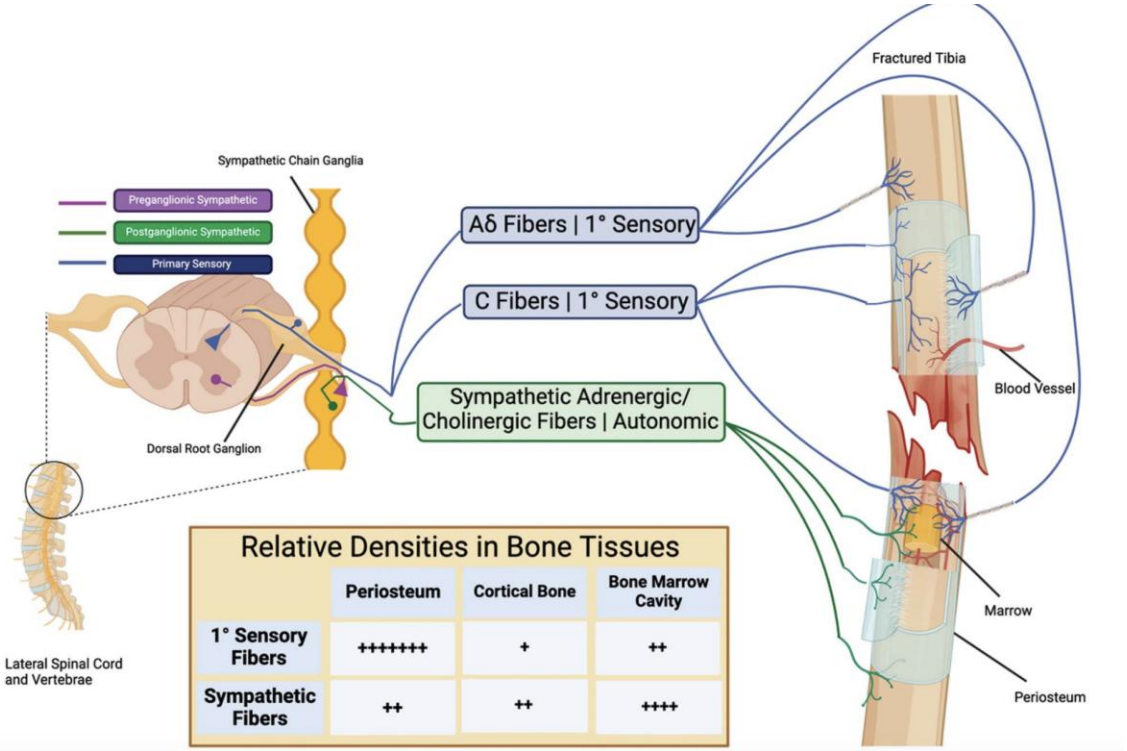
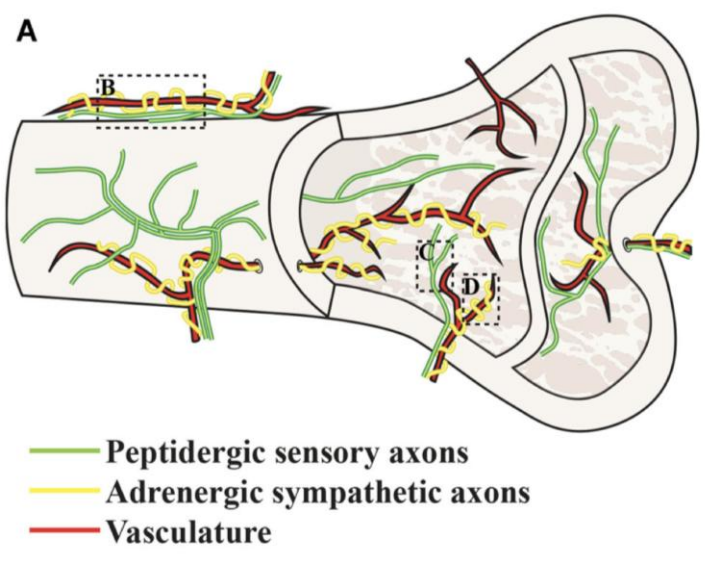
A Bad Break:
Unraveling Fracture Related Pain

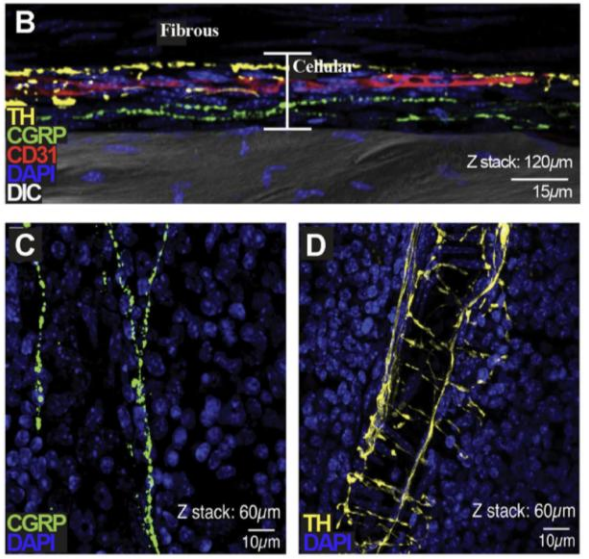
Dr. Chelsea S Bahney, PhD

Associate Professor, Orthopaedic Trauma Institute
University of California San Francisco (UCSF)

Bone Breaks Hurt!







PAIN®

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A bad break: mechanisms and assessment of acute and chronic pain after bone fracture

Haruki Nishimura[a,b], Jonathan Layne[a,c], Kohei Yamaura[a,d], Ralph Marcucio[c], Kazuhito Morioka[c], Allan I. Basbaum[e], Jarret Weinrich[f], Chelsea S. Bahney[a,c,*]

REVIEW

JBMR®

Nerves in Bone: Evolving Concepts in Pain and Anabolism

Jennifer M Brazill,[1] Alec T Beeve,[1,2] Clarissa S Craft,[1,3] Jason J Ivanusic,[4] and Erica L Scheller[1,3]

Opioids are the Standard of Care to Treat Post-Operative Fracture Pain

RESEARCH ARTICLE

Effect of NSAIDs on Bone Healing Rates: A Meta-analysis

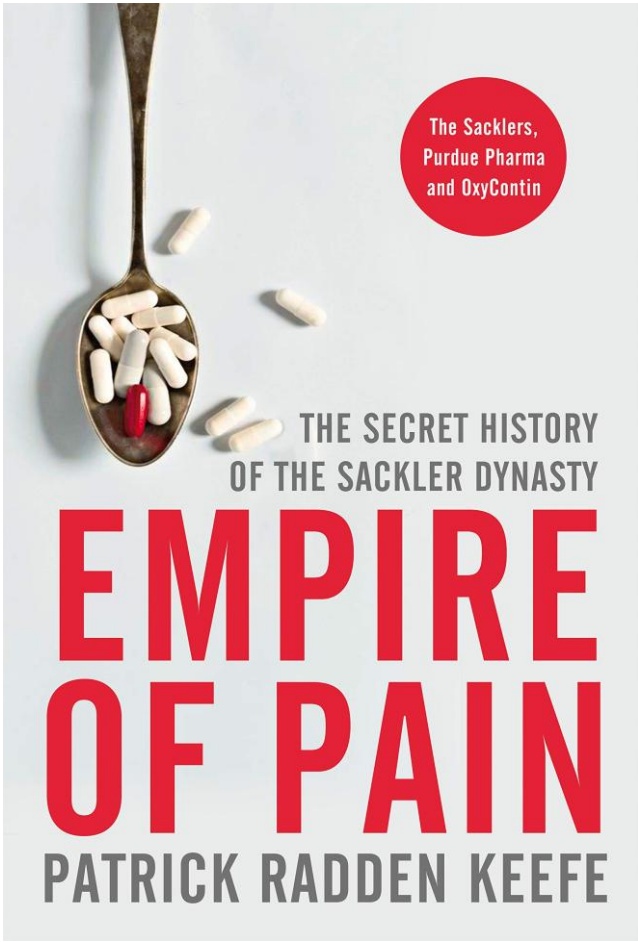
Wheatley, Benjamin M. MD; Nappo, Kyle E. MD; Christensen, Daniel L. MD; Holman, Ann M. MLS; Brooks, Daniel I. PhD; Potter, Benjamin K. MD

Author Information

Journal of the American Academy of Orthopaedic Surgeons Journal of the AAOS® AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

D-17-00727

Conclusion: Analysis of the literature indicates a negative effect of NSAIDs on bone healing. In pediatric patients, NSAIDs did not have a significant effect. The effect may be dose or time dependent because low-dose/short-duration exposure did not affect union rates.



- ❑ Opioid prescription rates after acute fracture (2017): 56% of Medicaid and 44% of privately insured
- ❑ Femur fracture prescription patterns: 47 x 10mg oxycodone, 3 refills[1]
- ❑ Acetabular fractures: average of 200 x 5mg oxycodone over 1 year[2]
- ❑ Kids under 4: average of 28 pills (at scaled mg/kg)[3]

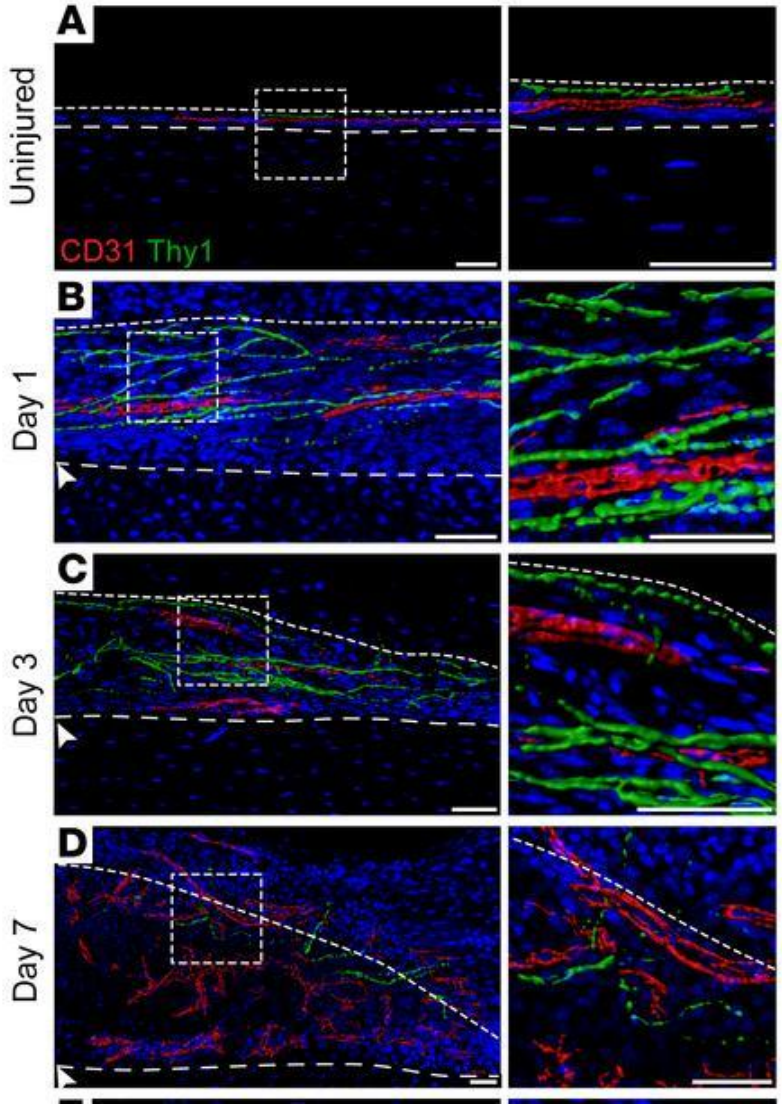
[1]Attum et al, JOT 2017. [2]Lee et al, *Plast Reconstr Surg Glob Open* 2023. [3]Iobst et al, *J Clin Orthop Trauma* 2020 .

