The Resilience of Muscle Regenerative Capacity Following Volumetric Muscle Loss

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in support of

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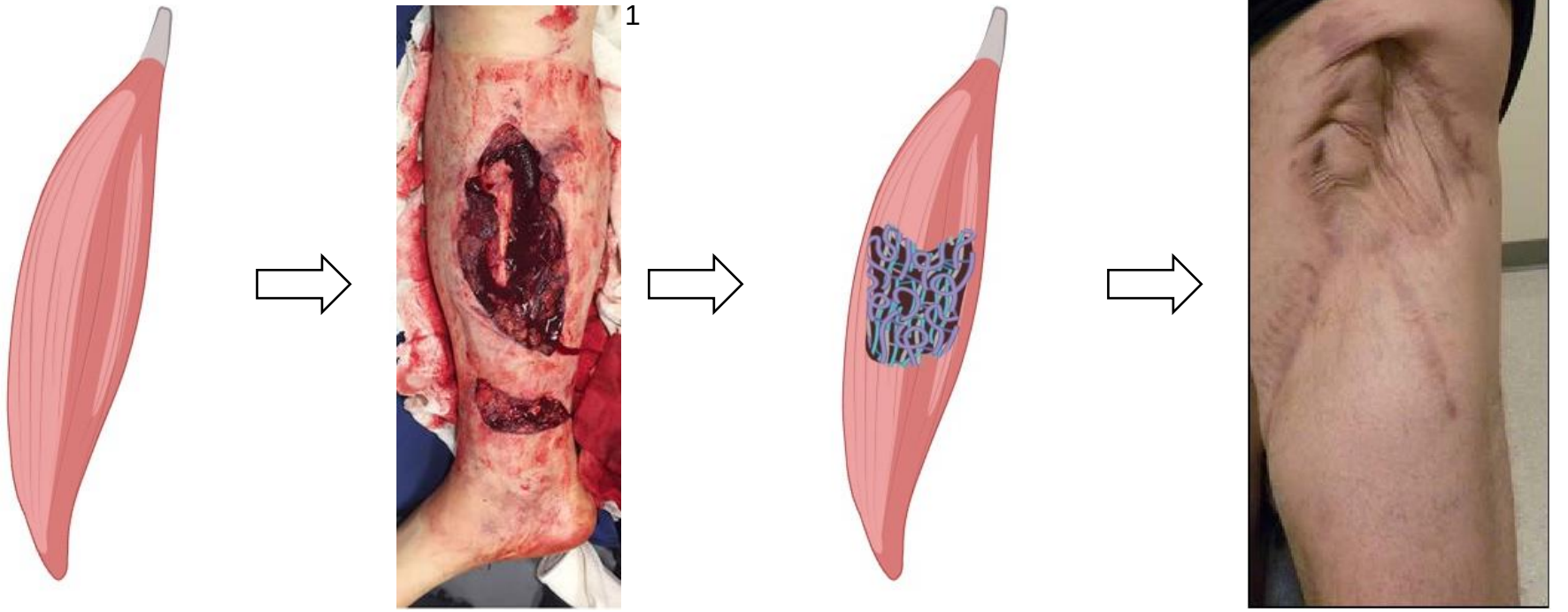
No Conflicts of interest

Volumetric Muscle Loss (VML)

Healthy **Injury** **Scarring**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2

↑ Fibrosis + ↓Function = ↓ Quality of Life

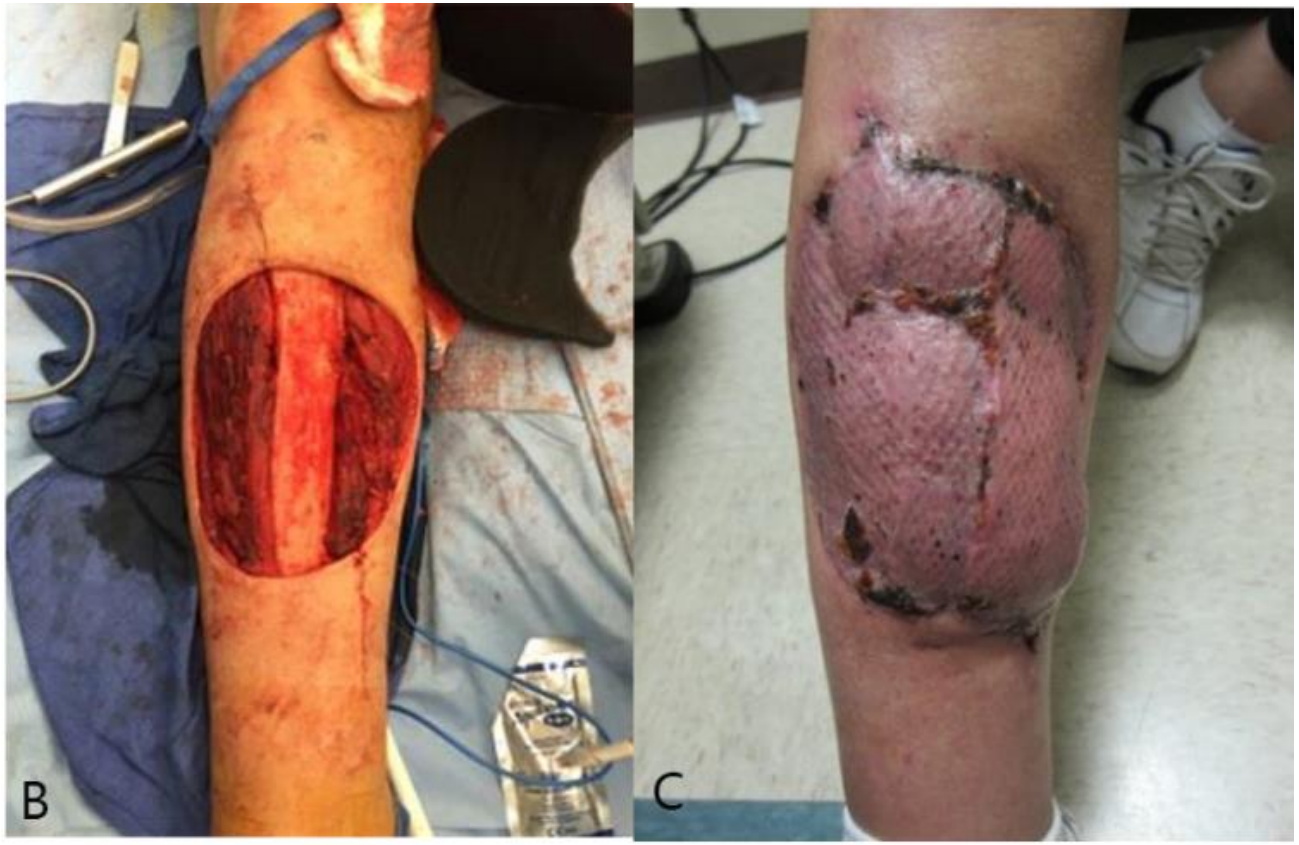
[1]Young-Woo Kim, Ho-Youn Park, Yoo-Joon Sur. Soft Tissue Reconstruction for Open Tibia Fractures. *Archives of Hand and Microsurgery.* 2020.
[2]Dziki, Jenna L.. "Extracellular matrix bioscaffolds for treatment of volumetric muscle loss." (2017).

