MHSRS 2026

# “Too much of a good thing”

## How TrkA+ nerves enhance or subvert tissue regeneration

Manyu Zhu, PhD
Department of Pathology
Johns Hopkins University

# Background

TrkA$^{+}$ sensory nerves regulate acute tendon repair — a tractable therapeutic target

**High-impact training**

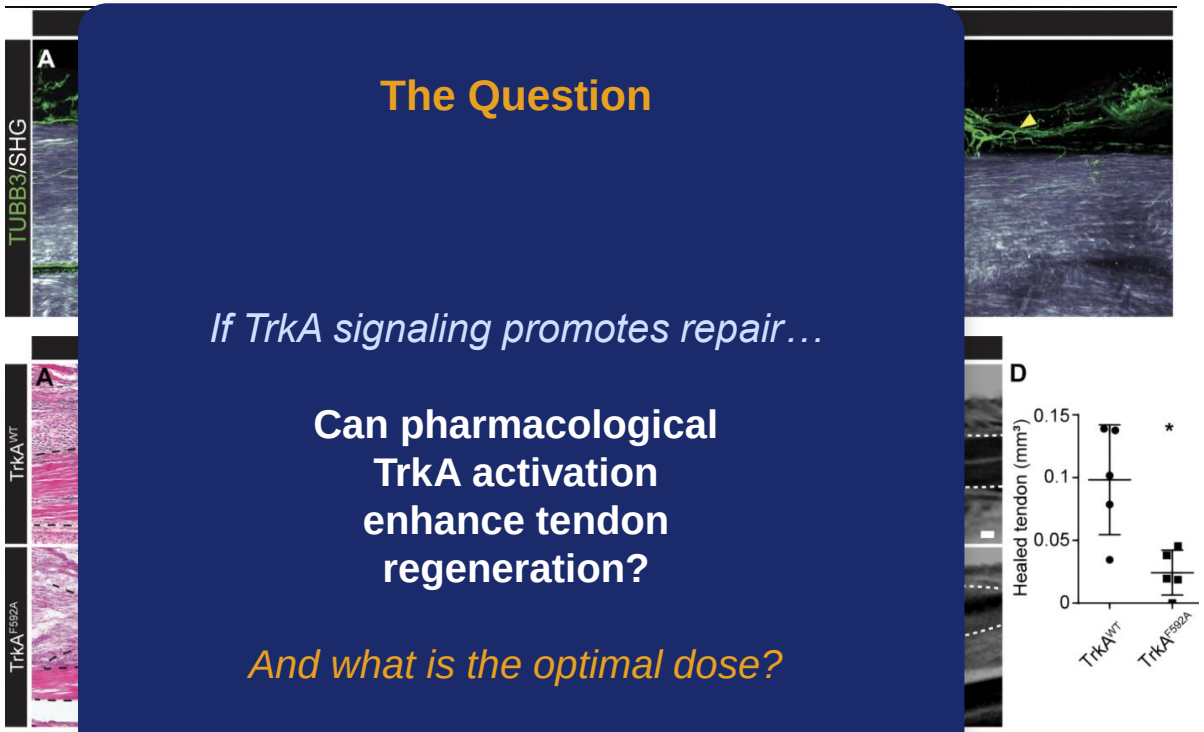
Repetitive loading and trauma often injure tendons.

**Prolonged recovery**

Tendon healing is slow and often produces scar-like matrix rather than native tendon.

**Unmet need**

Better treatments are needed to restore tendon structure and function.




## The Question

*If TrkA signaling promotes repair…*

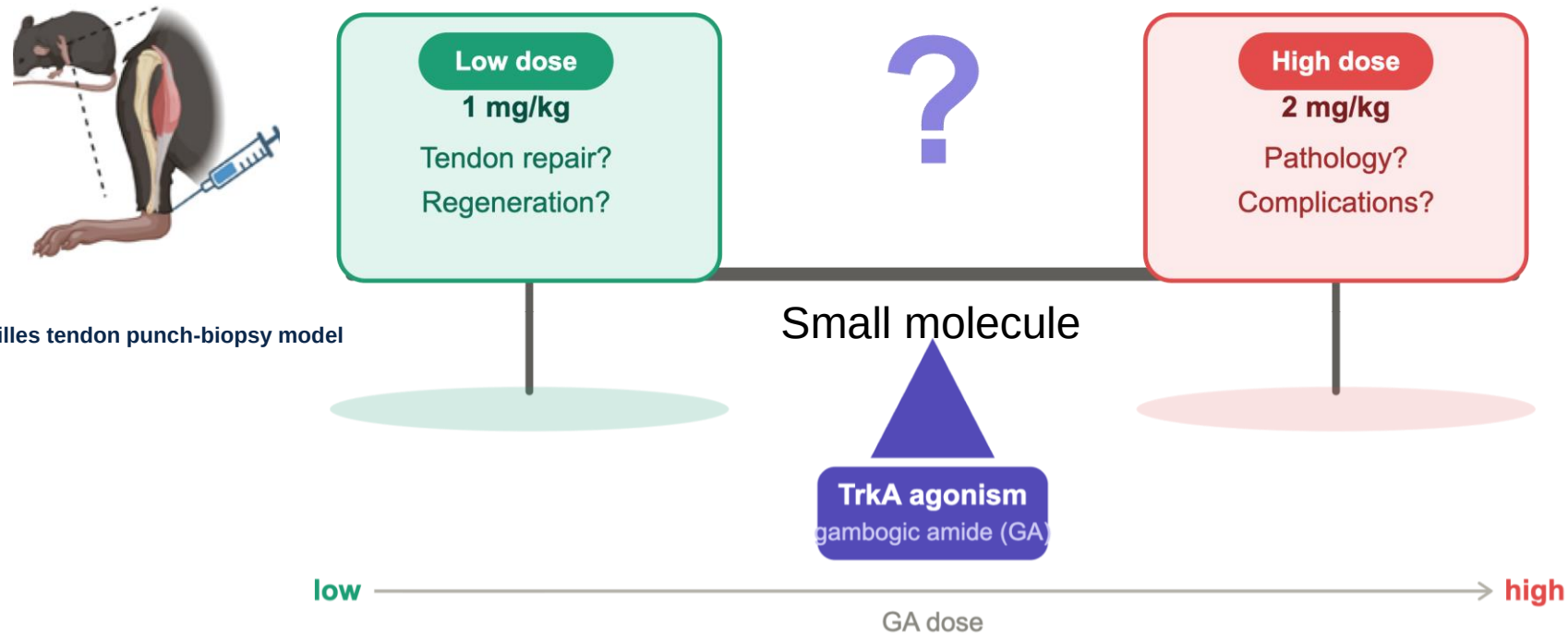
**Can pharmacological TrkA activation enhance tendon regeneration?**