High Incidence of Chronic Pain Following Fracture

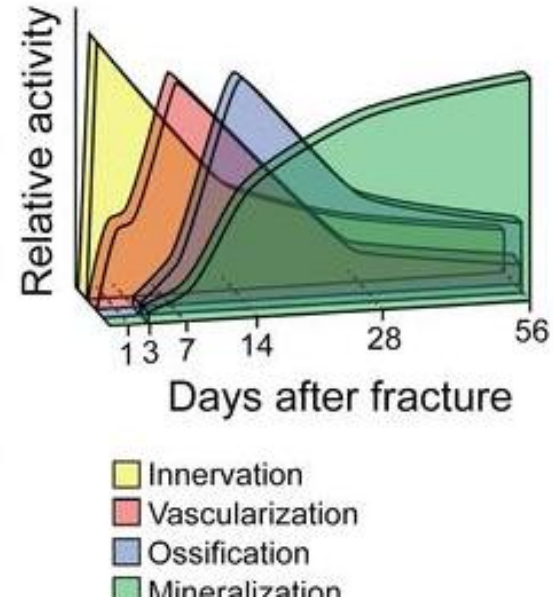
Chronic Pain: Pain persisting beyond 3 months

Incidence of chronic post-fracture pain	Type of fracture	Author
78%	Lower extremity fracture	Griffioen et al.[91]
55%	Tibial fracture with surgery	Khan et al.[143]
45%	Lower extremity fracture	Wyngaarden et al.[251]
60%	Distal radius fracture with surgery	Yoon et al.[276]
20%	Distal radius fracture	MacDermid et al.[161]
64%	Rib fracture	Fabricant et al.[68]
19%	Wrist or ankle fracture with surgery	Friesgaard et al.[74]
51%	Fragility fracture (vertebrae, hip, shoulder, wrist, other)	Gheorghita et al.[82]
52%	Fragility fracture (vertebrae, hip, wrist, other)	Sale et al.[221]
90%	Vertebral body fragility fracture	Suzuki et al.[236]
13%	Hip fracture with surgery	Dasch et al.[52]

Innervation is an Important Part of the Healing Process



Zhu et al. J Clin Invest. 2019



PNAS

NGF-TrkA signaling in sensory nerves is required for skeletal adaptation to mechanical loads in mice

Ryan E. Tomlinson[a], Zhi Li[a], Zhu Li[a], Liliana Minichiello[b], Ryan C. Riddle[a,c], Arun Venkatesan[d], and Thomas L. Clemens[a,c,1]

[a]Department of Orthopaedic Surgery, Johns Hopkins University, Baltimore, MD 21287; [b]Department of Pharmacology, Oxford University, Oxford, OX1 3QT, United Kingdom; [c]Baltimore Veterans Administration Medical Center, Baltimore, MD 21201; and [d]Department of Neurology, Johns Hopkins University, Baltimore, MD 21287

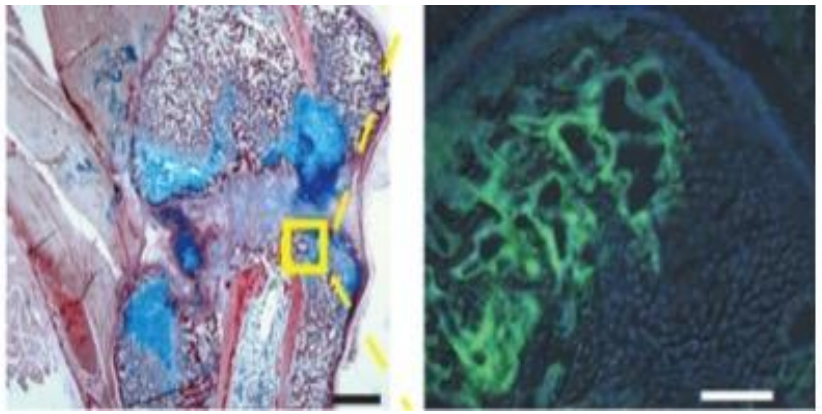
Edited by Clifford J. Tabin, Harvard Medical School, Boston, MA, and approved March 23, 2017 (received for review January 25, 2017)

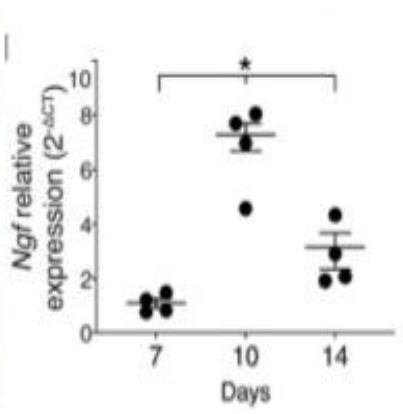
JCI The Journal of Clinical Investigation

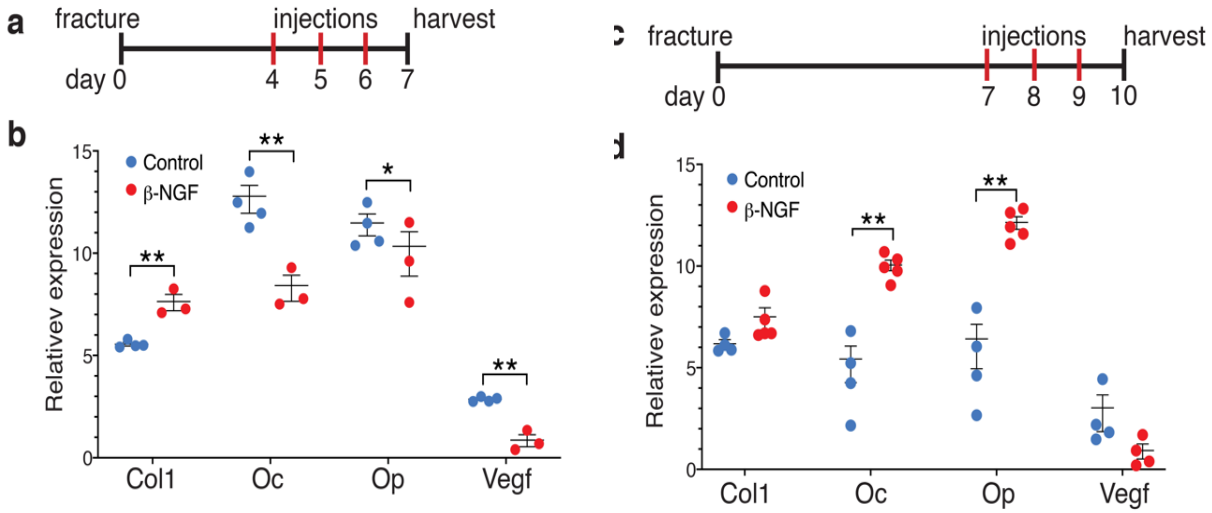
Fracture repair requires TrkA signaling by skeletal sensory nerves

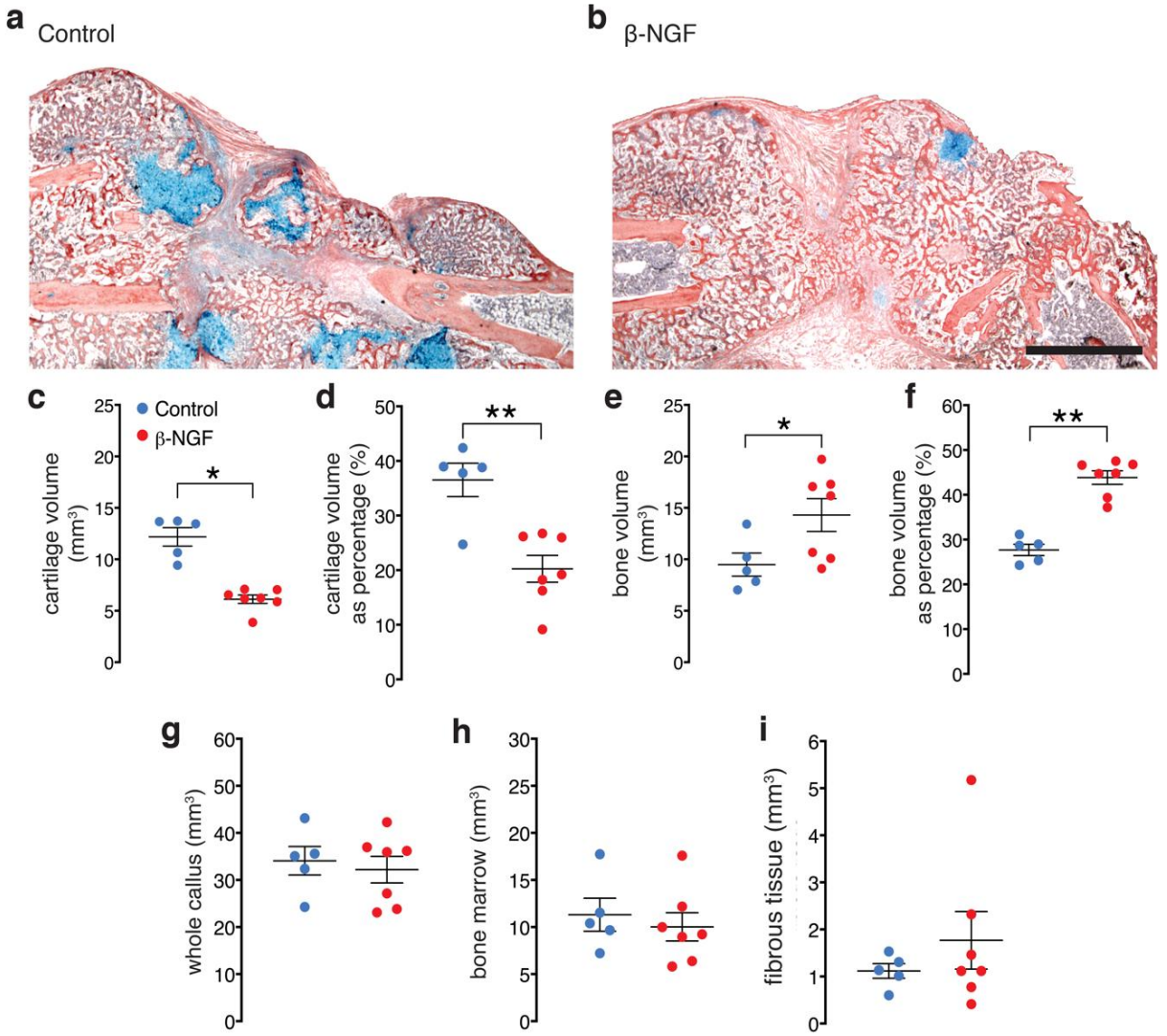
Zhu Li, … , Thomas L. Clemens, Aaron W. James

