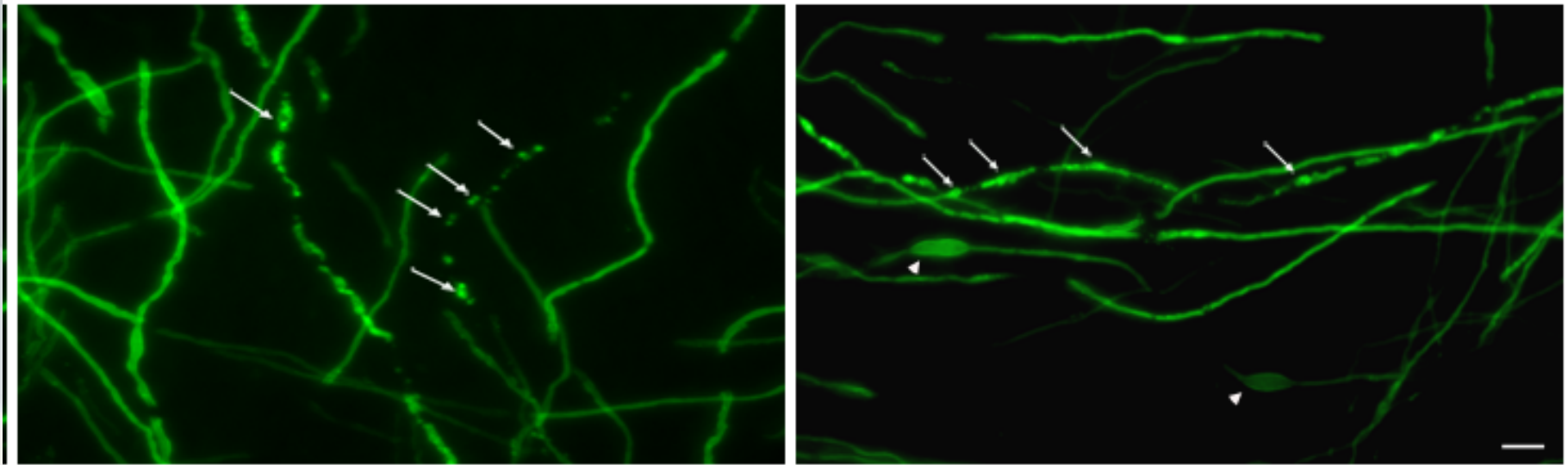


- Houses several isolated culture wells of equal dimensions.
- Allows for microscopic visualization and imaging of the cells during pressurization using an inverted microscope.
- Neurons and Schwann cells are cultured on coverslips and transferred into the chamber prior to experimentation.