*And what is the optimal dose?*

Masnsen Cherief,*et.al Sci. Transl. Med*.15,eade4619(2023).

# Therapeutic gap: how can we harness NGF–TrkA signaling safely?

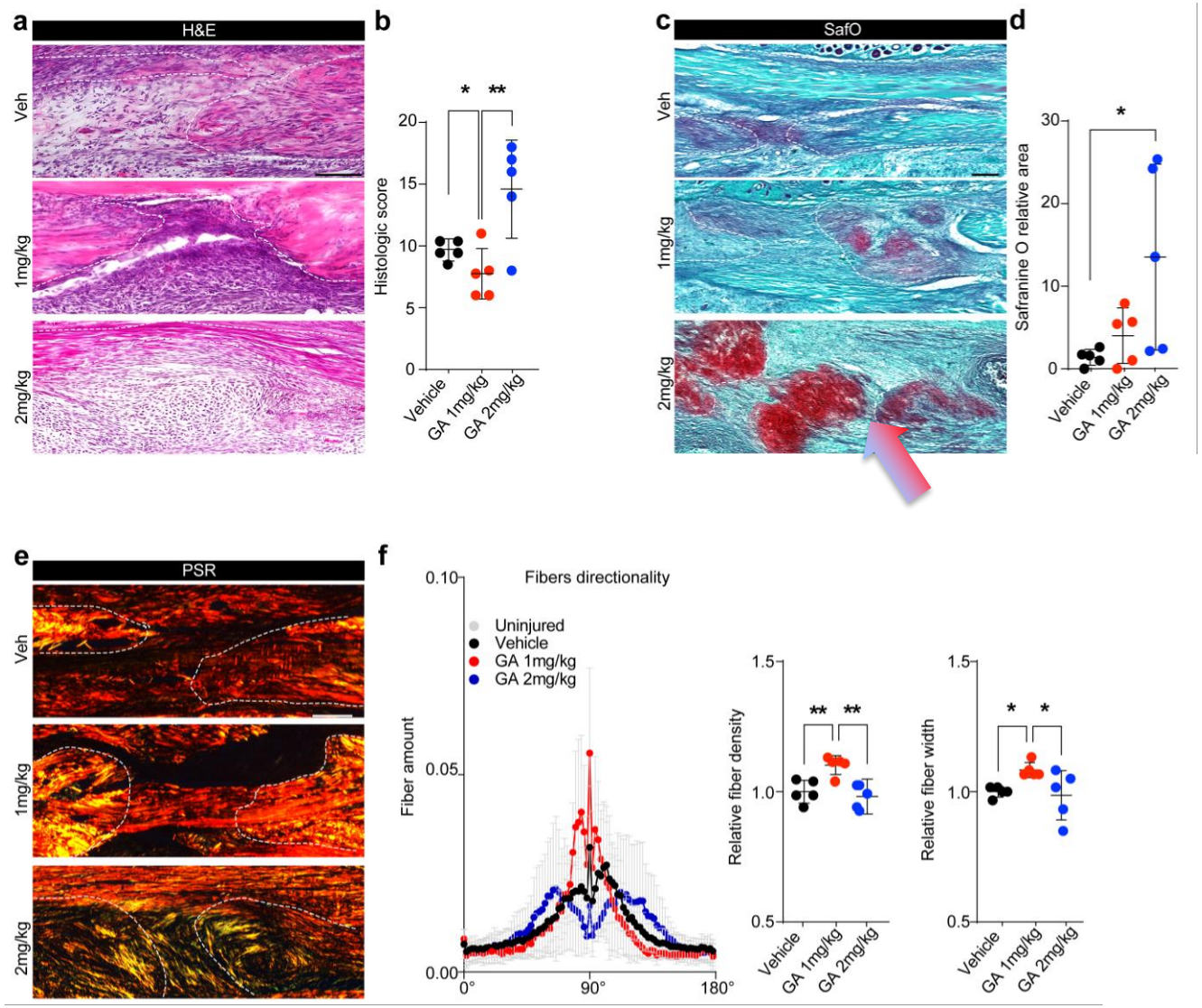





Mouse Achilles tendon punch-biopsy model

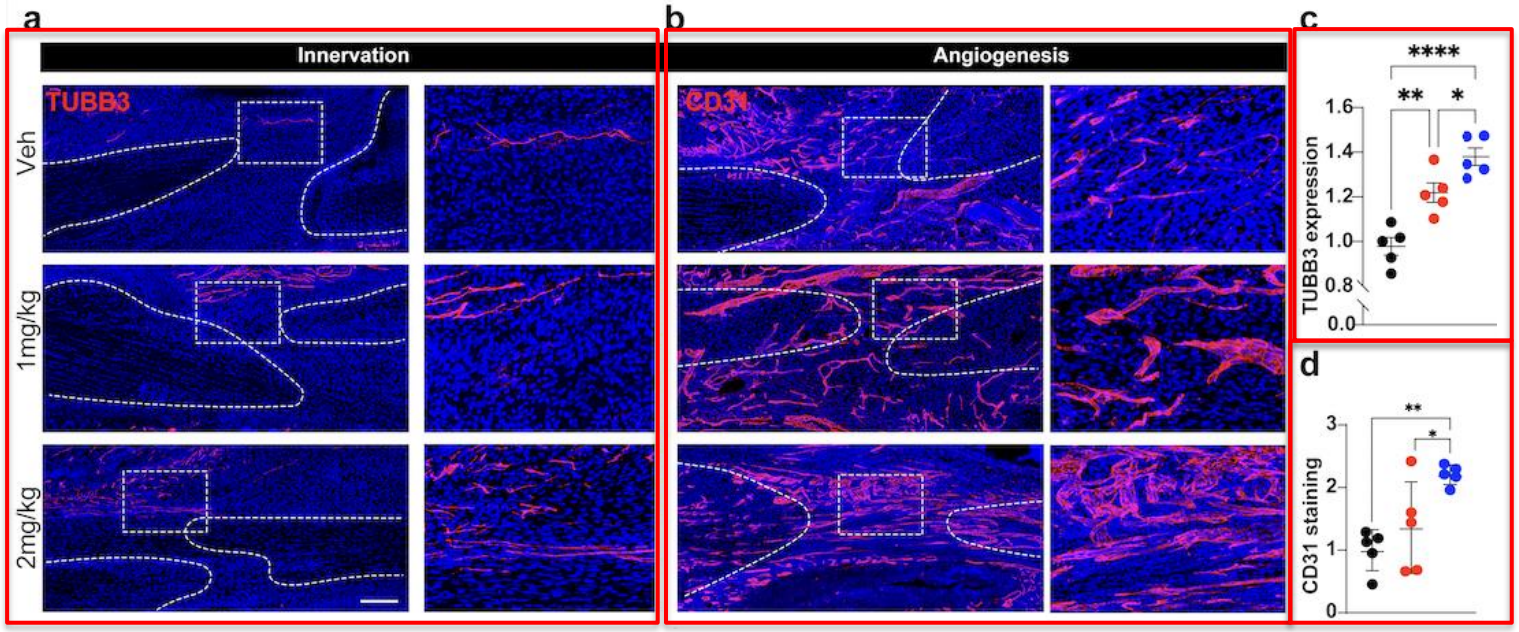
Question 1

# Is there a therapeutic window for TrkA agonism?




**Take-home**
**A narrow therapeutic window exists: too much TrkA activation is not good.**

# TrkA activation regulates cellular programs after tendon injury.

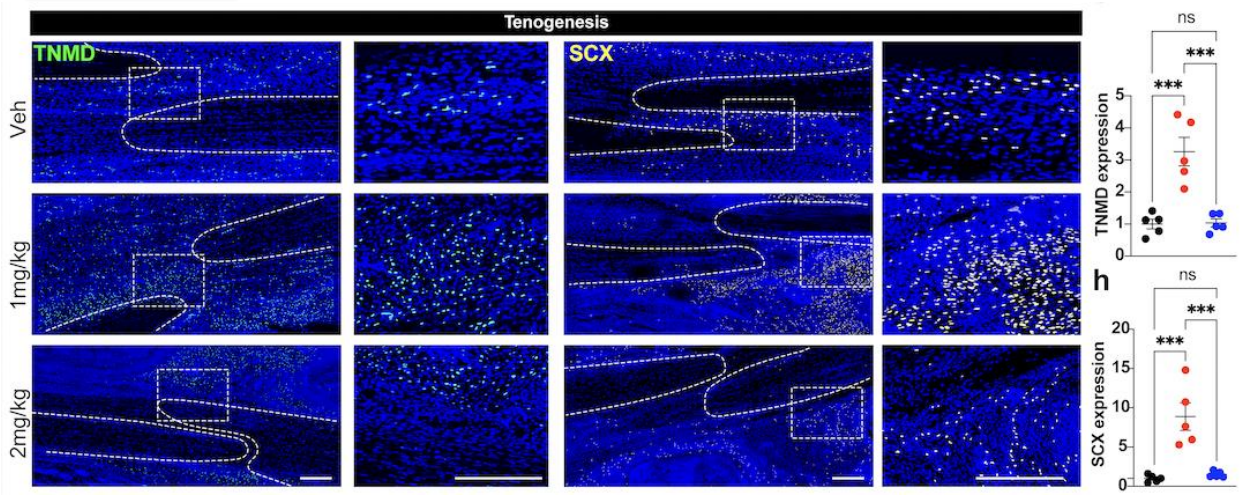



## Key observation

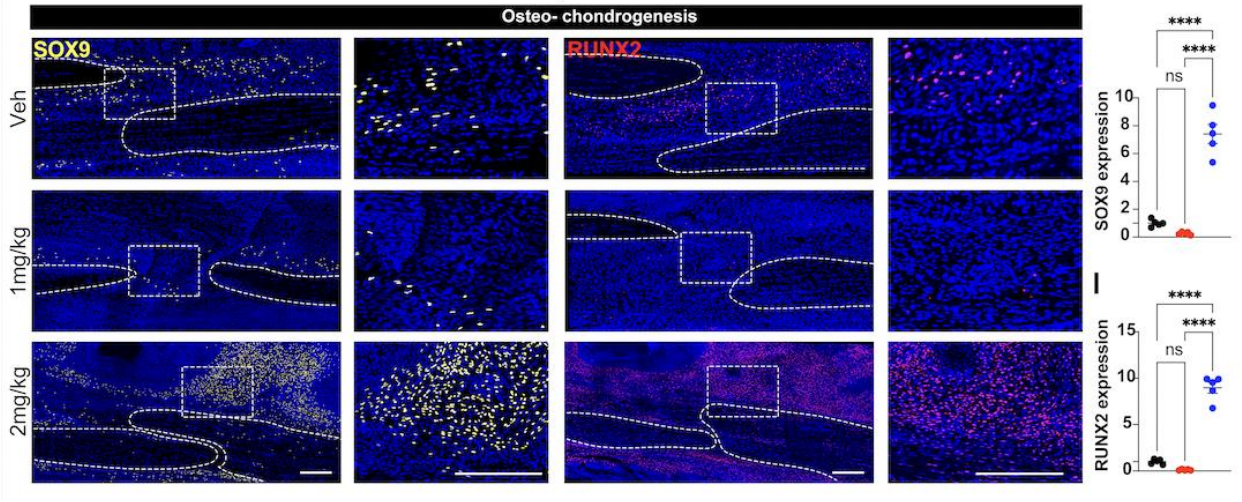