Volumetric Muscle Loss

- Present in annual:
  - 150,000 open fractures
  - 30,000 gunshot wounds
  - 36,000 chainsaw accidents
  - 13,000 soft tissue sarcomas
- 77% of medically evacuated military personnel

Available Treatments

- Muscle Graft
- Muscle Transposition
- Rehabilitation



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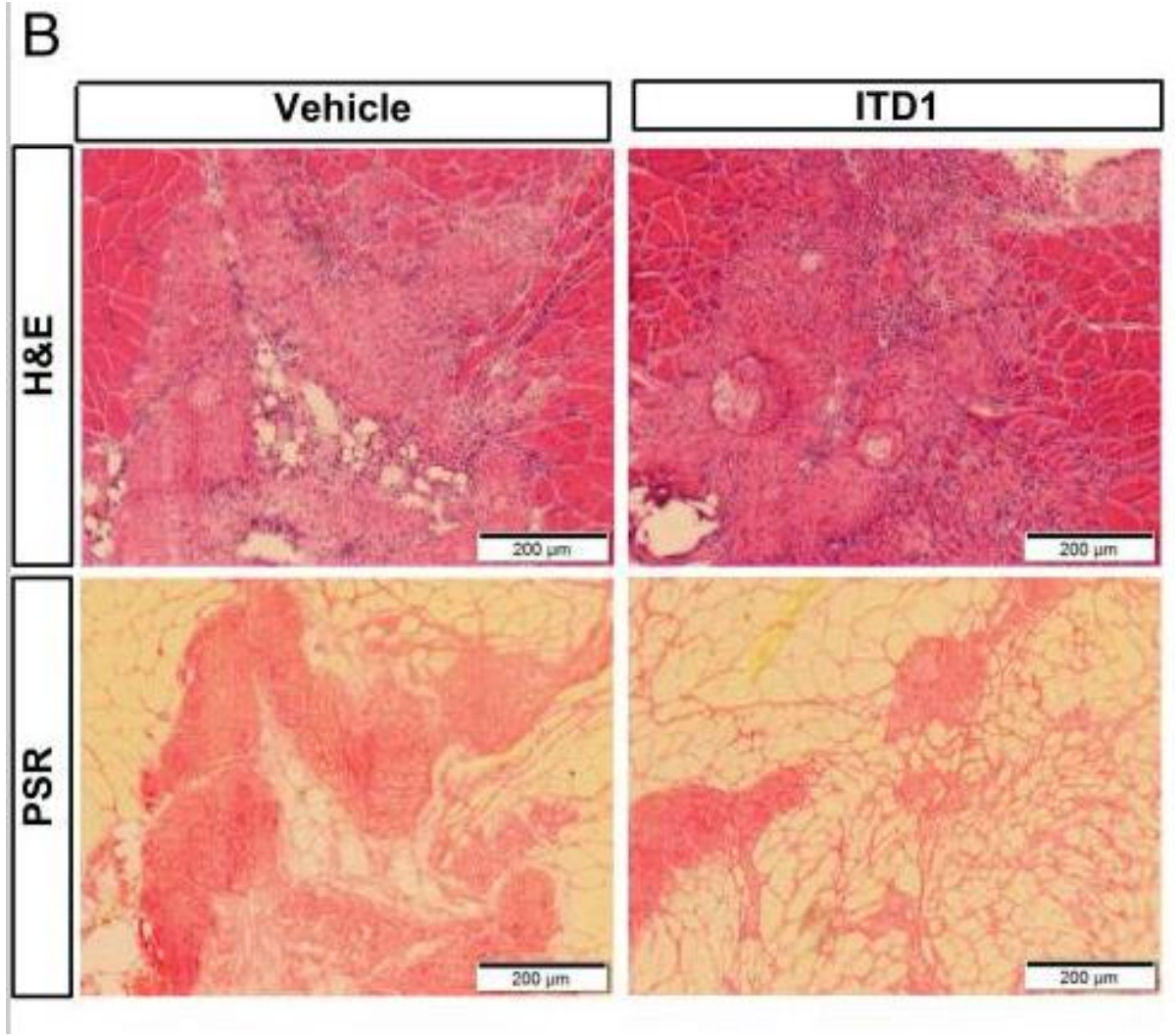
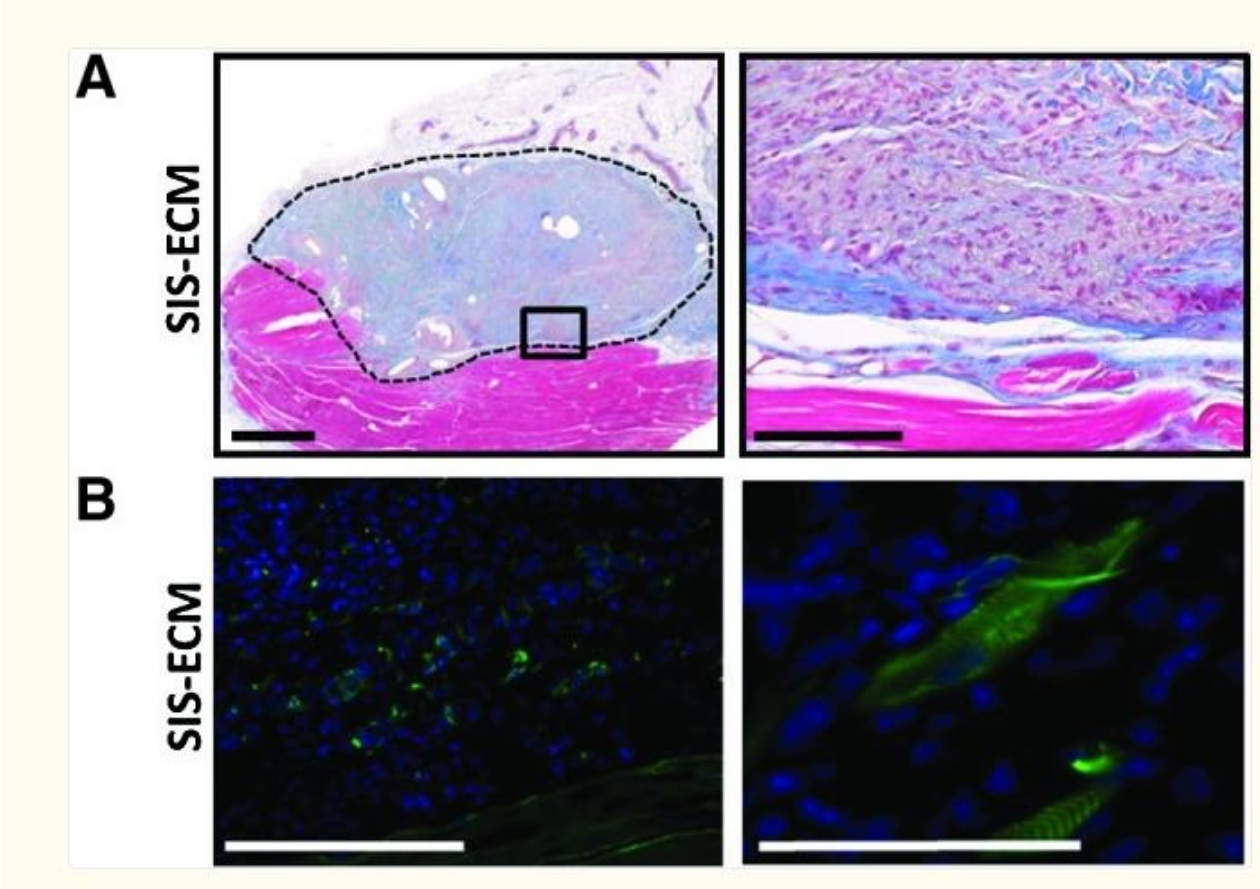
State of Preclinical Research

- Drugs
  - Little to no effect



State of Preclinical Research

- Scaffolds
  - Almost exclusively fibrose (turn into scar)
  - No new muscle growth without cell-based therapy
  - All muscle <0.2mm from defect border