Hydrostatic Compression Chamber

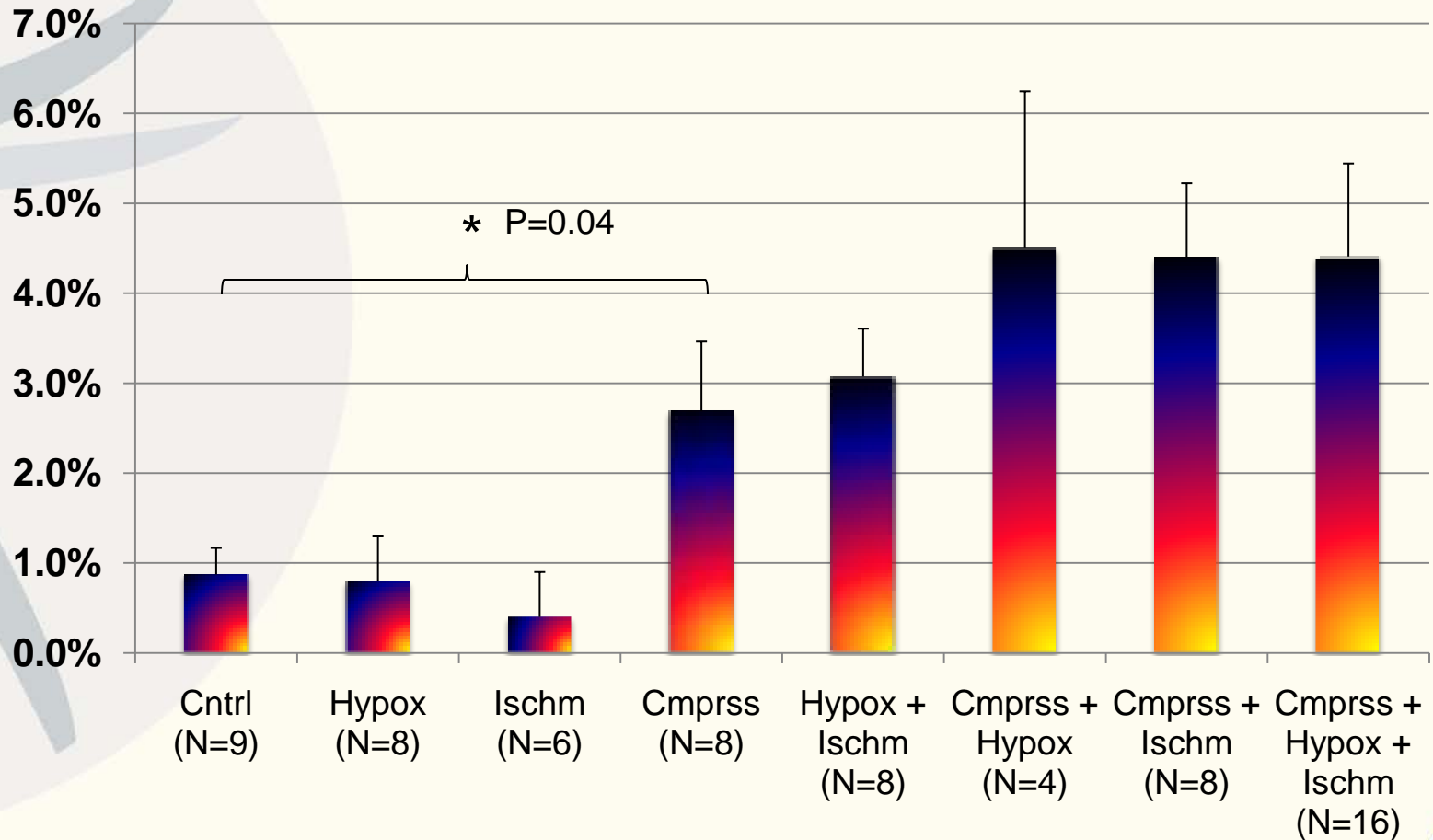


Demyelination assayed by immunostaining myelin basic protein (MBP)