Nerve Growth Factor (NGF) Promotes Fracture Repair





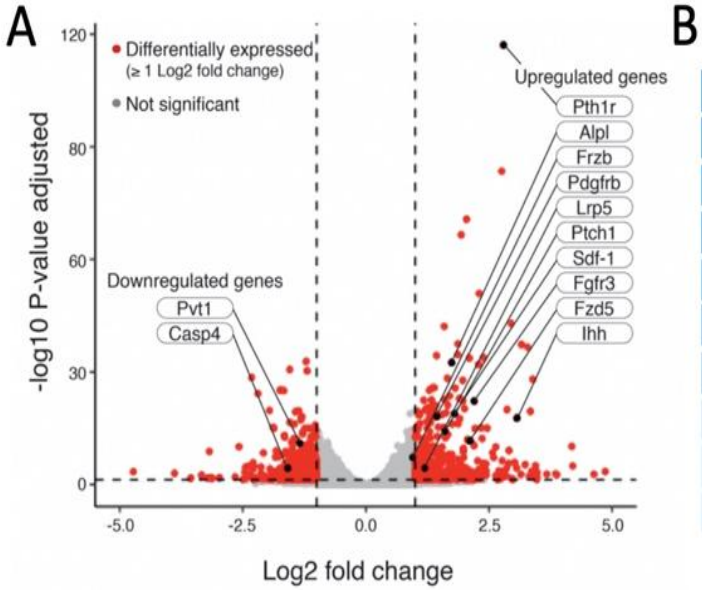


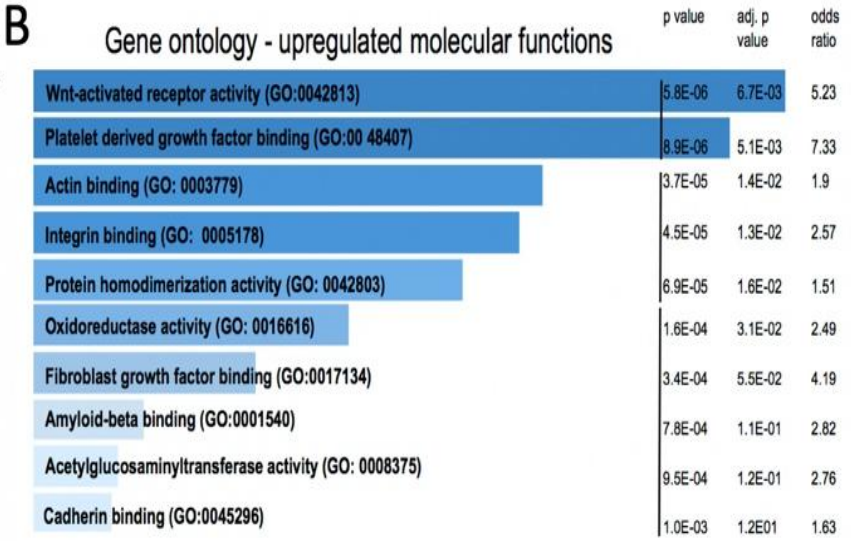


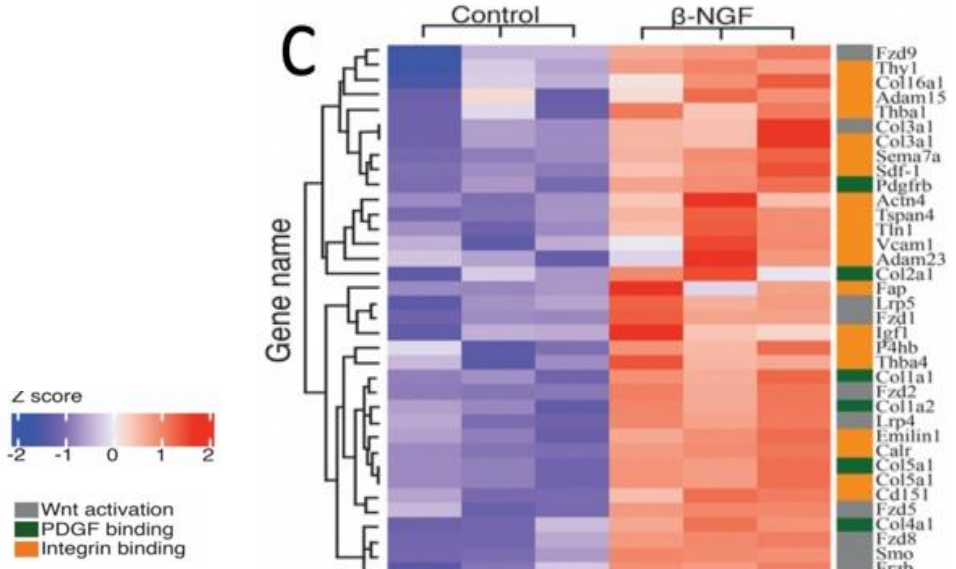
Rivera *et al.* Nature Sci Reports 2020

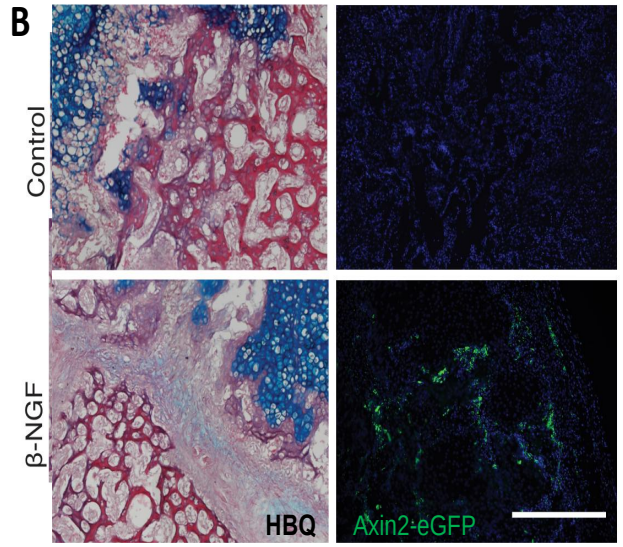
NGF Upregulated Endochondral Ossification and Down Regulated Apoptosis

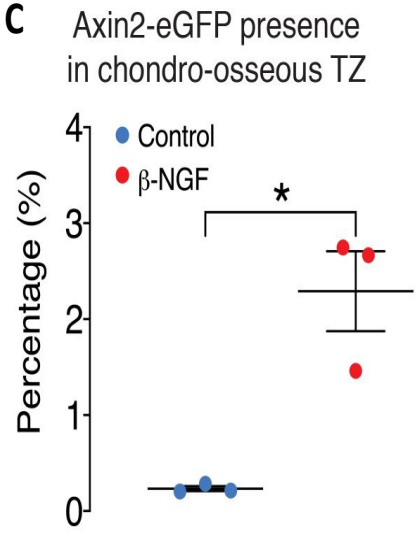
Rivera *et al.*
Nature Sci
Reports 2020



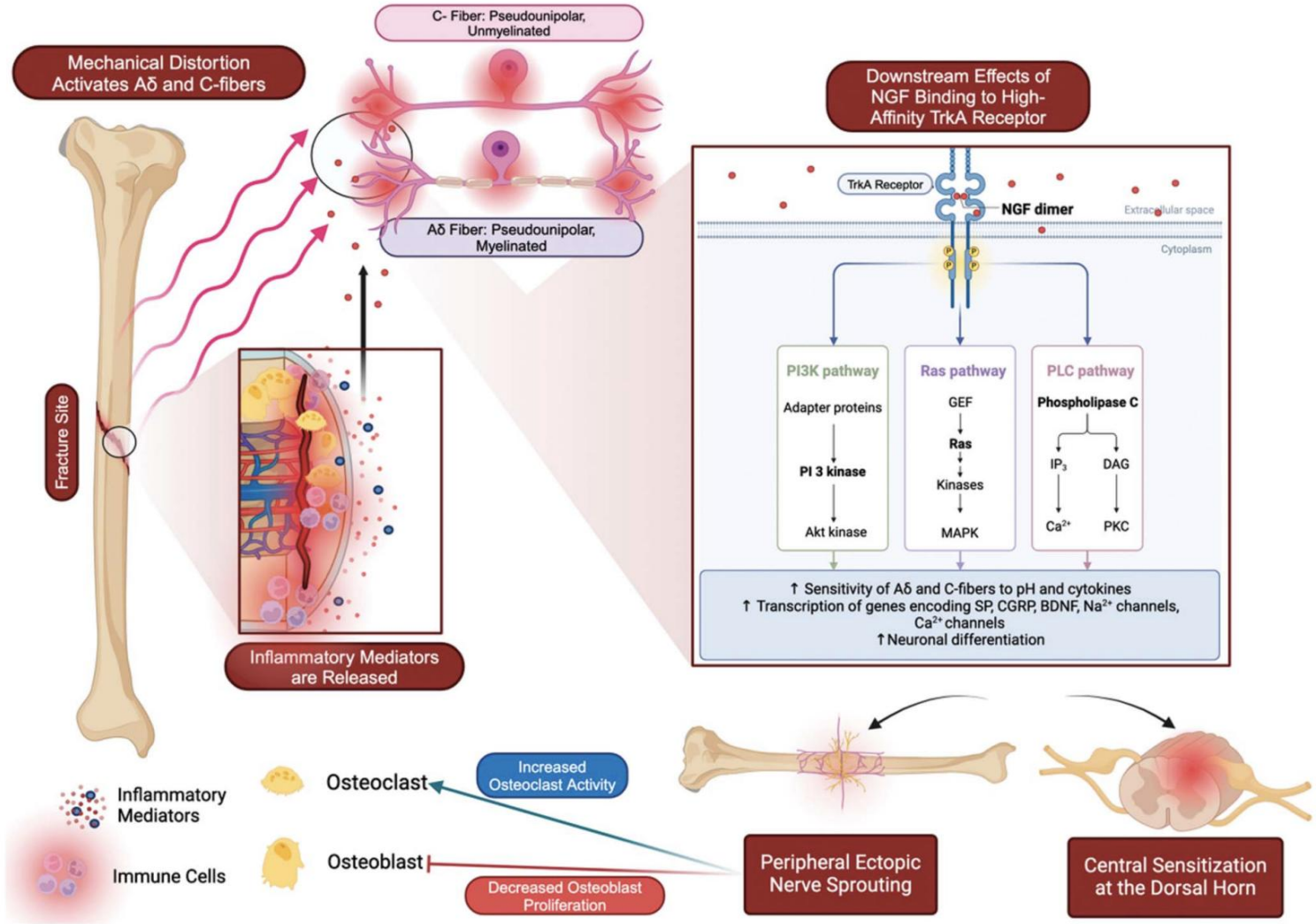






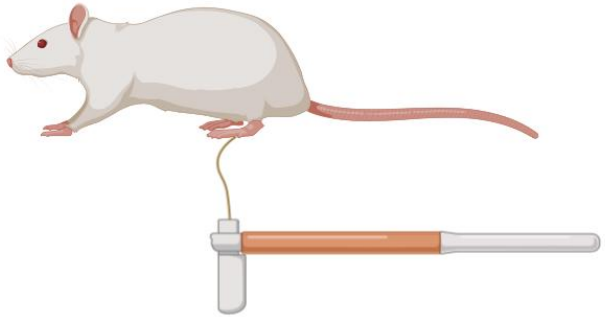


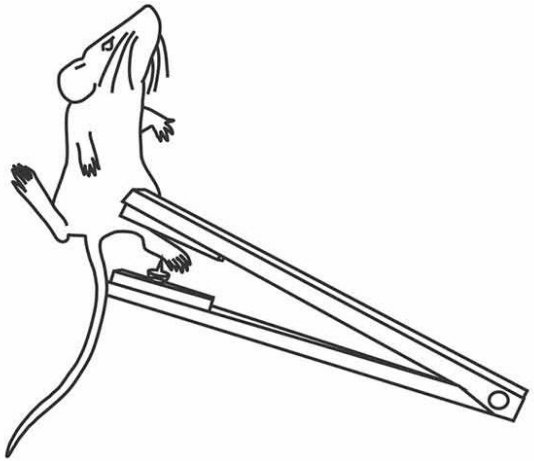
Research Goal: Correlate Retrograde Pain Signaling After Fracture to Behavioral Deficits in Mice



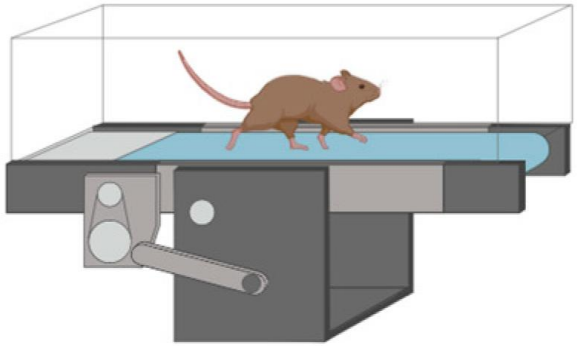
Shortcomings of Standard Pain Testing Methods Post Fracture