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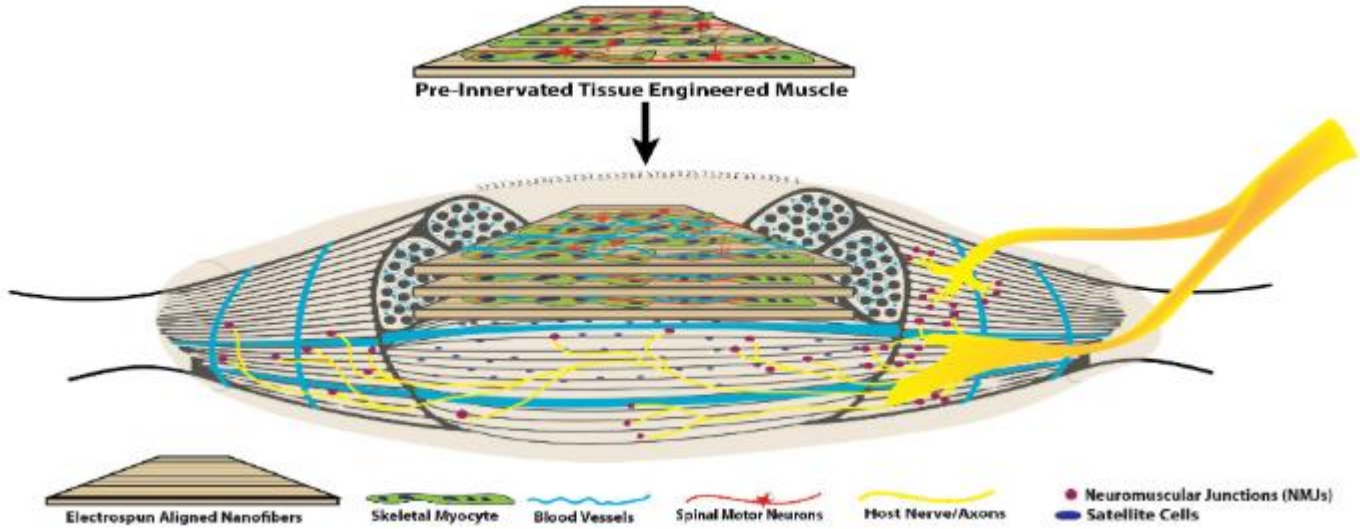
State of Preclinical Research

- Cells/tissue engineering
  - Some functional improvements
  - Integration, survivability, and regulatory issues
  - Scalability



https://cdmrp.health.mil/prorp/research_highlights/22Cullen_Das_highlight.aspx

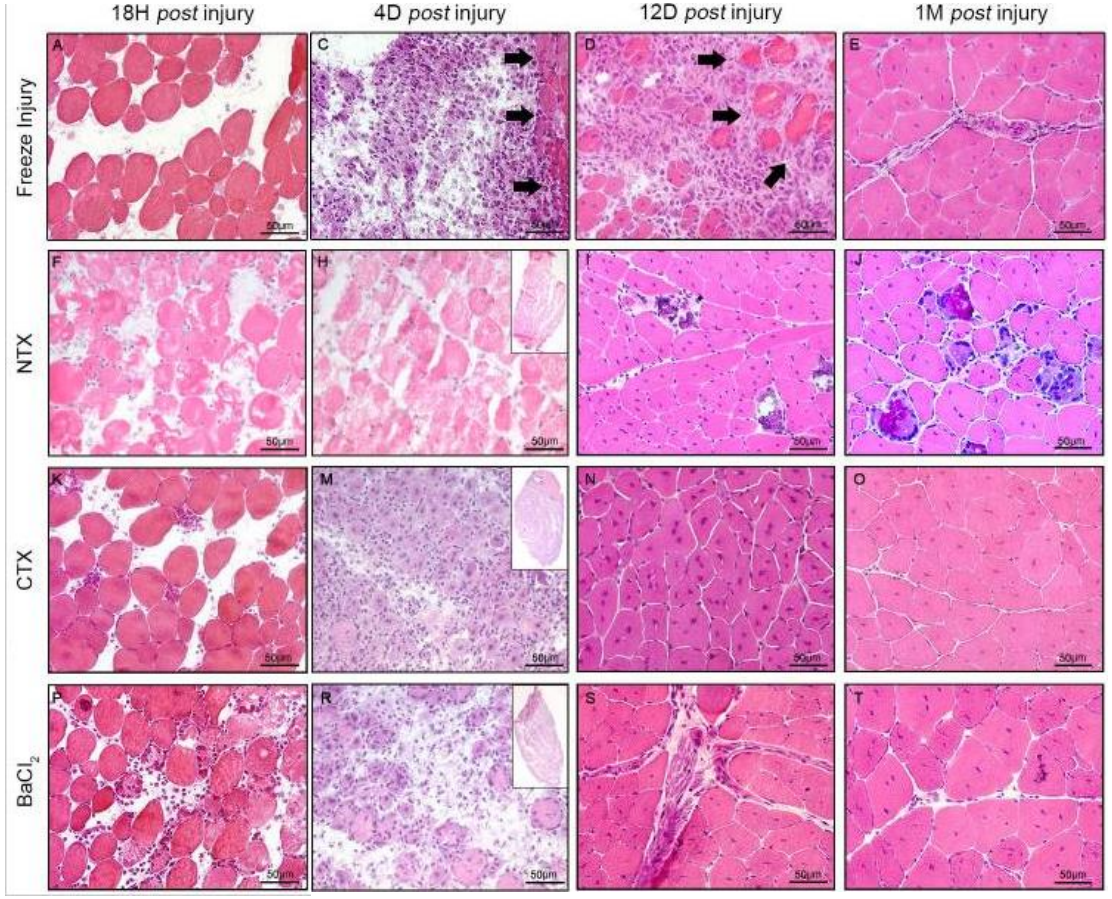
?No new muscle formation

=

Muscle used up all its regenerative capacity?

Muscle the “highly regenerative tissue”

- Regrows perfectly after 80% death from:
  - Freeze injury
  - Mild blunt trauma
  - Toxins
    - 6 consecutive times



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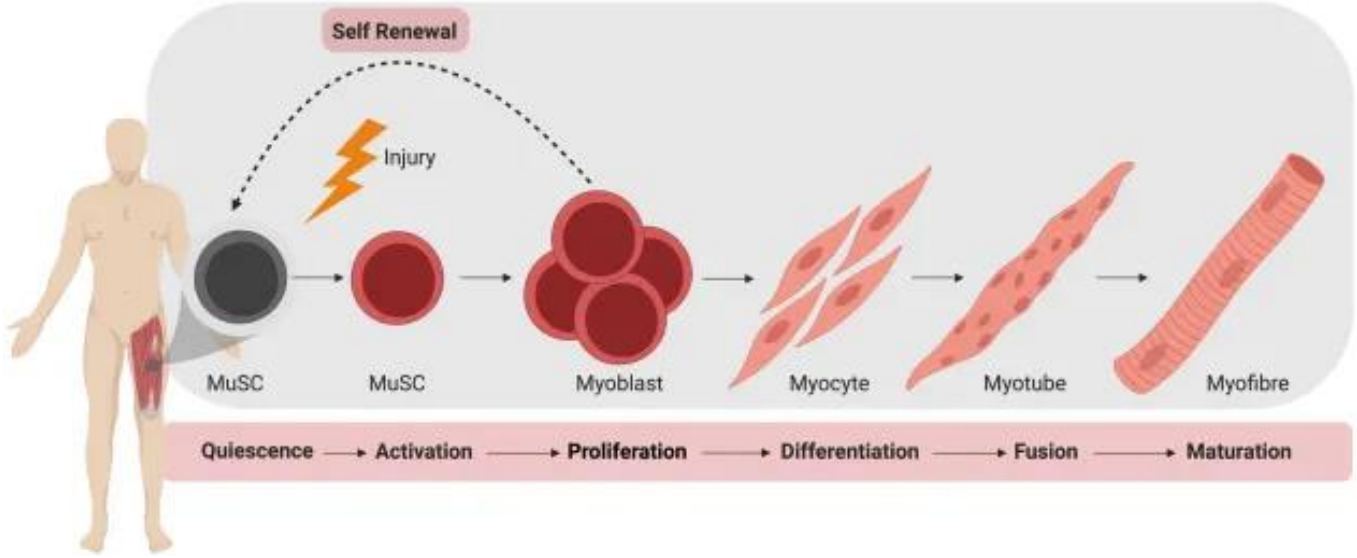
Muscle Stem Cells (Satellite Cells)

- Low in number
- Supposed to repopulate during activation
- 1 transplanted muscle stem cell can make ~50,000
- Depletion/senescence causes failure to regenerate/hypertrophy