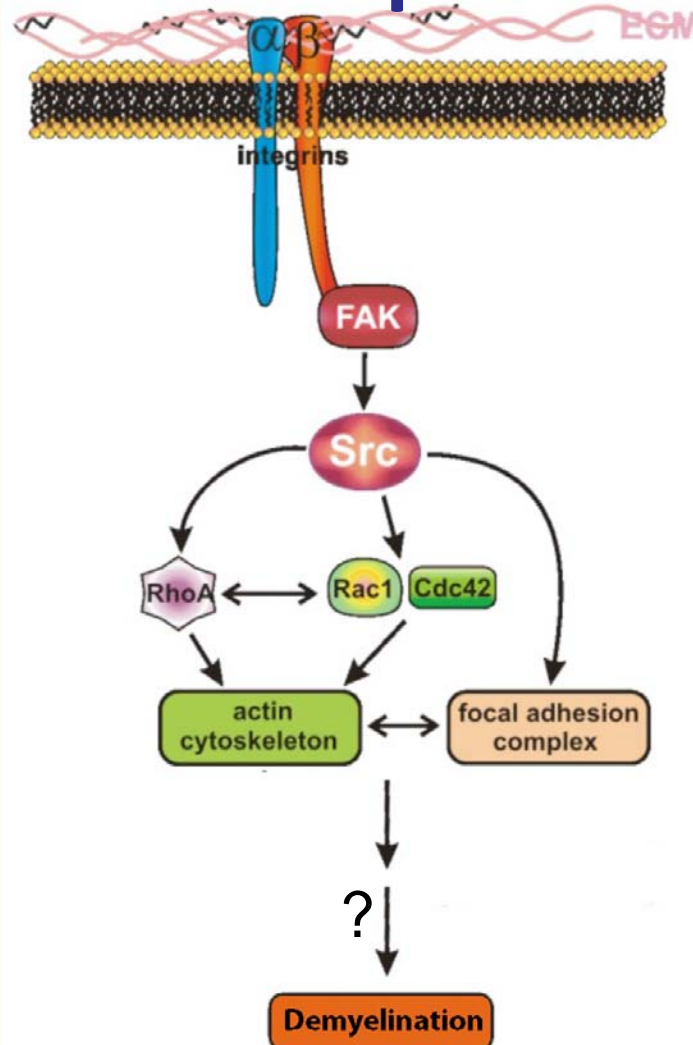


Scale bar = 50um

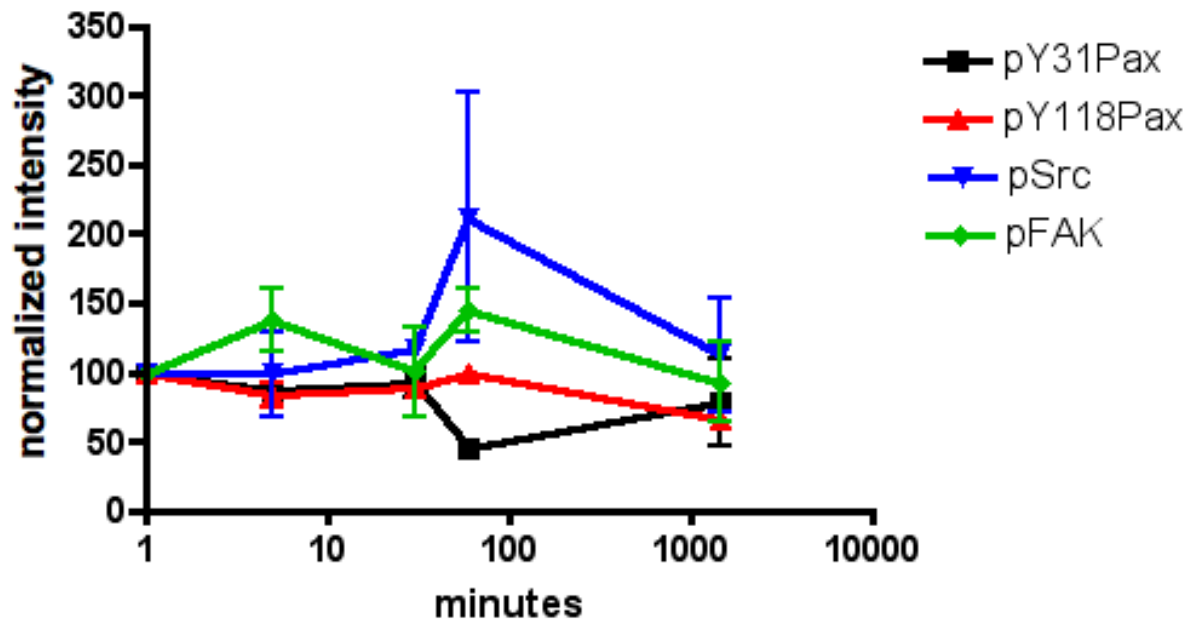
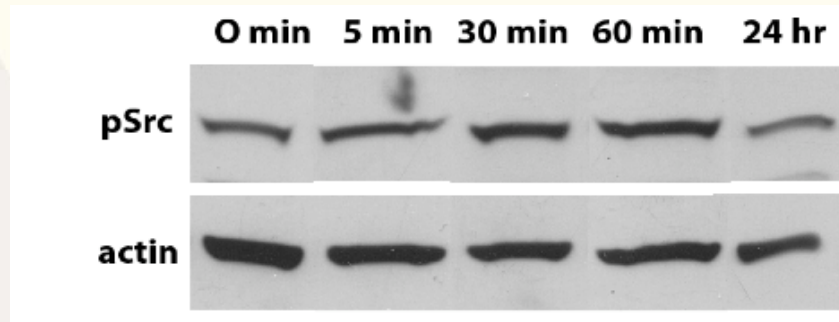
Biophysical Stimuli induces Demyelination