Hindpaw reflexive avoidance assays

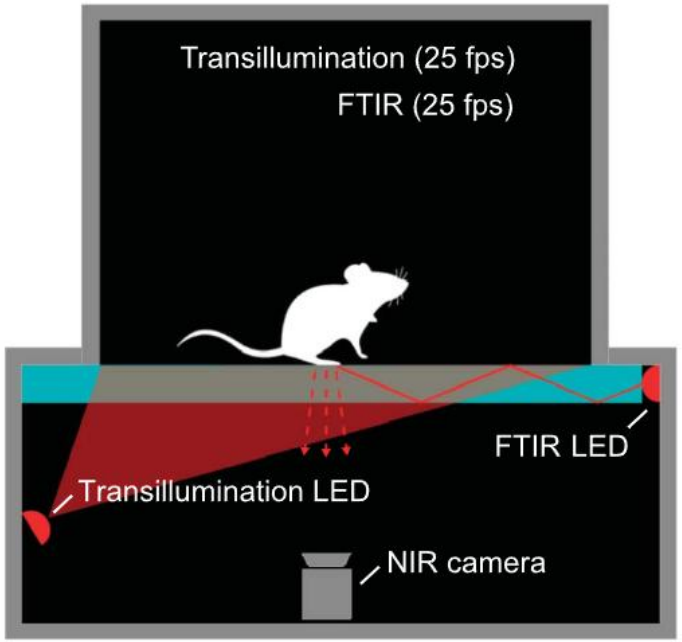


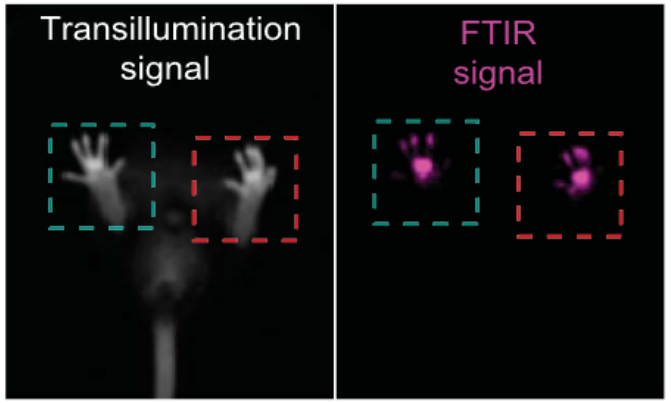


Gait Analyses



BlackBox Imaging Technology

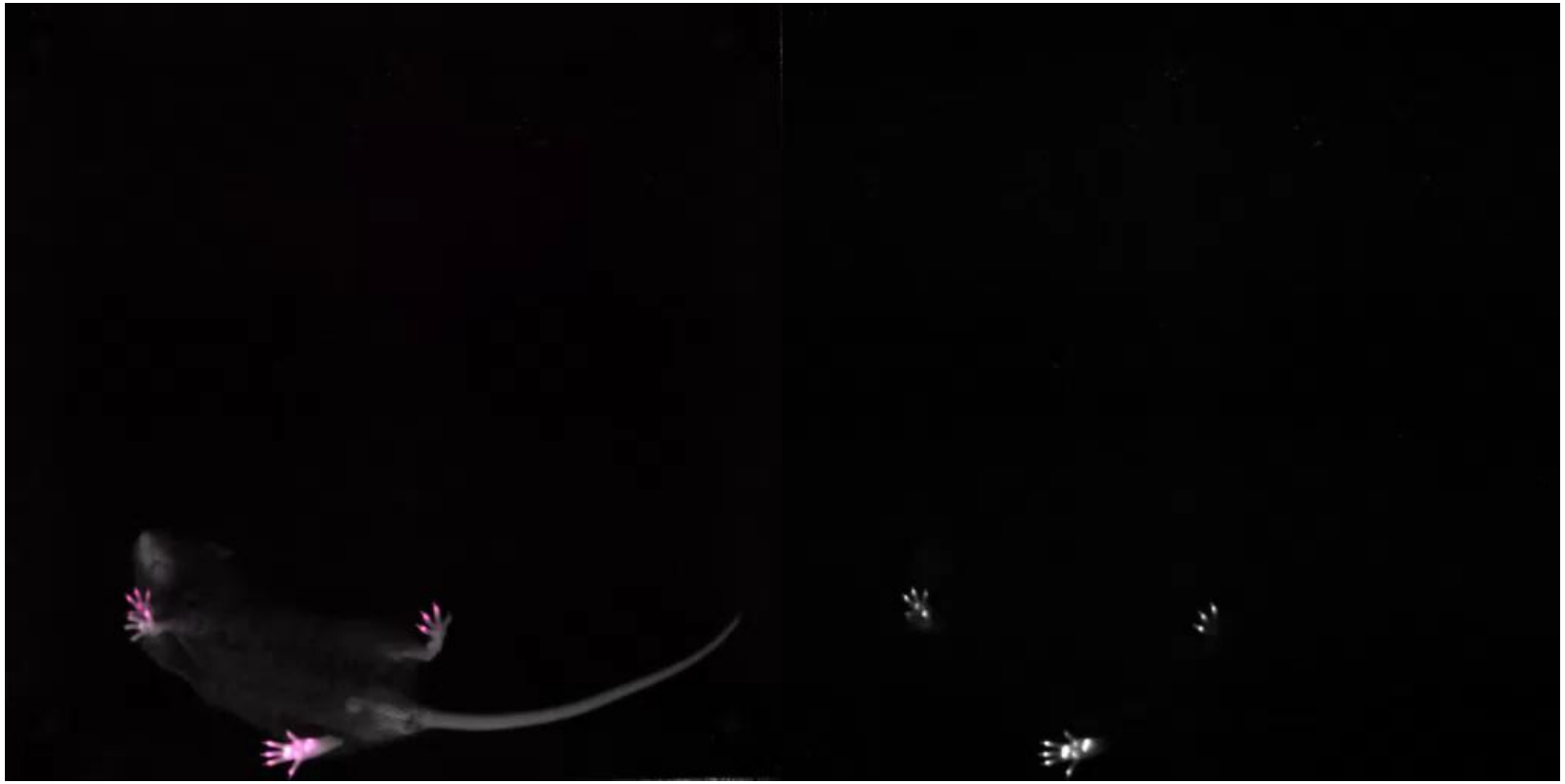


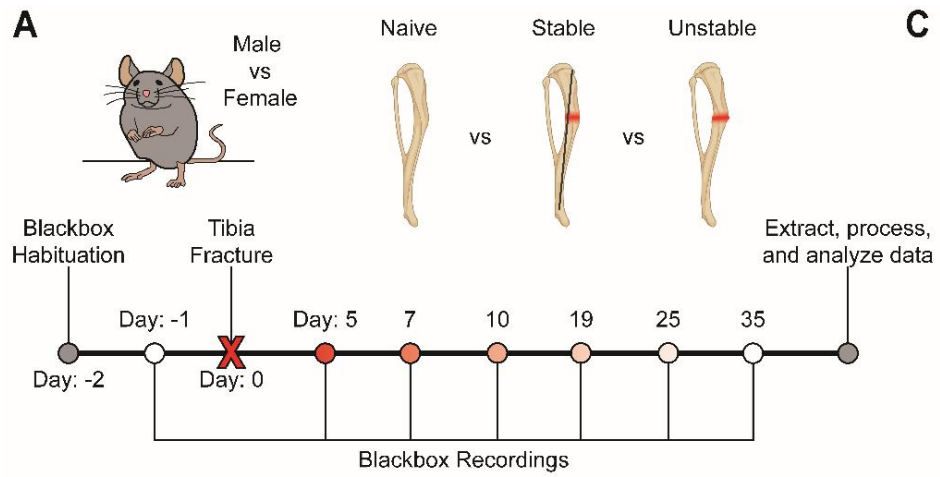


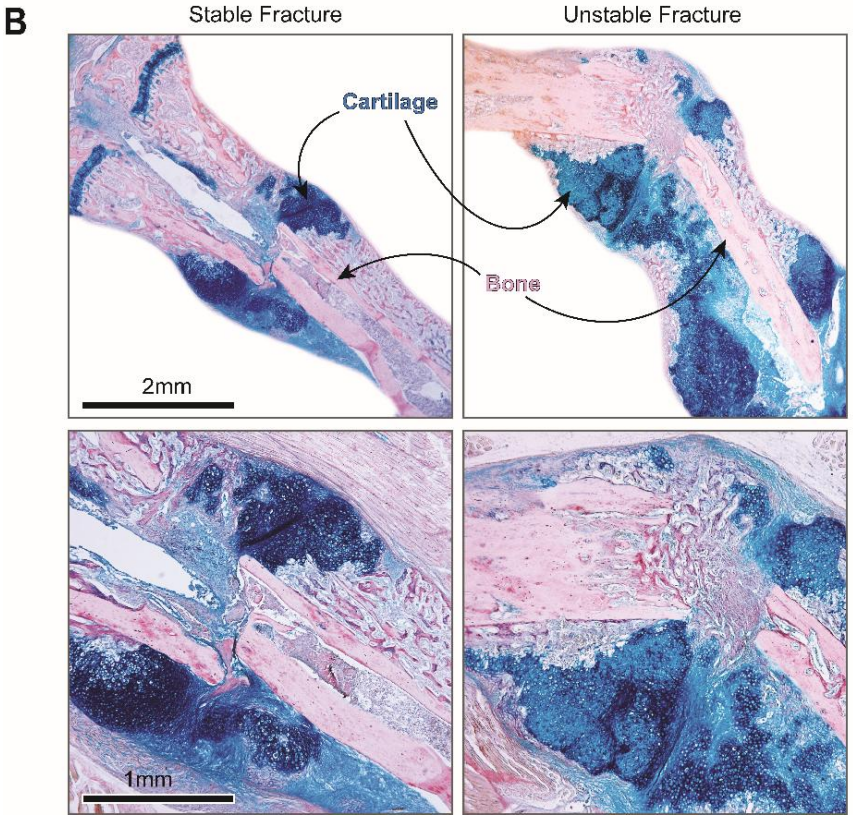
Zhang and Roberson, *et al*. 2022

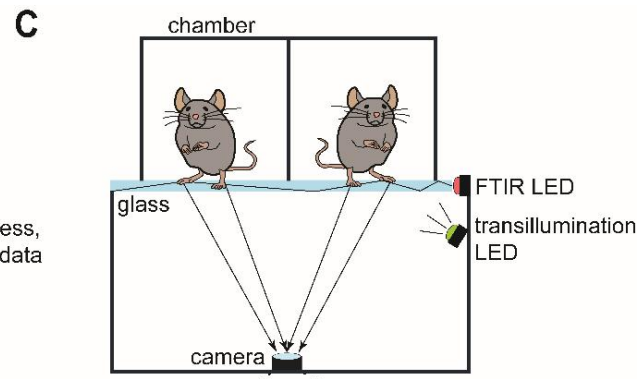
Behavioral Phenotyping Using the BlackBox

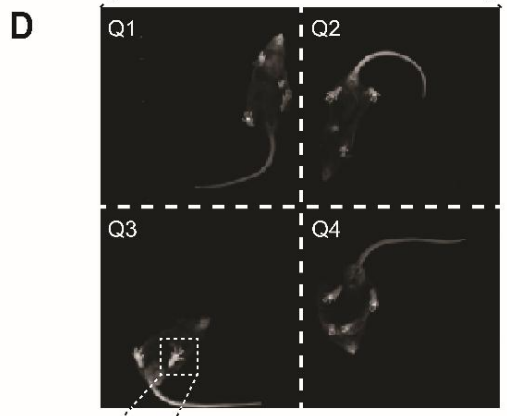
Naïve mouse, no pain

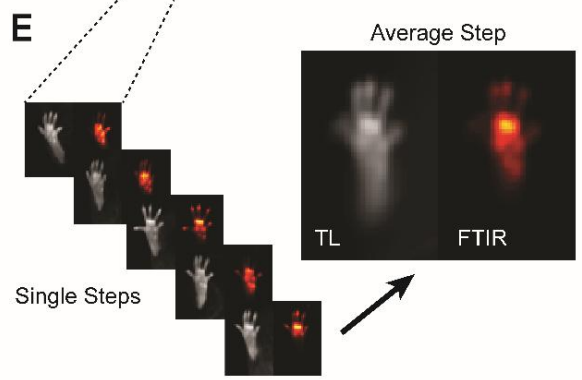



A
Male
vs
Female
Naive
Stable
Unstable
vs
vs
Blackbox
Habituation
Tibia
Fracture
Extract, process,
and analyze data
Day: -1
Day: 5
7
10
19
25
35
Day: -2
Day: 0
Blackbox Recordings