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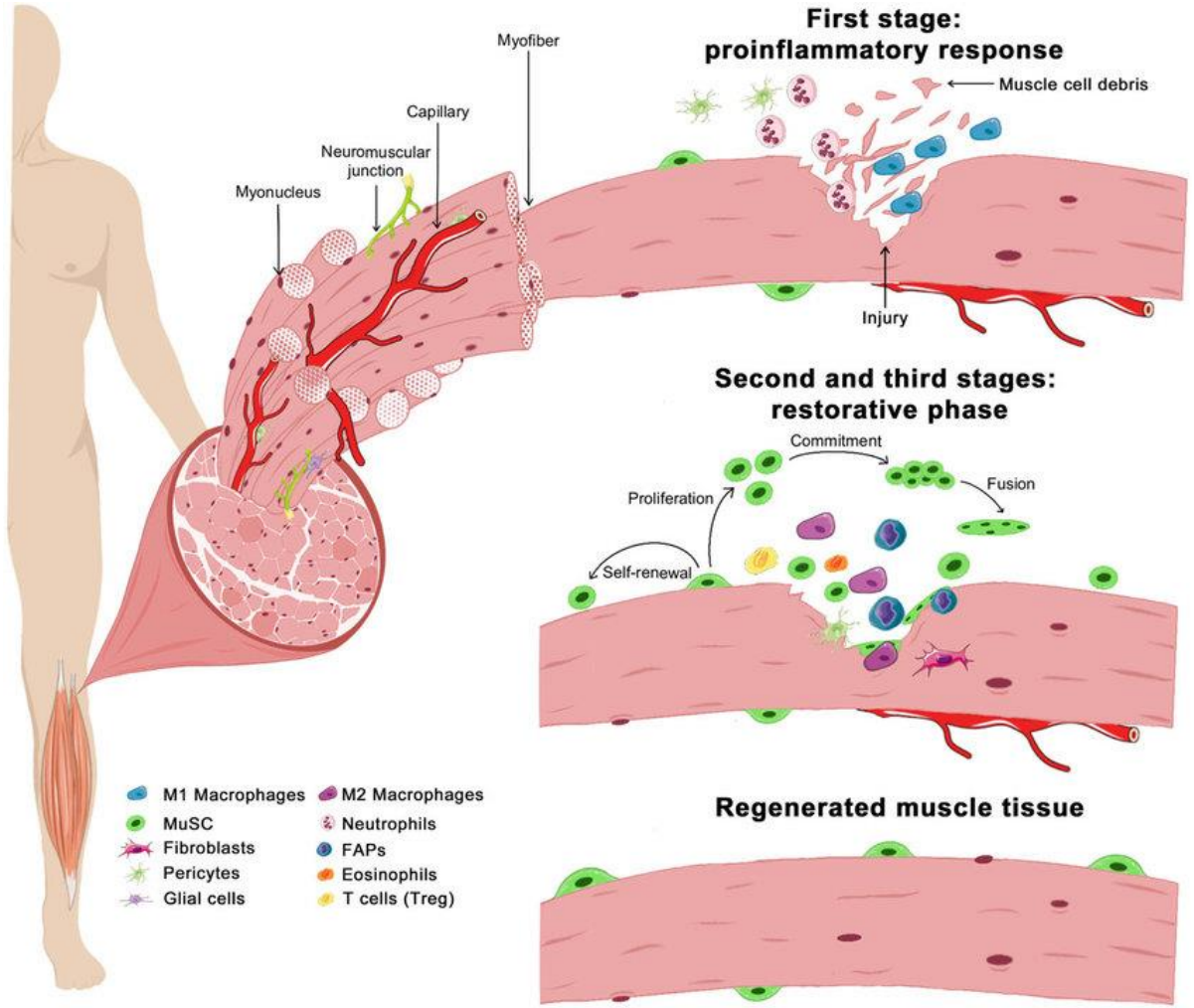
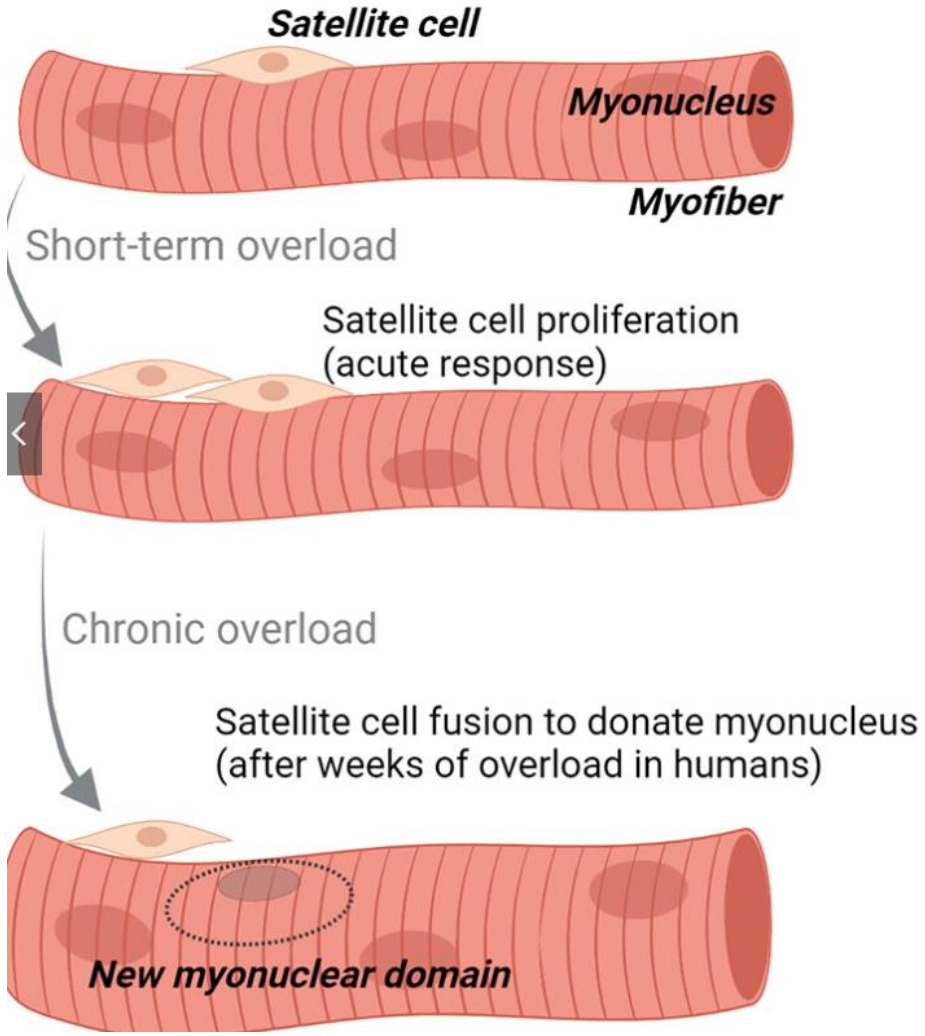
Muscle Injury Regeneration



https://www.nature.com/articles/s41536-022-00204-z

Hypertrophy (myonuclear accretion)