TUBB3+ innervation and CD31+ vessel density rises with GA dose.

**Interpretation**
**Neurovascular expansion appears permissive, but excessive activation can be maladaptive.**

# low dose supports tenogenesis, high dose triggers osteochondrogenesis




**Low-dose GA**
**↑ TNMD and ↑ SCX, consistent with active tenogenic differentiation.**




**High-dose GA**
**↑ SOX9 and ↑ RUNX2, consistent with osteo-chondrogenesis.**

Question 2

# How does dose change the cellular fate of tendon healing?

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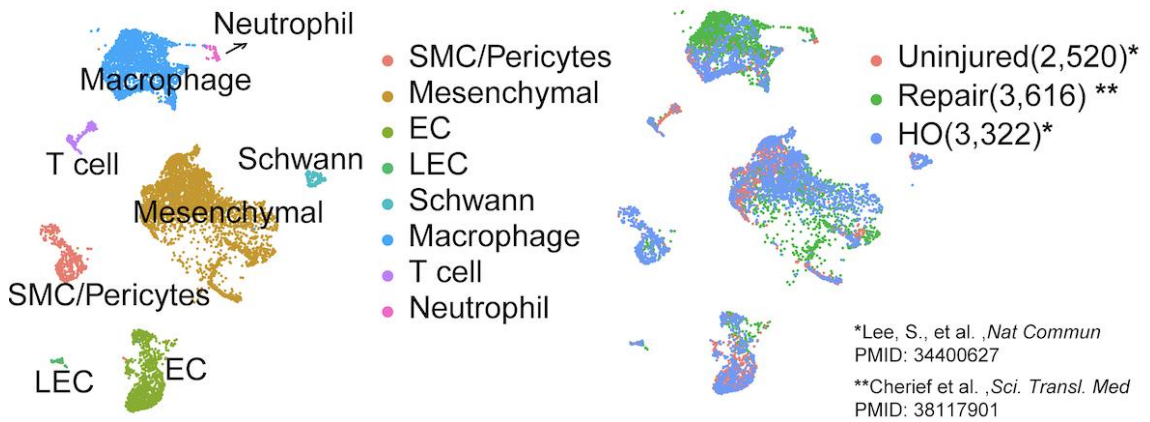