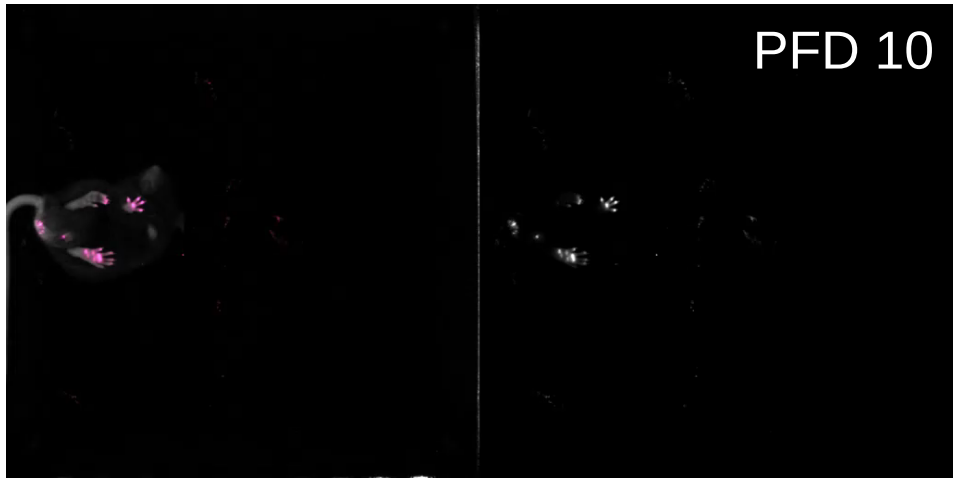

B
Stable Fracture
Unstable Fracture
Cartilage
Bone
2mm
1mm


C
chamber
FTIR LED
glass
transillumination
LED
camera


D
Q1
Q2
Q3
Q4

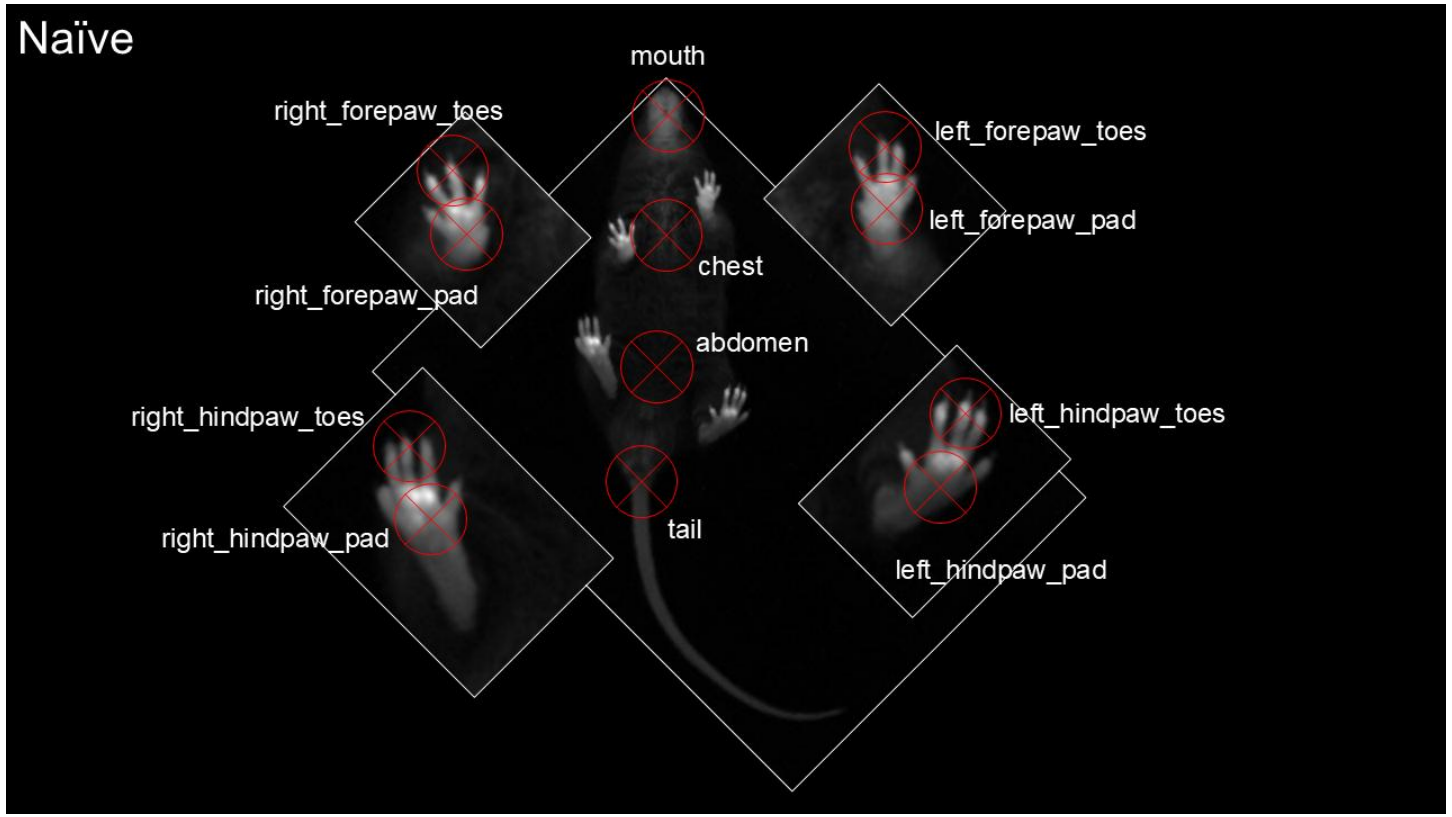

E
Average Step
TL
FTIR
Single Steps

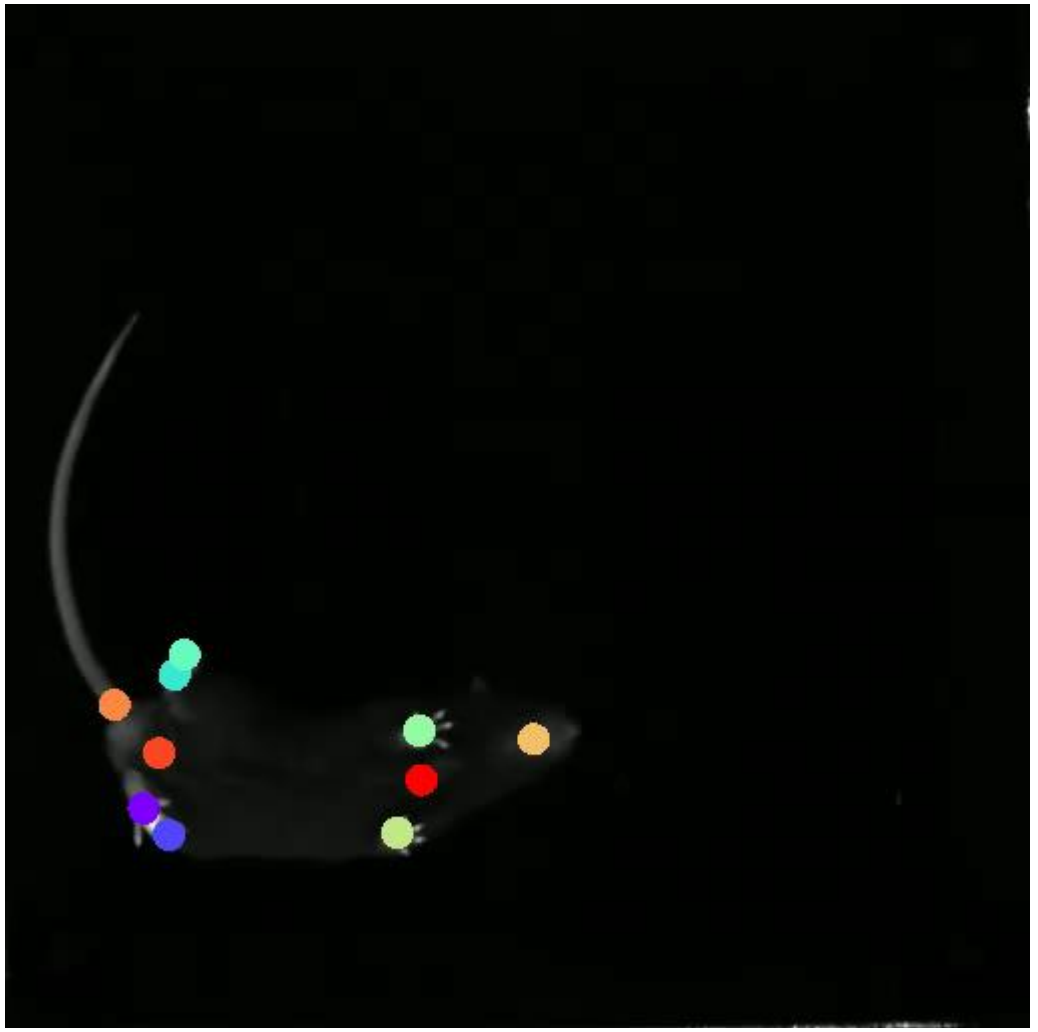

Post Fracture Day
PFD 5


PFD 10

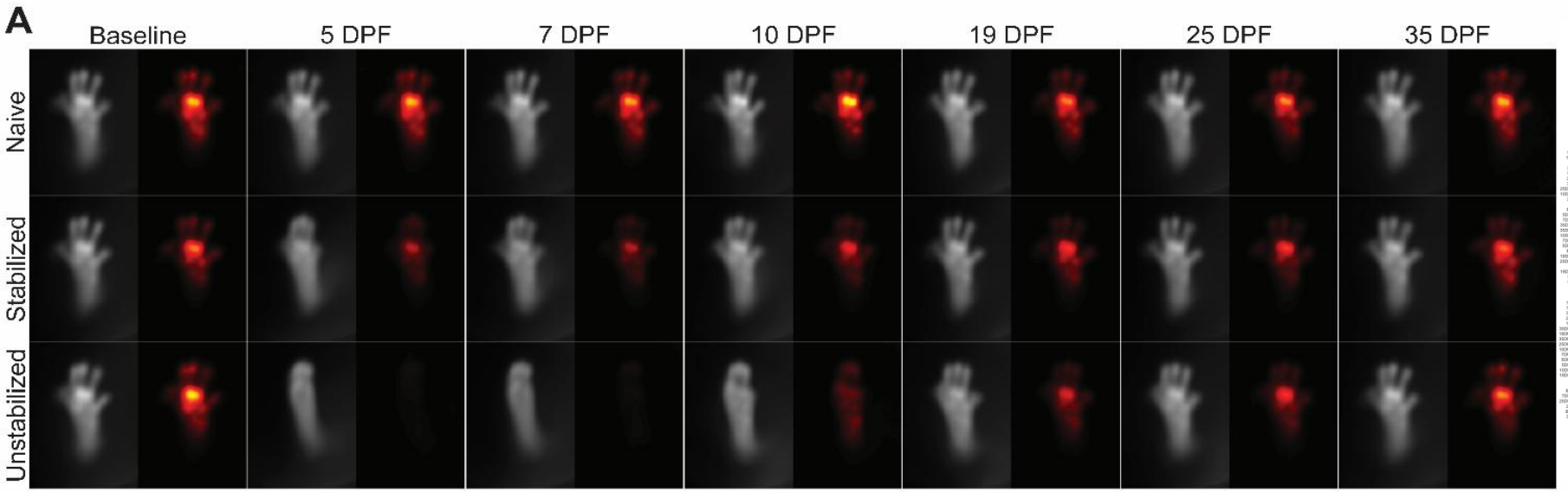

PFD 19

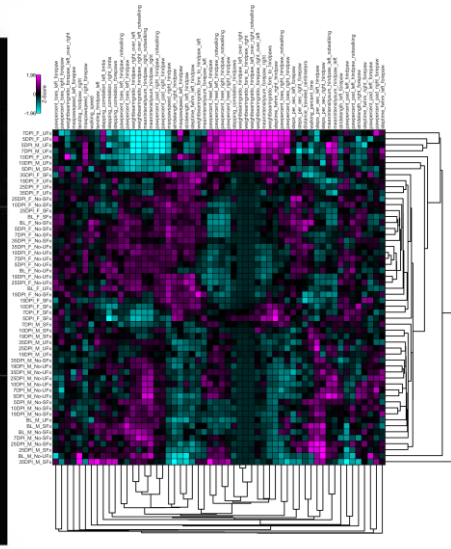
Automated tracking of mouse behavior using machine learning tools (DeepLabCut)