https://journals.physiology.org/doi/10.1152/physrev.00039.2022

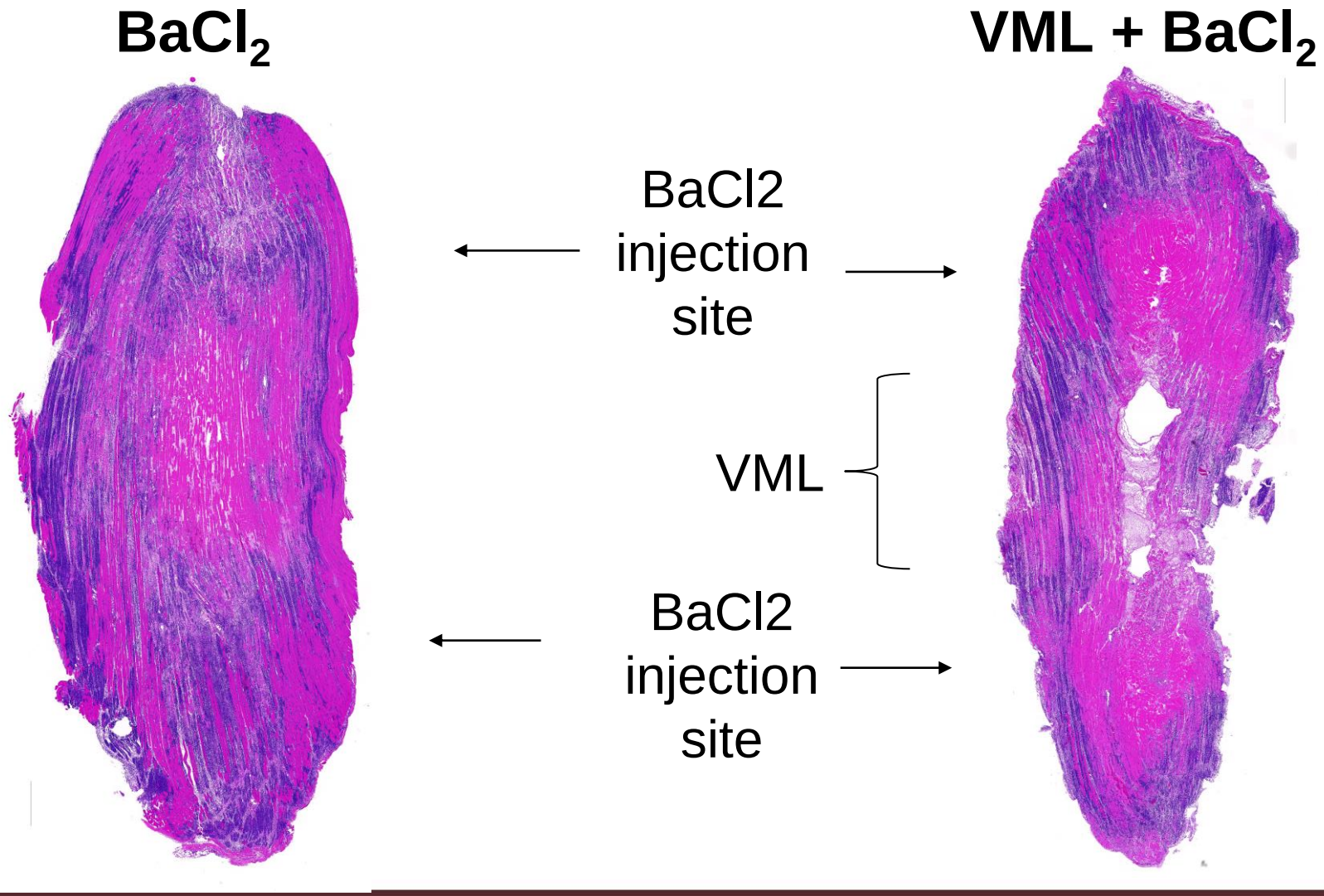
“VML exceeds the muscles capacity to regenerate”

If true:

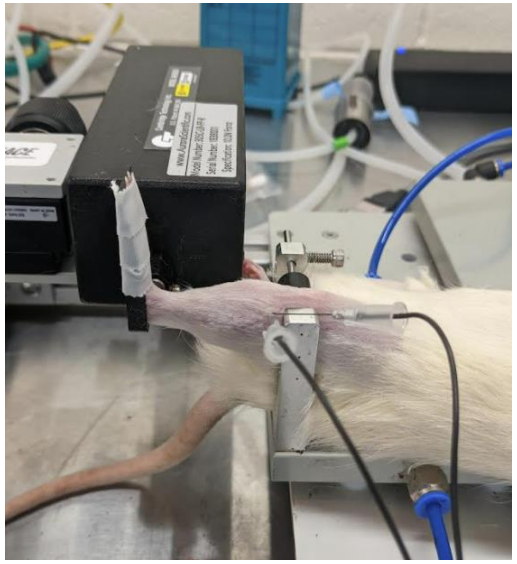
1) No muscle will regrow without cell transplant
2) Rehab limited to neurological-based strength gains
3) Future injuries won’t recover at all

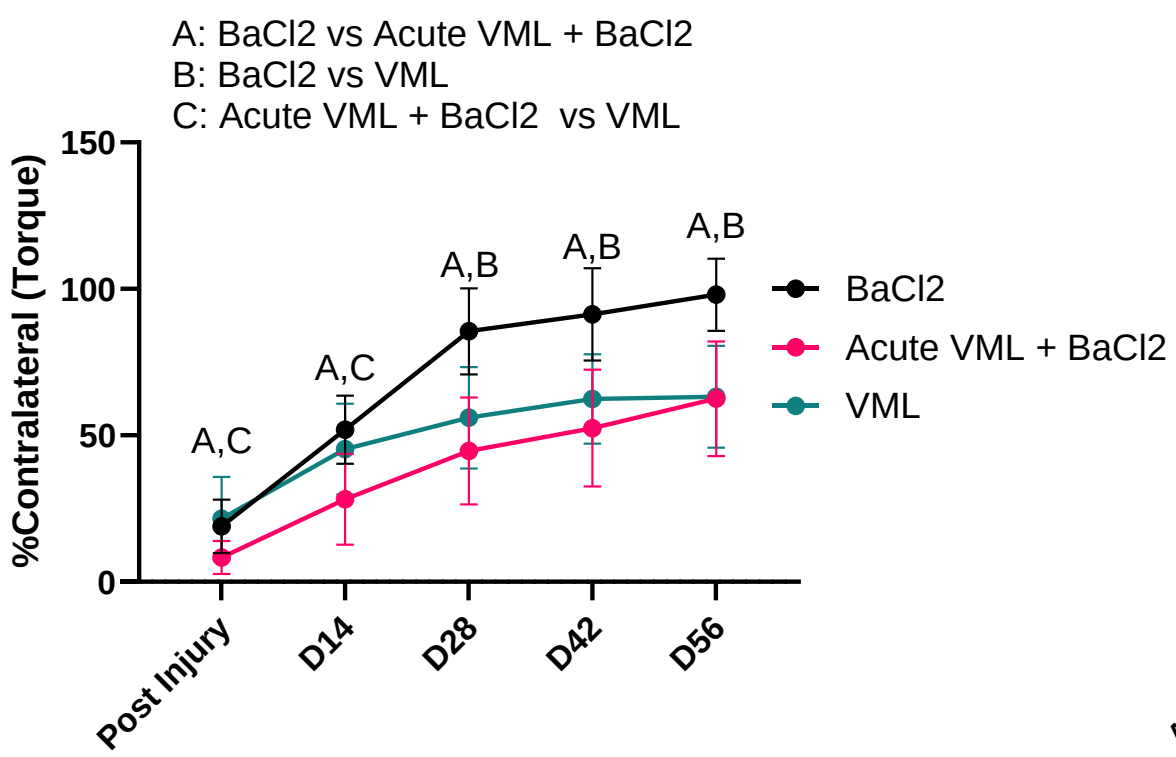
Injury Model

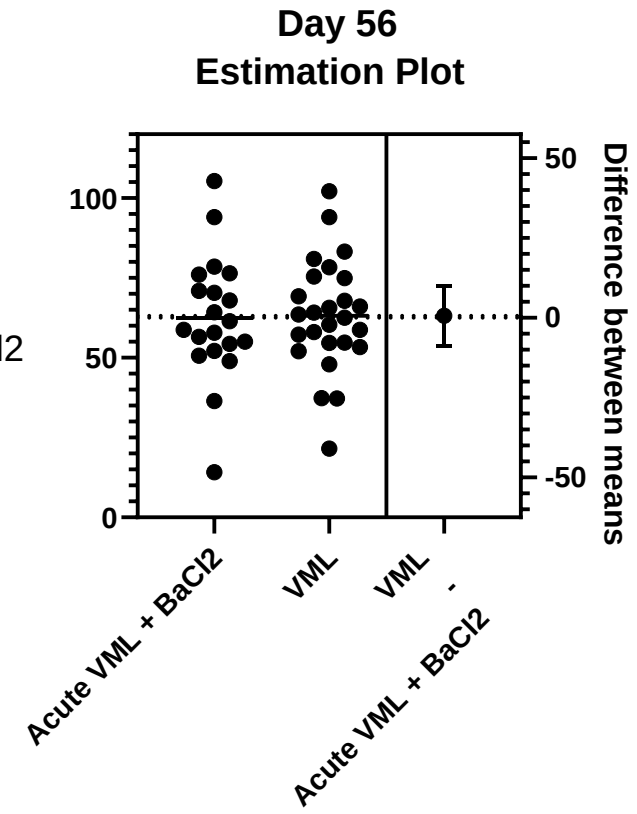
- Lewis Rat
- Tibialis Anterior muscle (lower limb)
- $BaCl_2$ injections
  - Causes myofiber necrosis (60%)
  - Fully recovers
- VML
  - 6 mm full thickness biopsy
  - 15% muscle mass