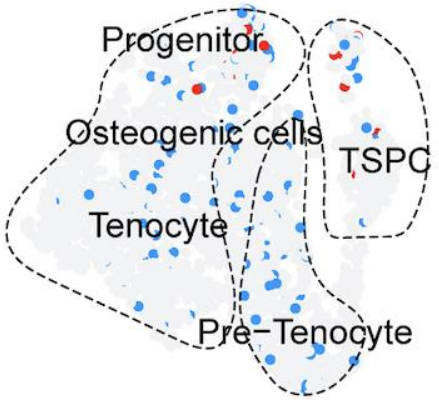


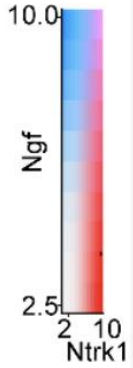


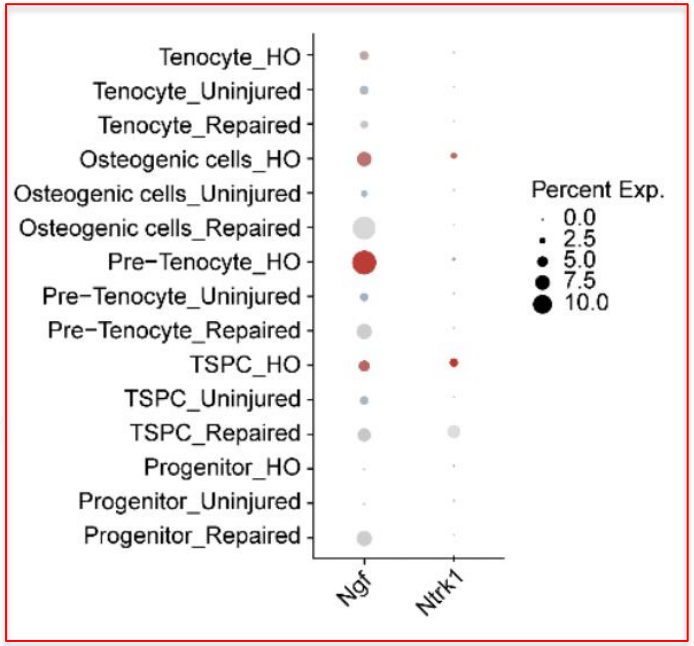


Repair : Low *Ngf* expression
HO (Heterotopic ossification): High *Ngf* expression