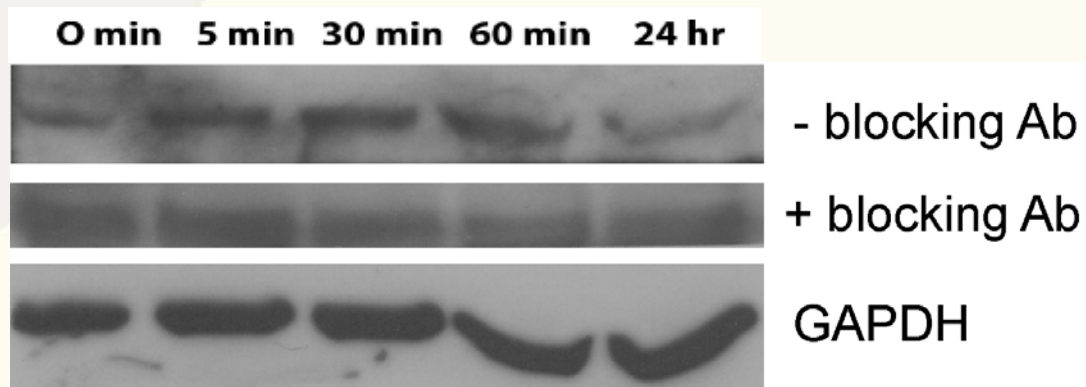
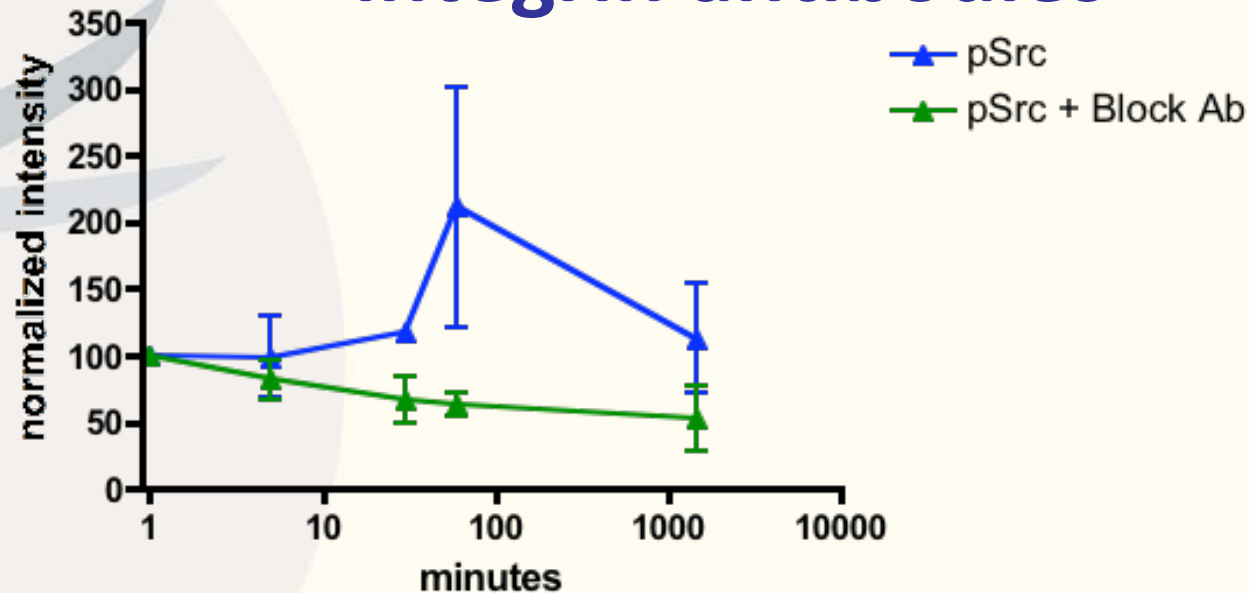
Are integrins mediating the observed in-Vitro response?