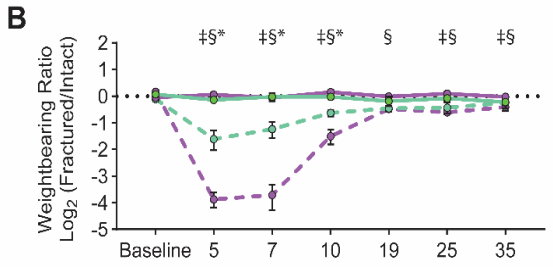


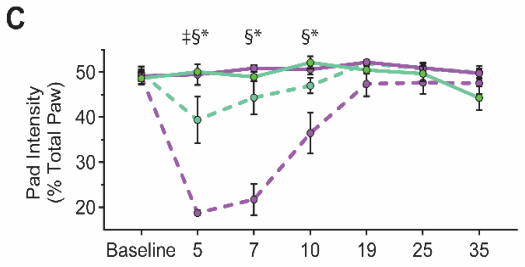


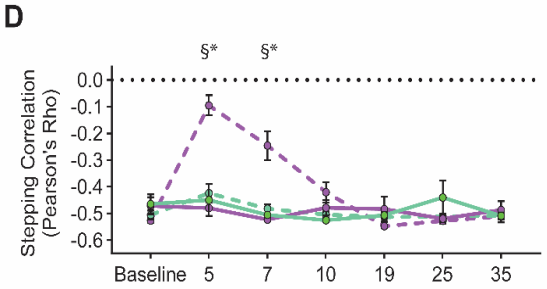
Functional Recovery Following Tibia Fracture in Mice

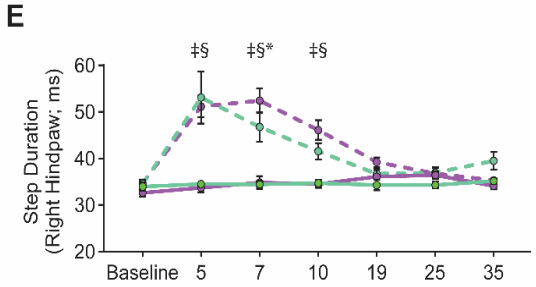


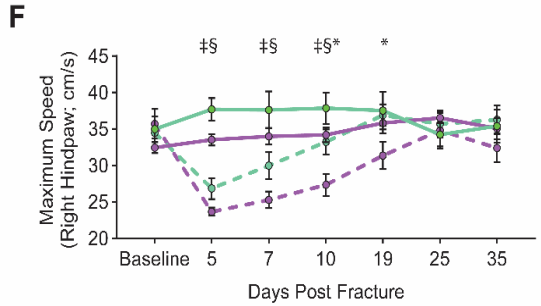


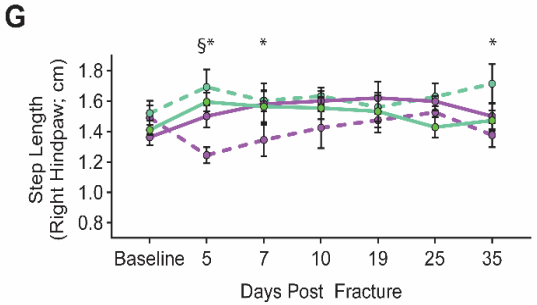


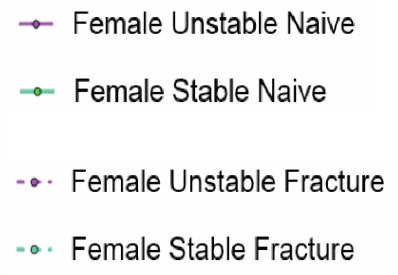




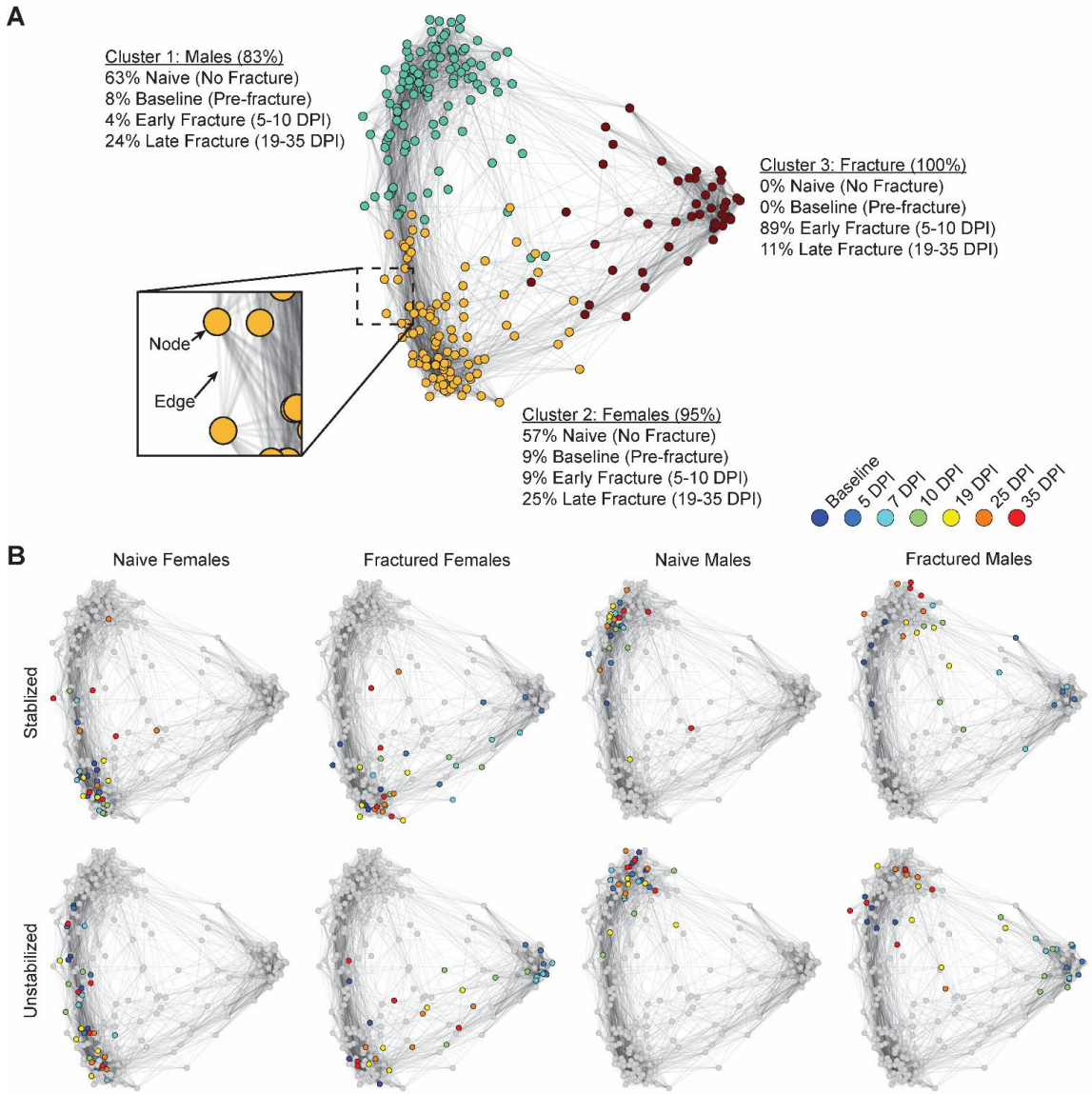


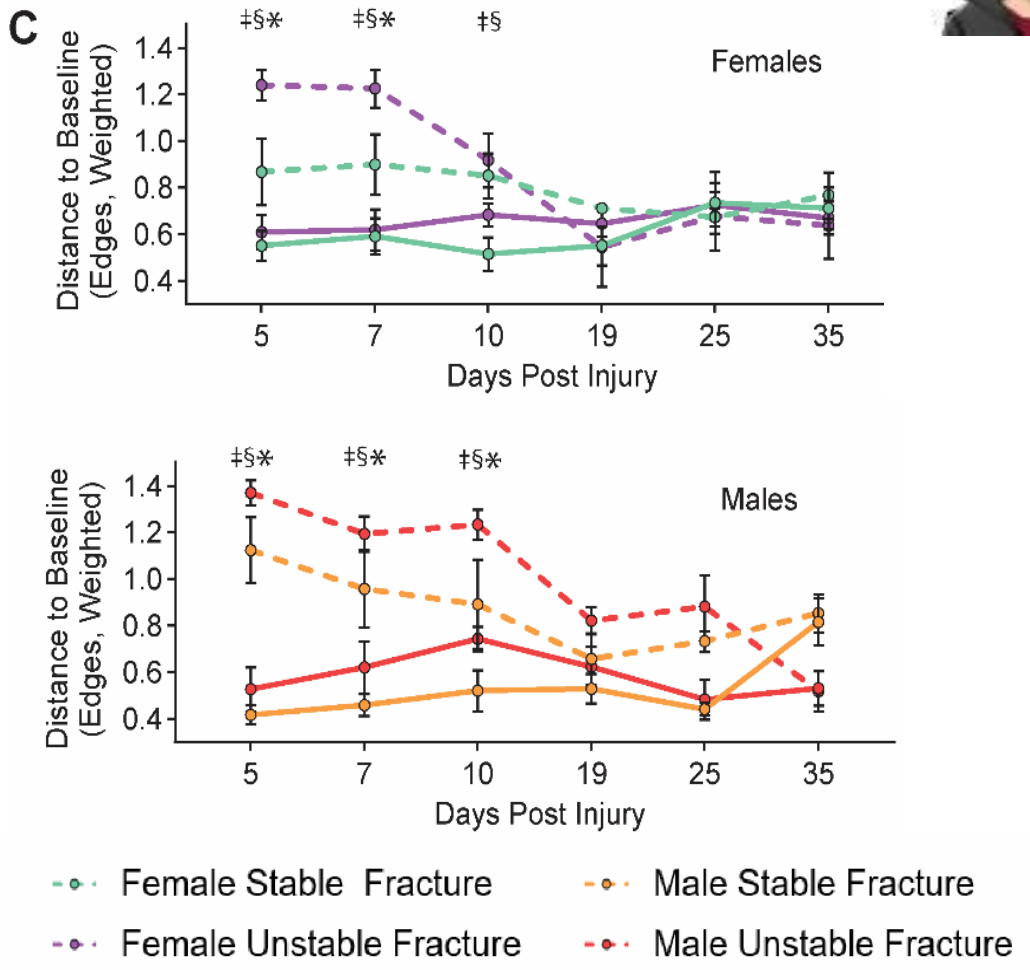






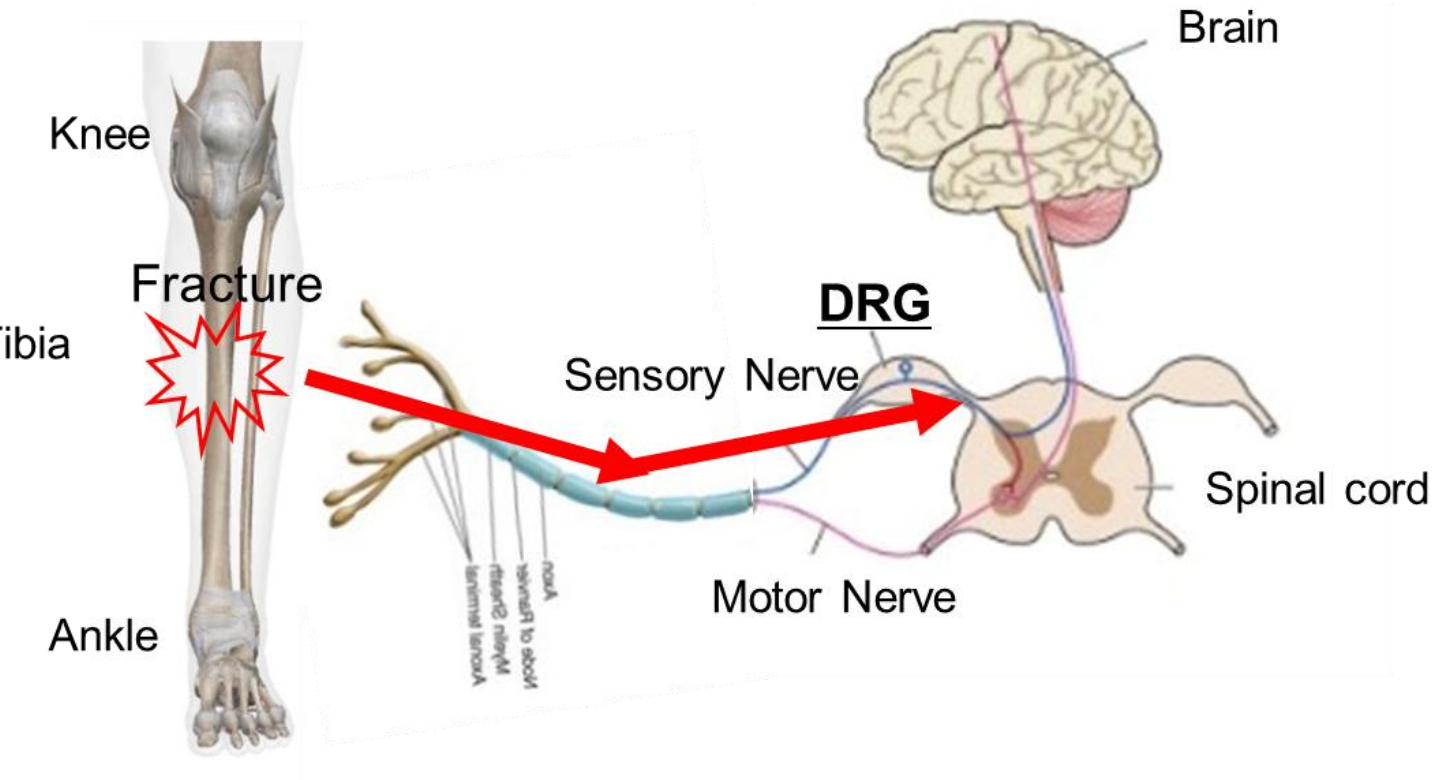
Graph Theory to Generate Unified Metric of Fracture Recovery