Question 2

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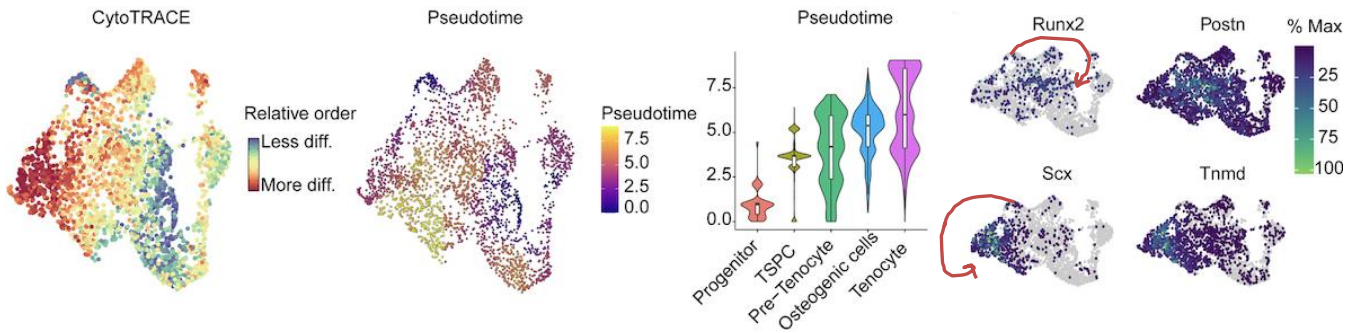
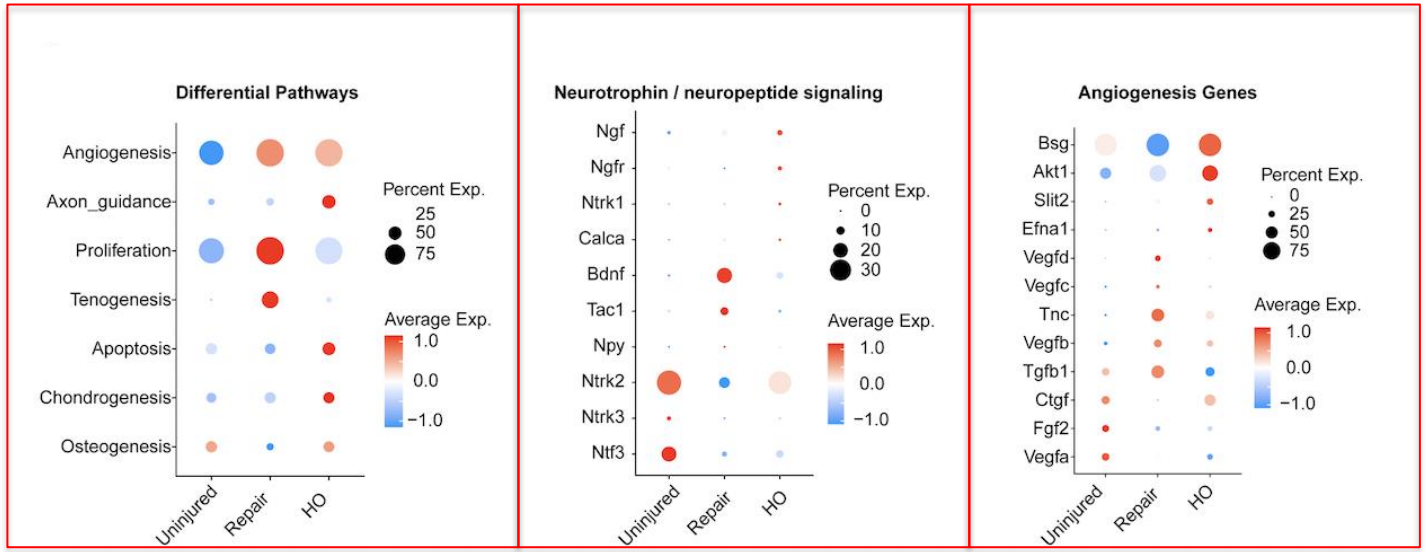
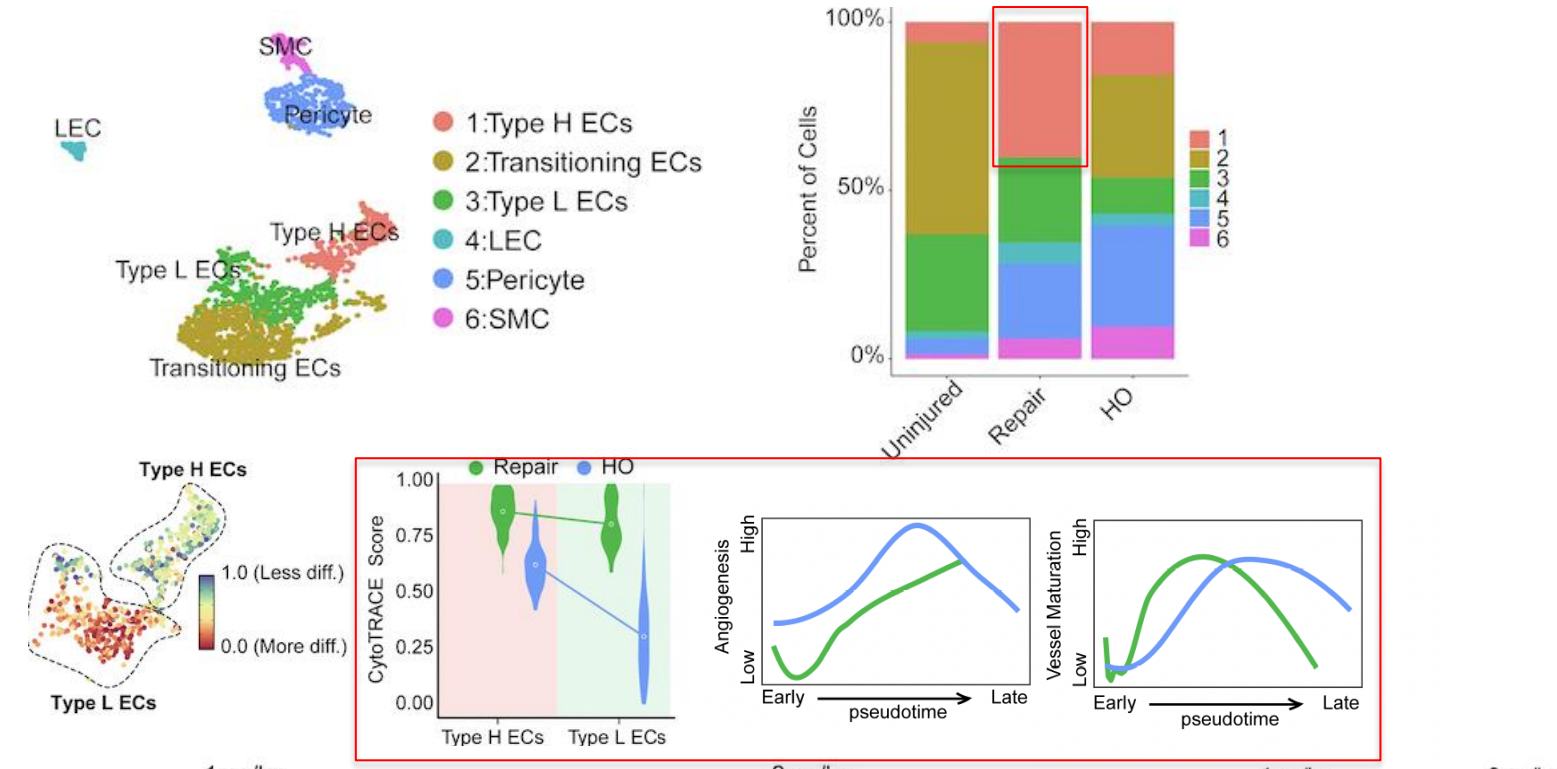