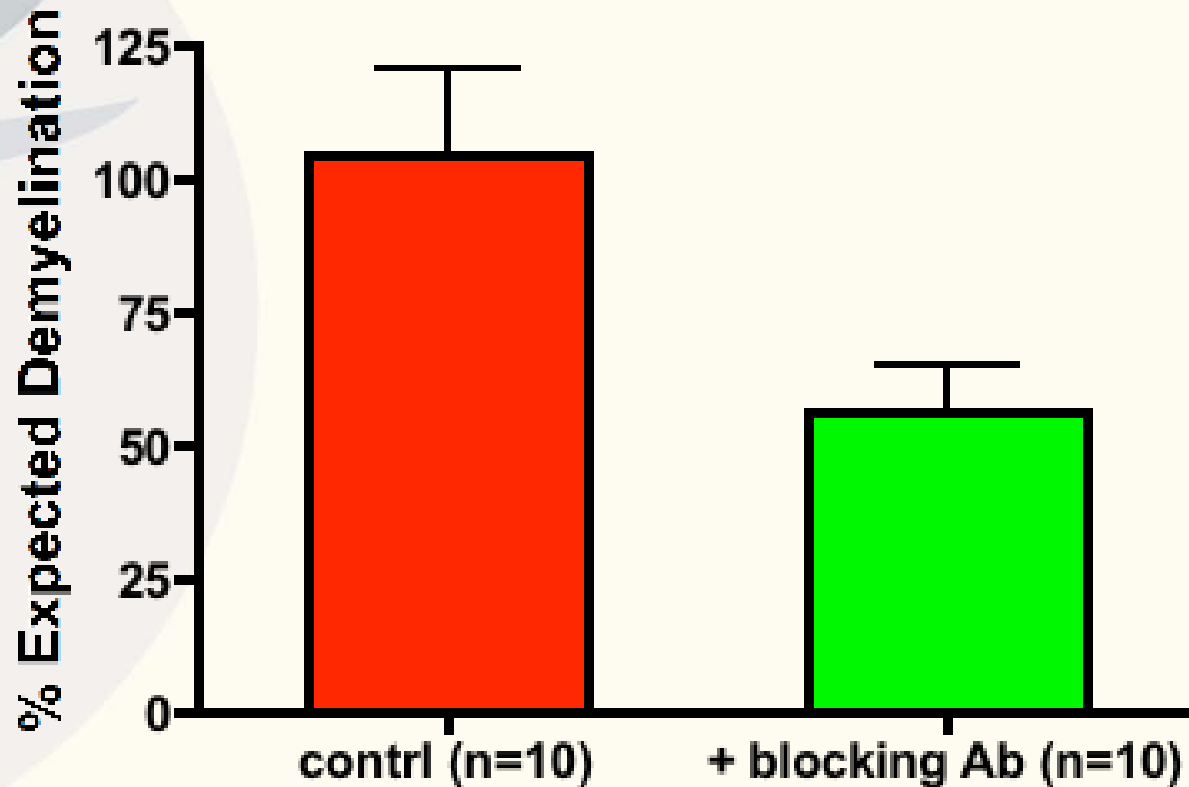
In-Vitro Injury Alters Phosphorylation of Integrin associated 2nd Messengers