Functional Recovery

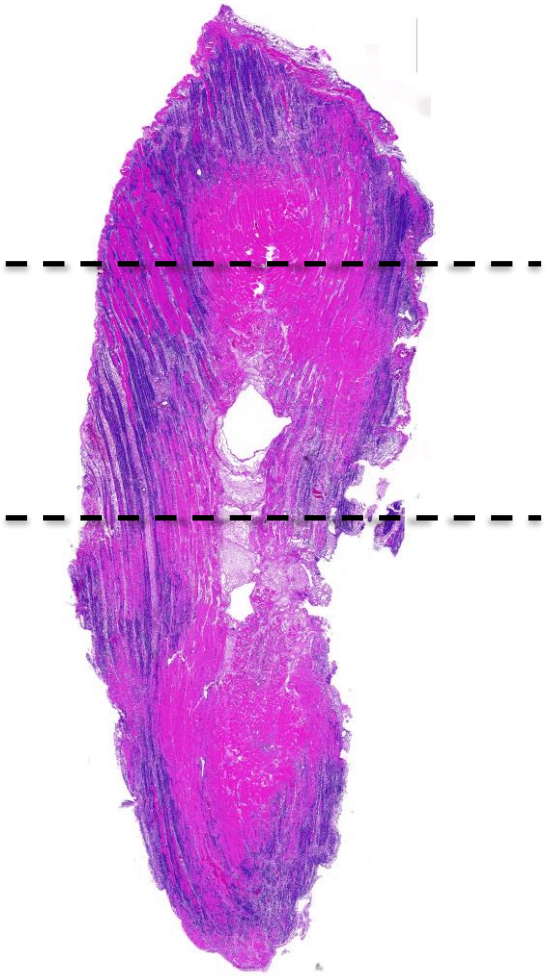


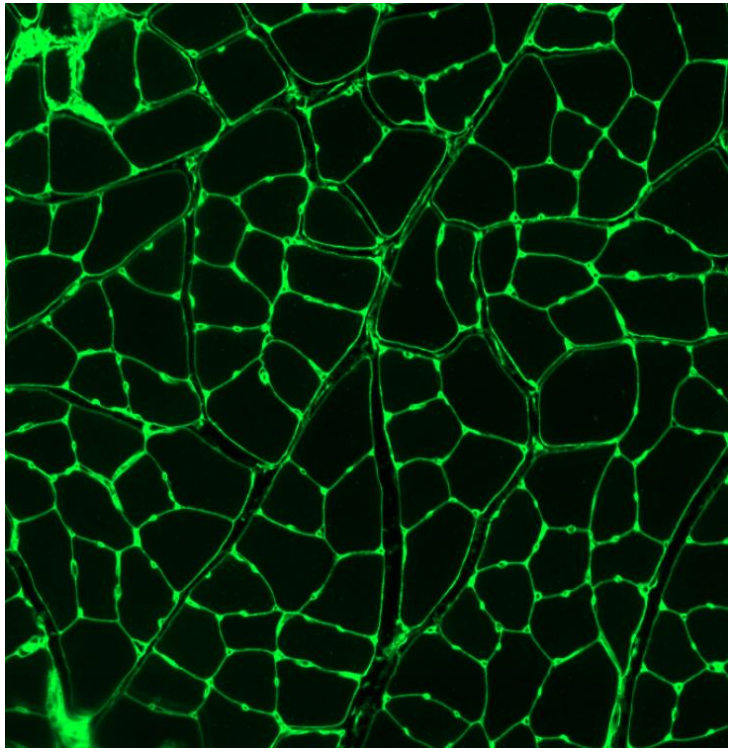




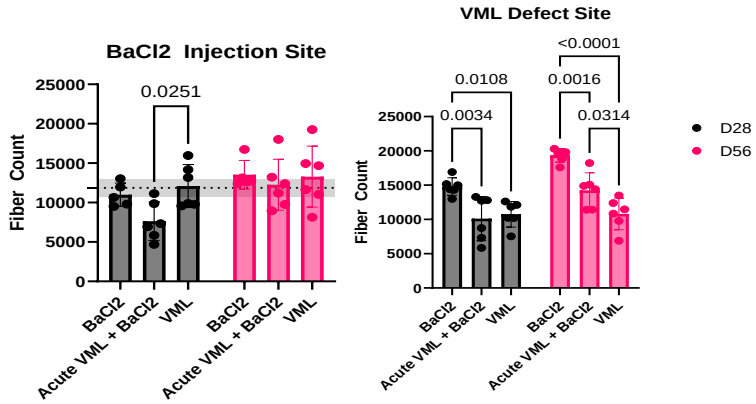
Muscle Fiber Histomorphometry

Histology cross-section site

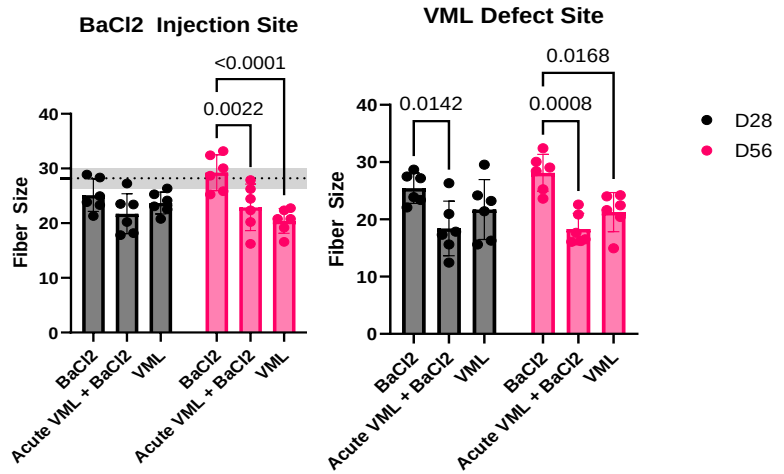




Muscle Fiber Count

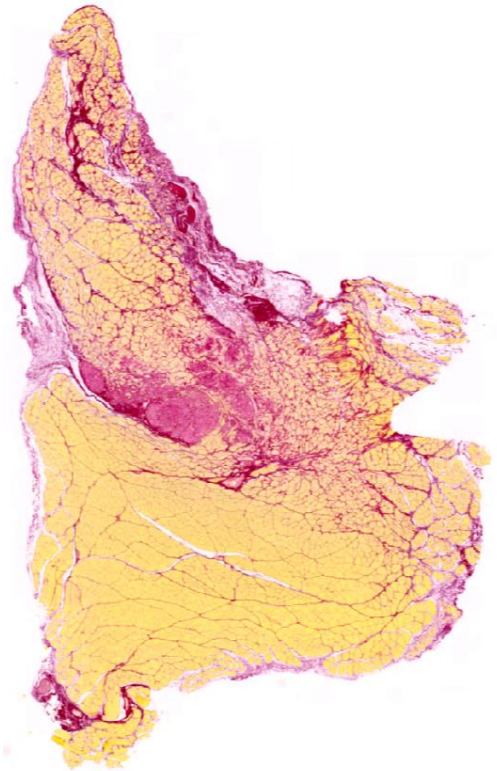


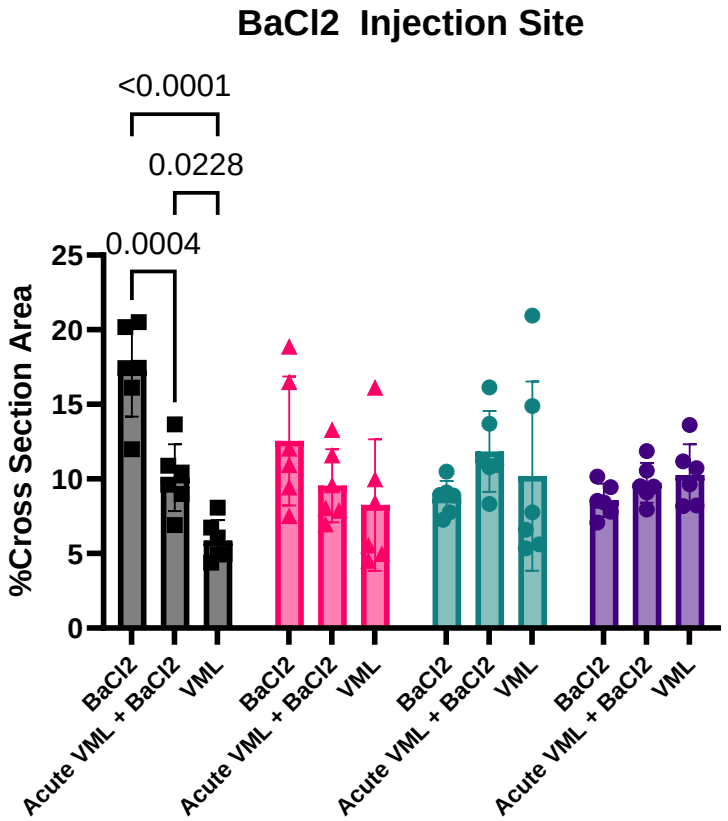
Muscle Fiber Size

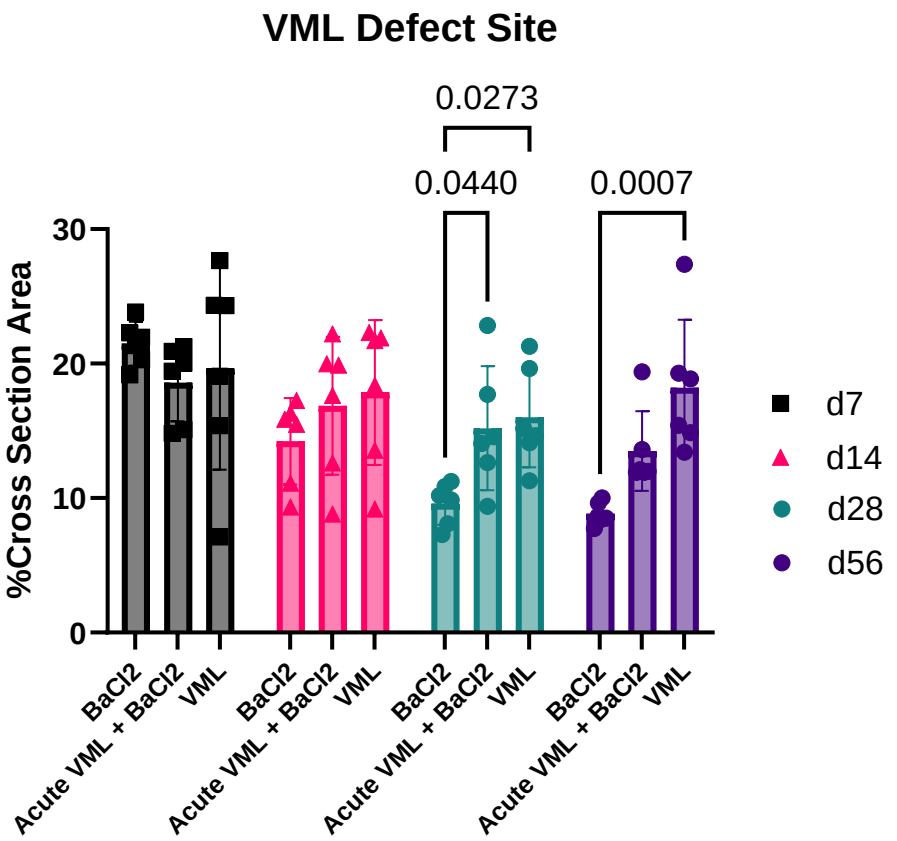


Fibrosis

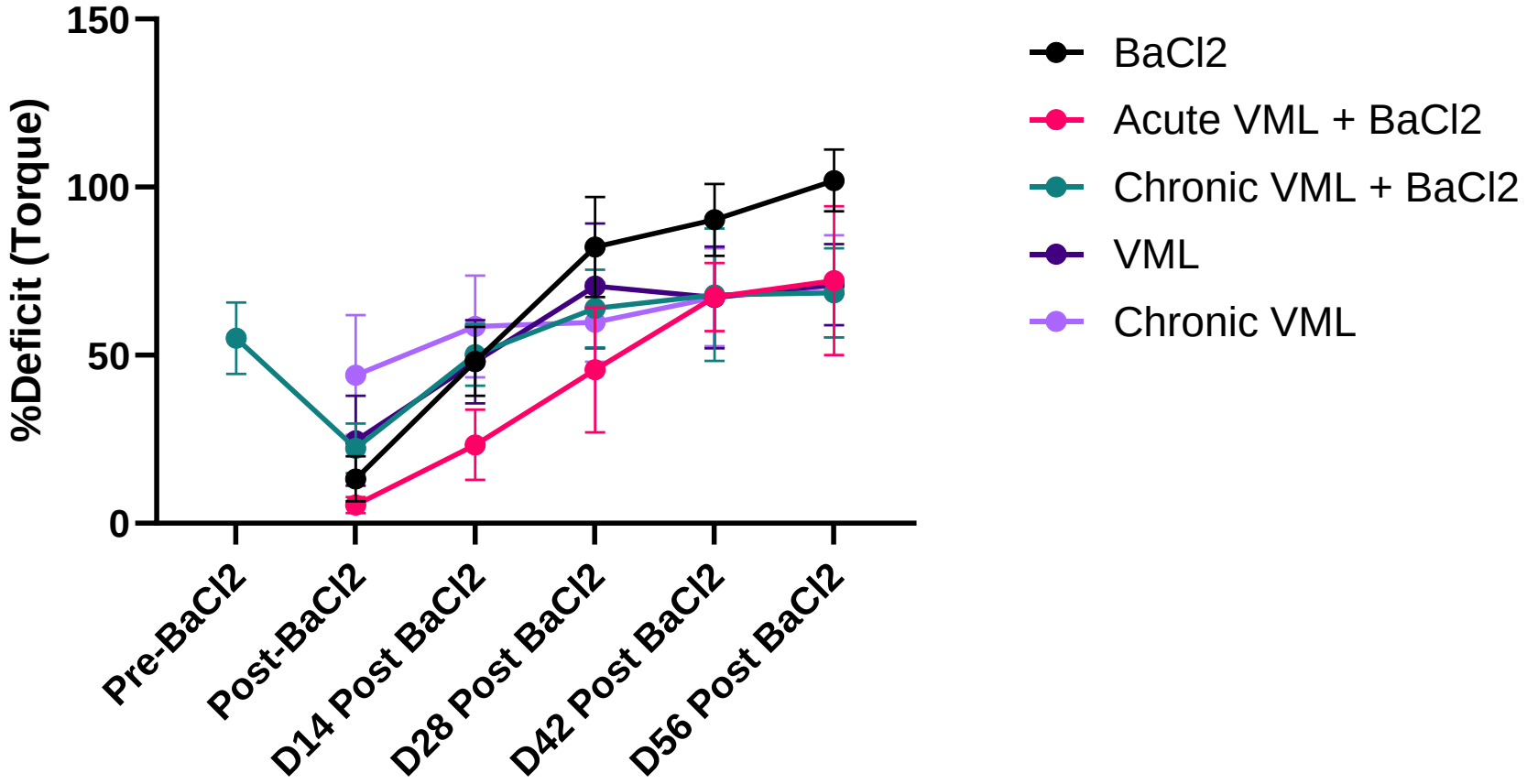
PSR



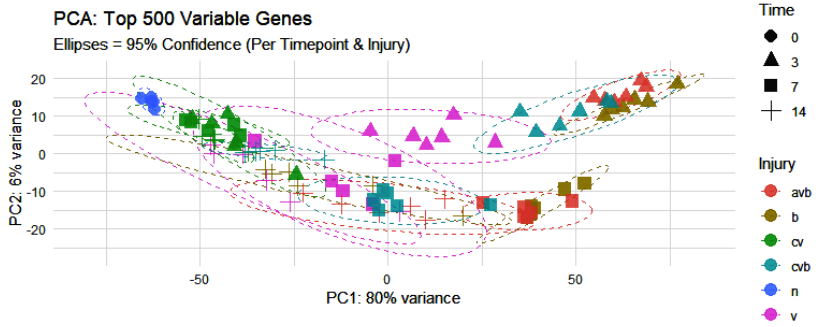