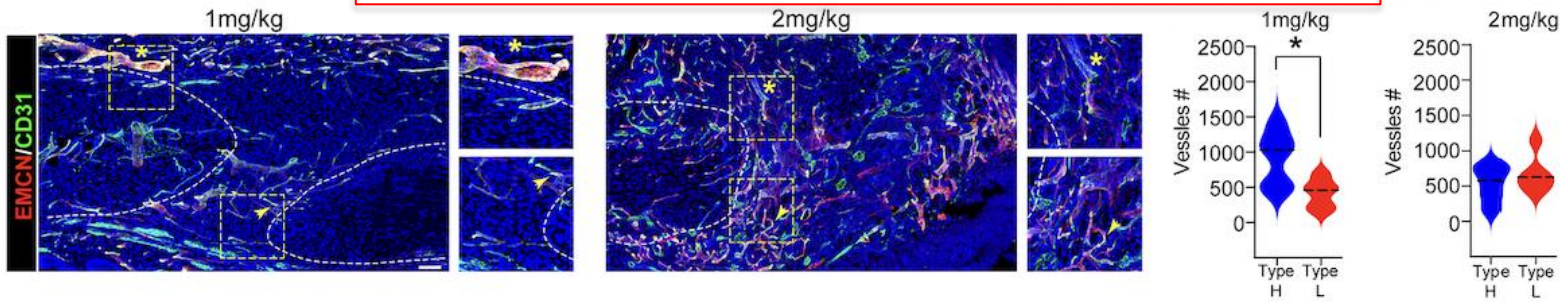




**Take-home**
**A coordinated shift in cell fate and signaling may drive the transition from tendon repair to pathological ossification.**