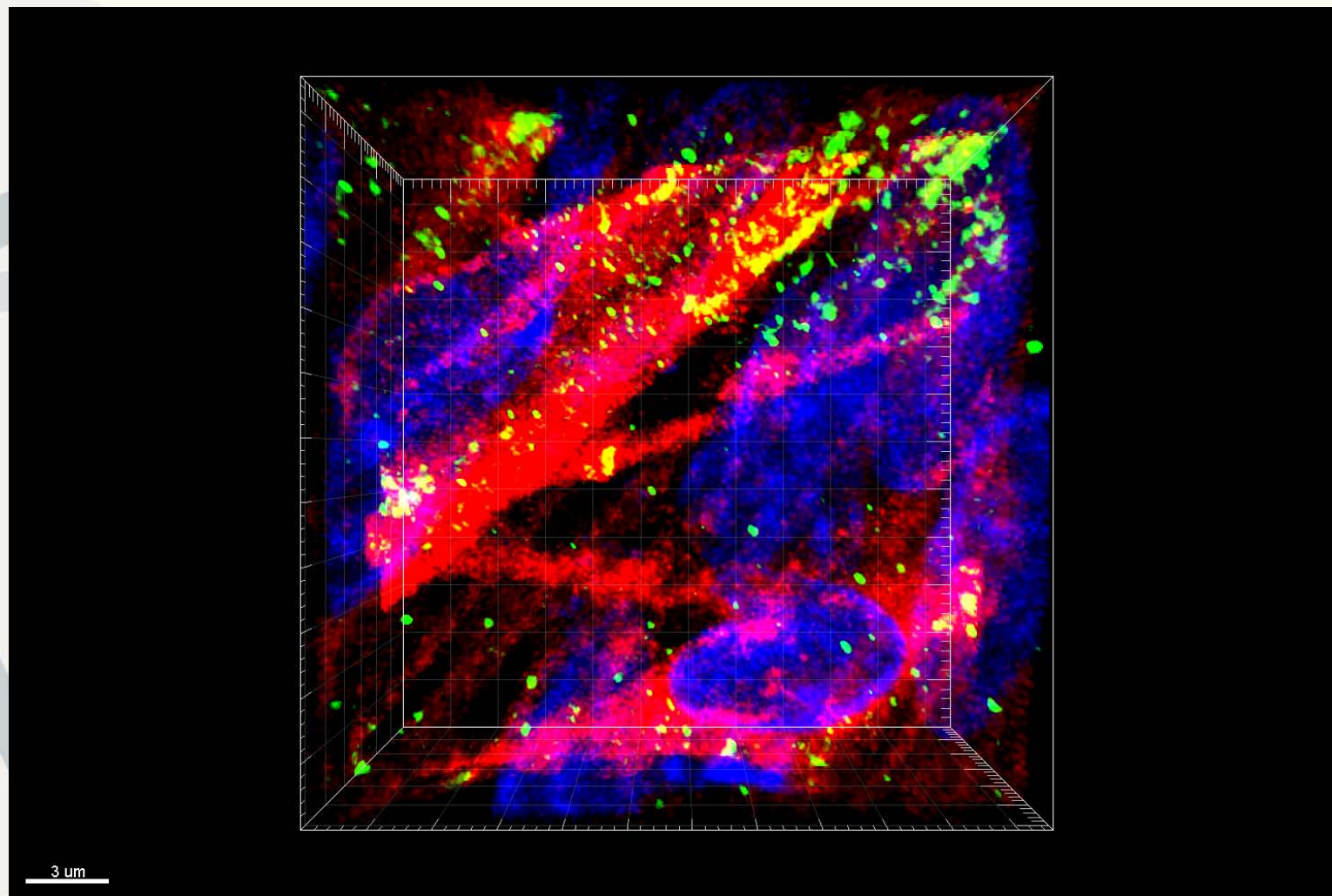
The effect of functional blocking integrin antibodies



functional blocking integrin antibodies alleviate demyelination



P=0.01



Summary

- Hydrostatic pressure induces demyelination. Biophysical stimuli appears to potentiate its effect.
- The 2nd messenger pSrc is upregulated with biophysical stimuli
 - This process appears to be mediated by integrins.
- Blocking integrin signaling reduces compression-induced demyelination
- 2nd messengers co-localize with Schwann cells.