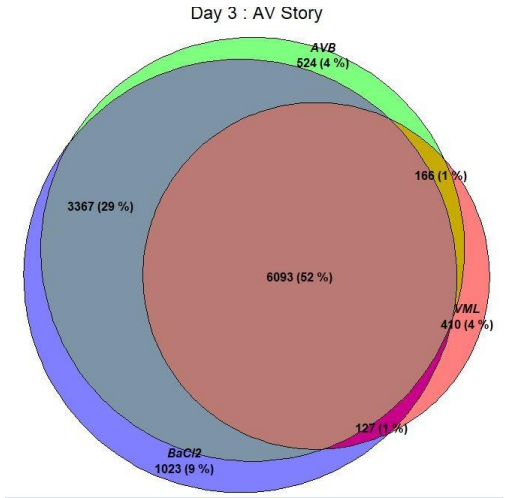


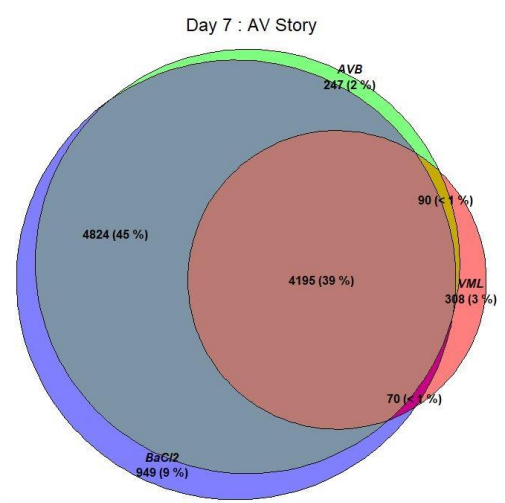
Chronic VML + $BaCl_2$

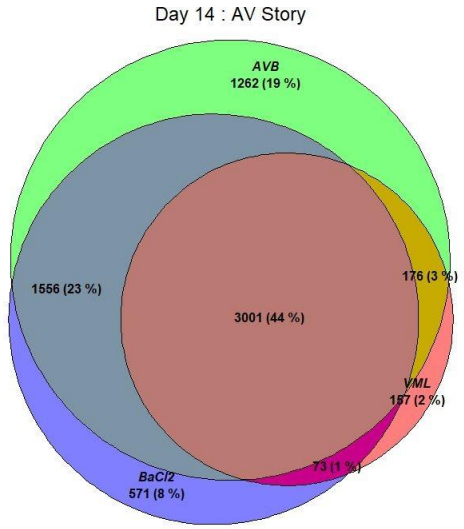


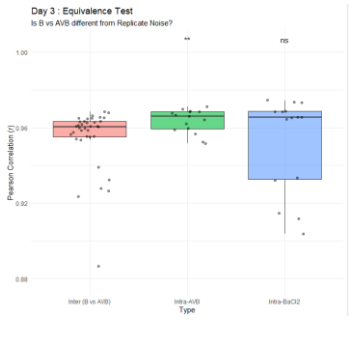
Gene analysis – VML doesn't make much difference

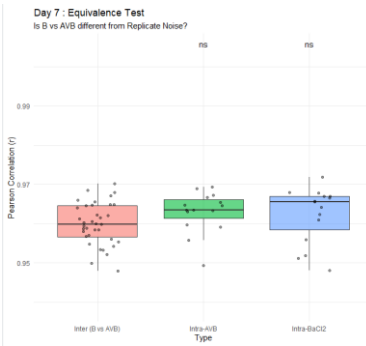


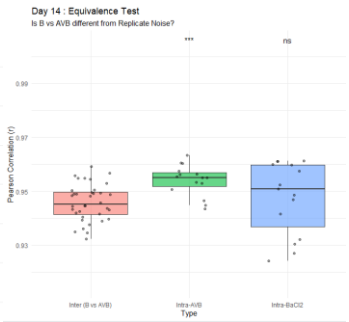


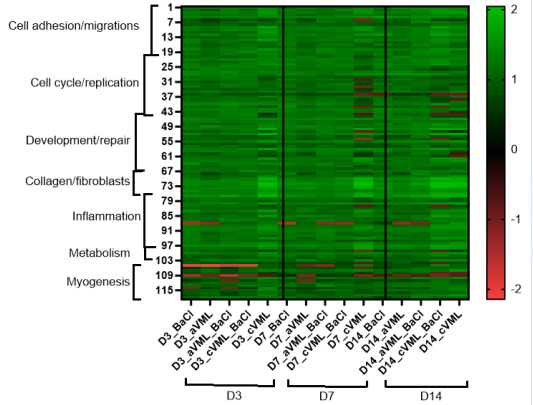


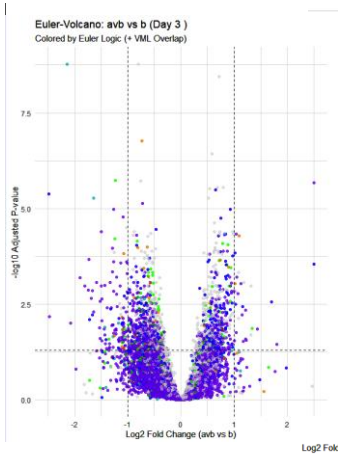


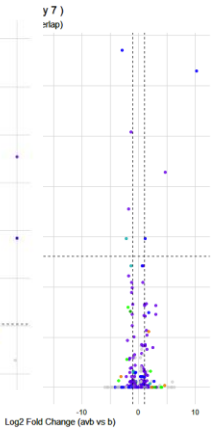


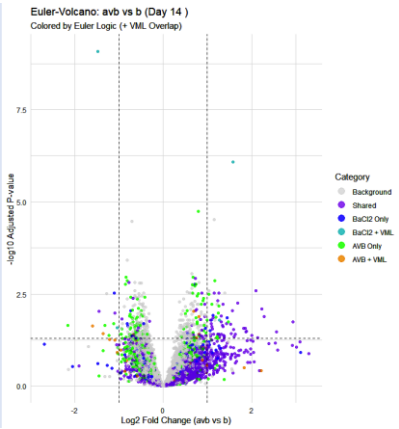












Conclusion

- $BaCl_2$ + VML
  - No functional deficits over VML
  - No reduced muscle fiber # or size compared to VML
  - No increased fibrosis over VML

VML injured muscles still have a capacity to form large amounts of muscle!

Summary

- VML causes long term disability
- Limited clinical treatments, few in the pipeline
- VML retains the capacity to regrow large amounts of muscle tissue
  - Recover from secondary injury

THANKS!







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