Question 3

# What endothelial state distinguishes productive repair from pathological ossification?

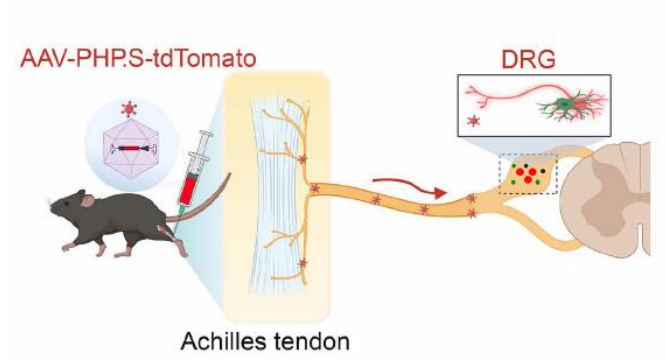


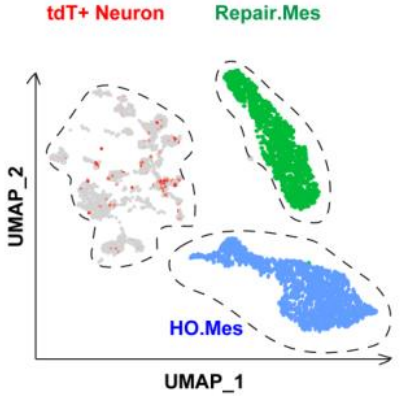

**Take-home**
**Excessive NGF–TrkA activation may disrupt the repair-associated vascular niche and shift healing toward HO.**

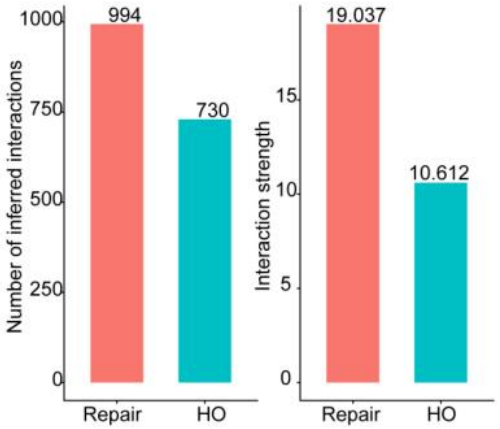
## Question 4

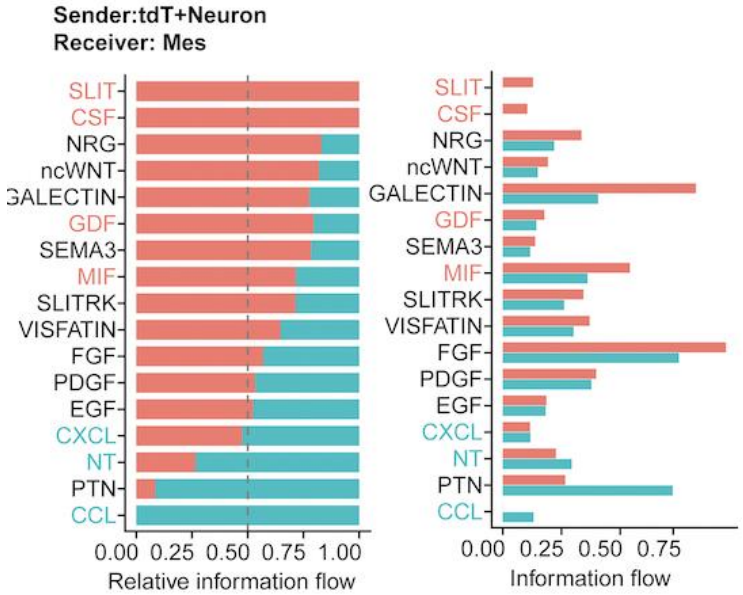
# How does neuron–mesenchymal signaling change during repair vs. HO?




Manyu Zhu *et al.*, *Sci. Transl. Med.*15, eaec1380. doi: 10.1126/scitranslmed.aec1380. Epub 2026 May 13. PMID: 42127222.