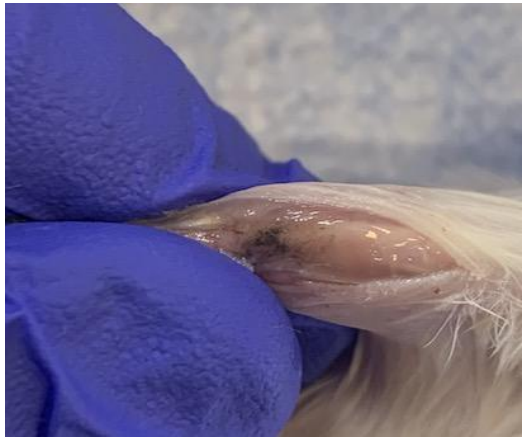




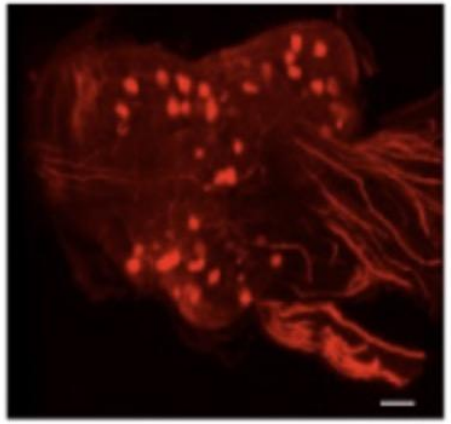
§ - unstable fracture and respective naive control; ‡ - stable fracture and respective naive control; * - unstable and stable fracture.

Identifying Retrograde Signaling Patterns





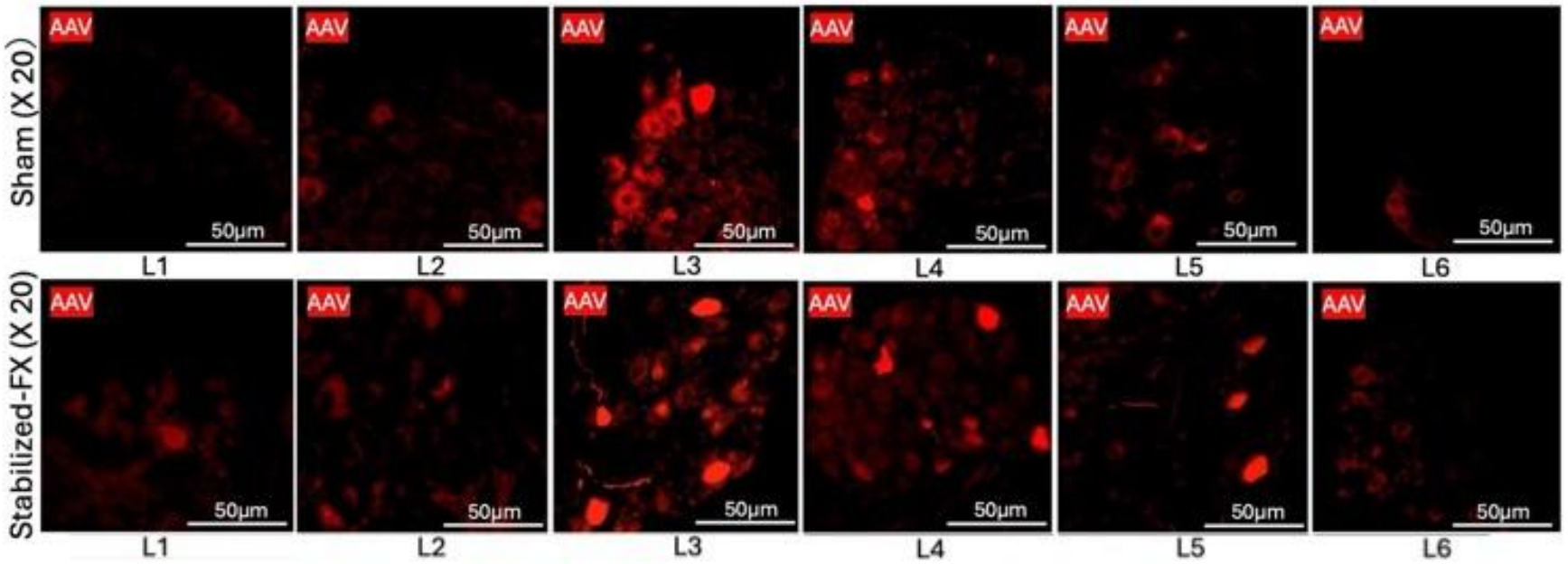
Mouse / AAV-tdT / Ulnar periosteum / with Stress Fx

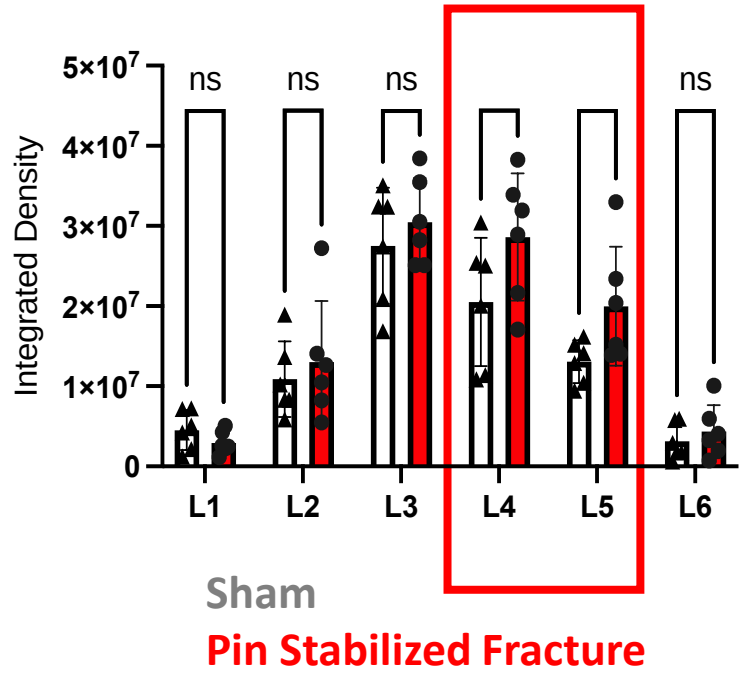


C7.8.T1 DRG *(Xu M. bioRxiv preprint 2024.)*

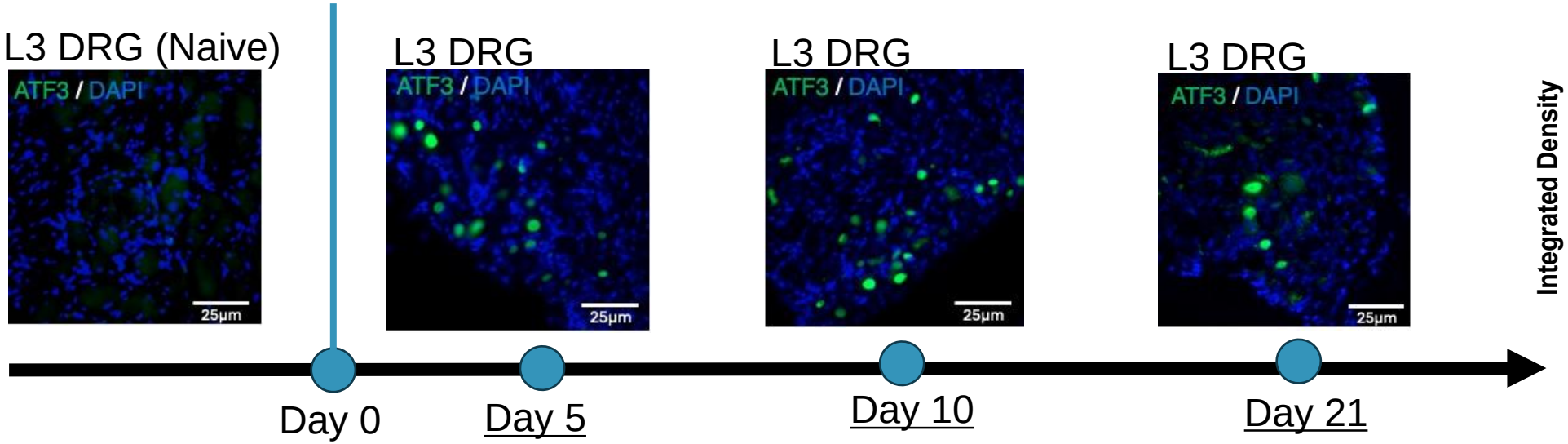
AAV: Adeno-associated virus PHP.S (AAV.PHP.S) carrying tdTomato reporter gene
Lasts Weeks to Months
Labels C fibers, Aδ fibers

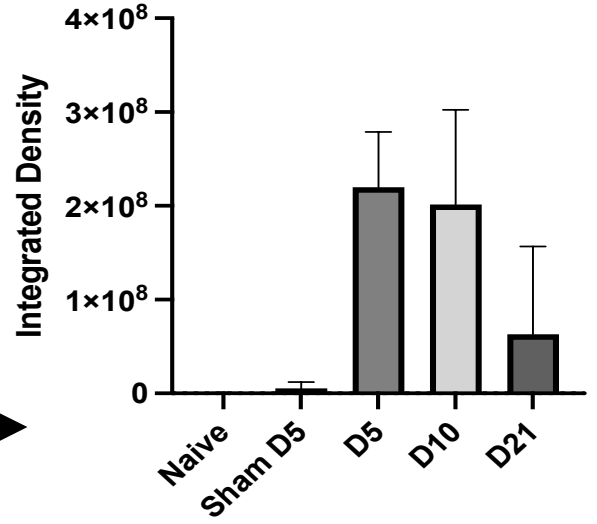
Fracture Activates L4 and L5 DRG Neurons