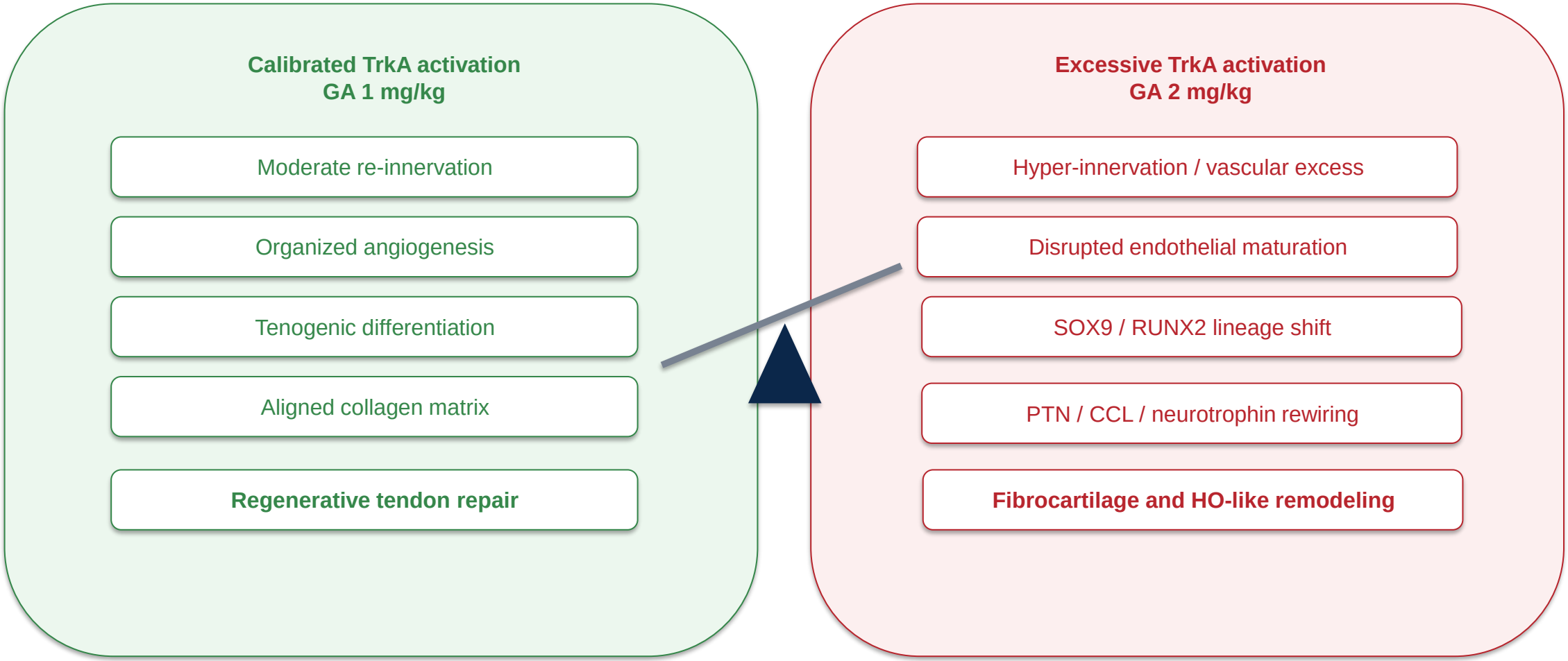




## Key message

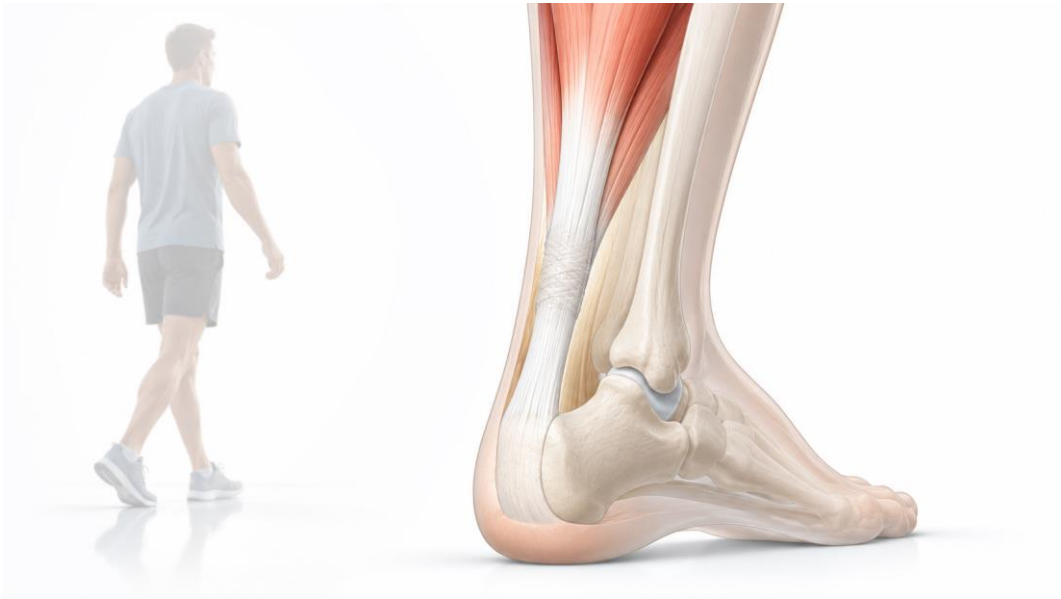
- Repair has a denser neuron→mesenchymal interaction network.
- Repair-enriched pathways include FGF / WNT / MIF-like signaling.
- HO shows stronger PTN / neurotrophin / chemokine-associated signaling toward osteogenic states.

**Take-home**
**The transition to HO reflects rewiring of signaling programs, not simply more or less nerve input.**

# Integrated model: calibrated TrkA signaling promotes repair, but excessive signaling drives HO



# Conclusions



**Translational message**
**TrkA-targeted therapies may improve tendon repair in trauma settings, but only when signaling stays within the therapeutic window.**

# Thank you

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# These authors contributed equally

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