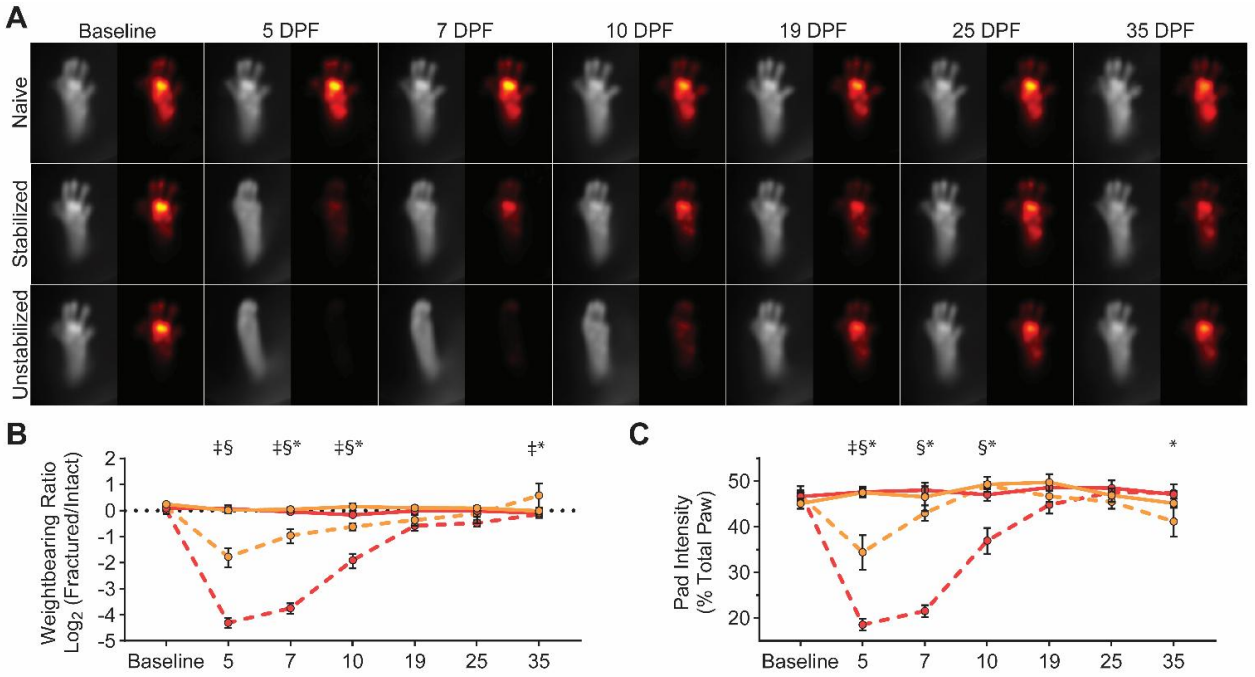


Nerve Injury in DRG Persists Longer than Functional Deficit

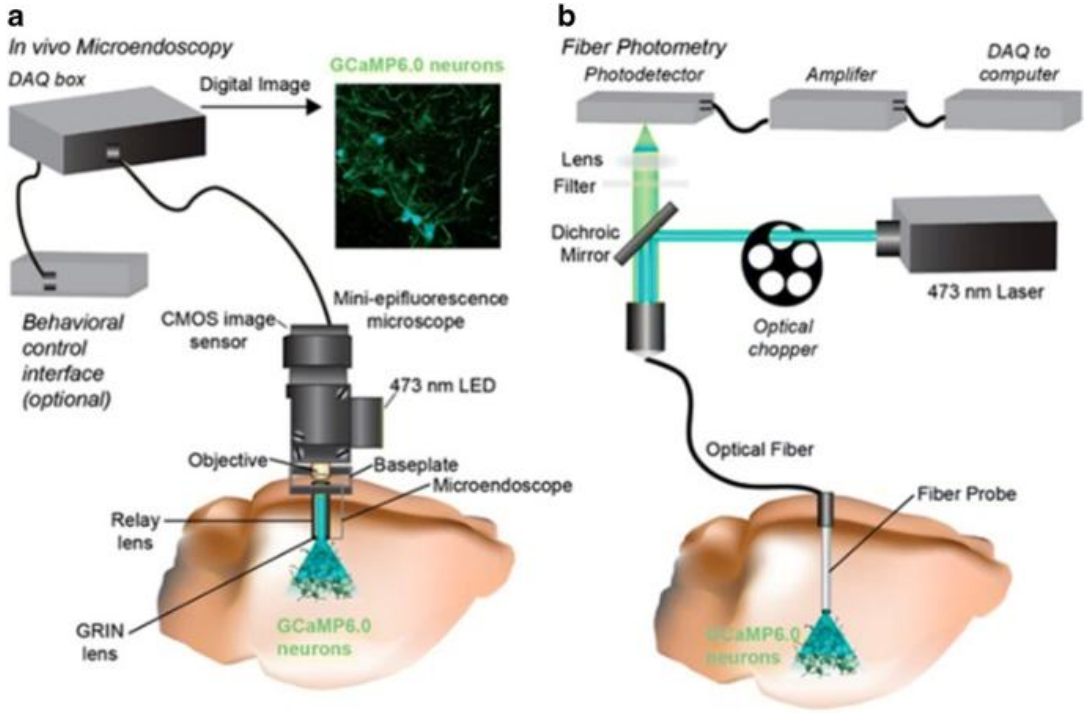


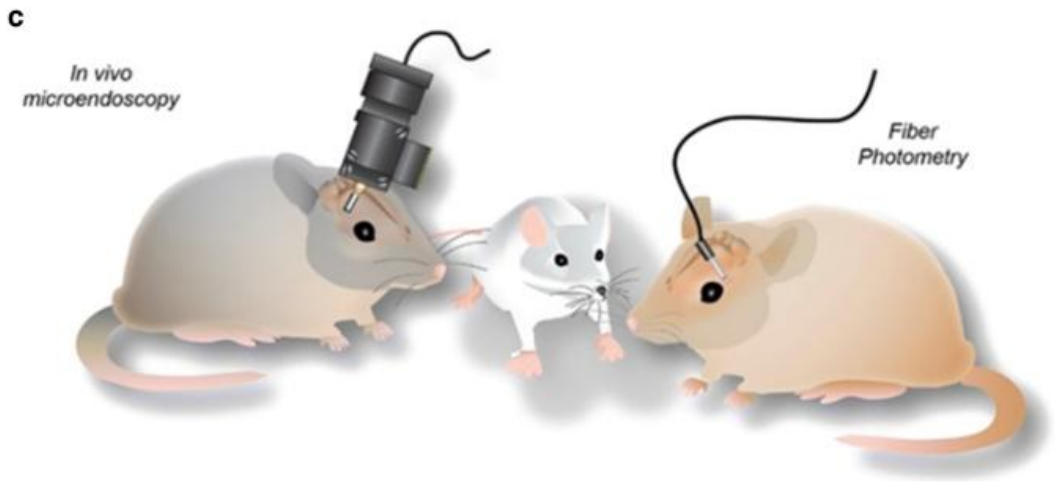


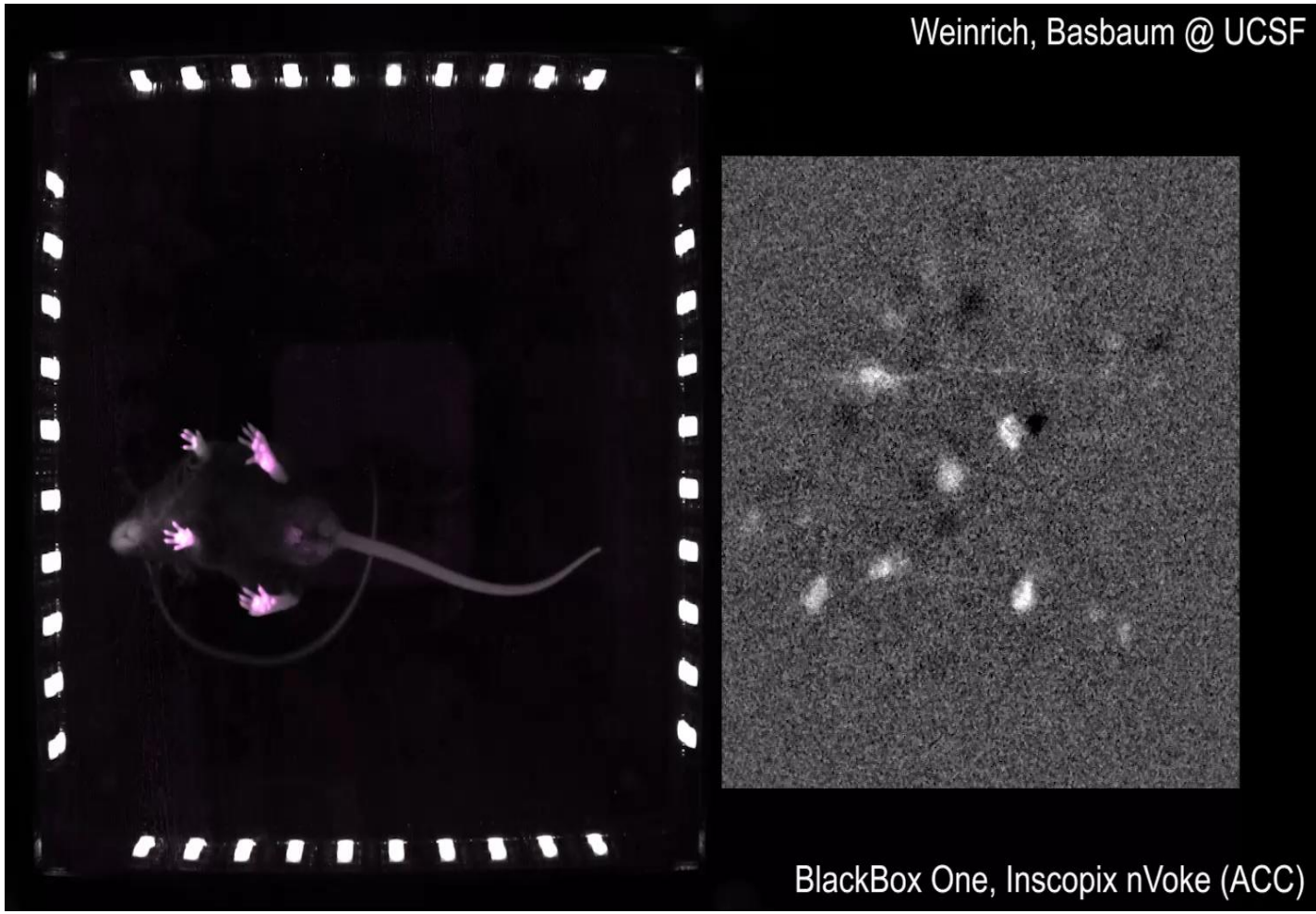
ATF = Activating Transcription Factor 3
Marker of Nerve Injury



Identifying Neural Biomarkers of Pain Following FX





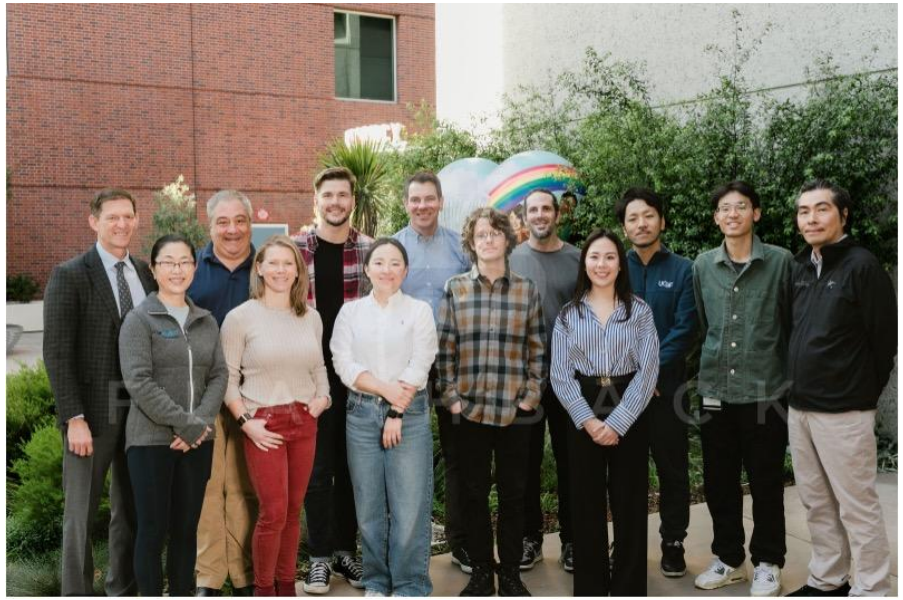


Conclusions

- ❑ Bone breaks hurt
- ❑ Nerves are important in fracture healing
- ❑ Standard methods for measuring pain in rodents translated poorly to fracture healing
- ❑ New method for behavioral phenotyping

Future Directions

- ❑ Chronification of pain in delayed healing
- ❑ Efficacy testing on novel therapeutics
- ❑ Testing non-opioid alternatives



National Institutes of Health

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Minimal sex specific differences after normalizing to baseline