New Biologic Platform Repairs Large Volume Skeletal Muscle Loss

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Introduction

Volumetric muscle loss (VML) disrupts skeletal muscle's regenerative capacity, causing chronic inflammation, fibrosis, and permanent functional impairment. Current treatments, including autologous tissue transfer, often fail to restore structure and function, leaving warfighters at risk for prolonged rehabilitation, lifelong disability, and limb-salvage complications.

Burden of Volumetric Muscle Loss (VML) in Warfighters

Selected military data show that extremity trauma and VML drive major battlefield morbidity and long-term disability.

During combat / acute care

54% of combat wounds involved the extremities [1]

65% of inpatient resource utilization was due to extremity injuries among battle injuries not returned to duty [2]

After injury / after duty

64% of soldiers found 'unfit for duty' were in the extremity-injured group. Extremity injuries also accounted for 64% of projected disability benefit costs. [2]

92% of muscle conditions were identified as VML in a medically retired battlefield-injured cohort [3]

Takeaway: VML is not only a battlefield injury—it is a major contributor to long-term disability in injured service members.

Sources

[1] Owens BD, Kragh JF Jr, Wenke JC, Macaitis J, Wade CE, Holcomb JB. Combat wounds in Operation Iraqi Freedom and Operation Enduring Freedom. *J Trauma.* 2008;64(2):295-299. doi:10.1097/TA.0b013e318163b875.

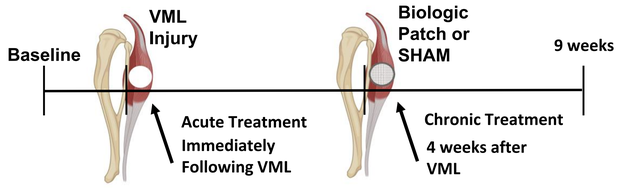
[2] Masini BD, Waterman SM, Wenke JC, Owens BD, Hsu JR, Ficke JR. Resource utilization and disability outcome assessment of combat casualties from Operation Iraqi Freedom and Operation Enduring Freedom. *J Orthop Trauma.* 2009;23(4):261-266. doi:10.1097/BOT.0b013e31819dfa04.

[3] Corona BT, Rivera JC, Owens JG, Wenke JC, Rathbone CR. Volumetric muscle loss leads to permanent disability following extremity trauma. *J Rehabil Res Dev.* 2015;52(7):785-792. doi:10.1682/JRRD.2014.07.0165.

Our lab has developed a non-integrating Biologic composed of human induced pluripotent stem cell (iPSC)-derived cardiomyocytes and human neonatal fibroblasts seeded onto a bioresorbable matrix. In models of chronic ischemic heart failure, this Biologic improves cardiac structure and function by inducing a biphasic repair response: early immune activation followed by resolution, TREM2+ reparative macrophage emergence, and stromal cell recruitment (Lancaster et al., 2023; PMID: 38007534). Its mechanism of action is not cardiac specific. Because VML is characterized by chronic inflammation, fibrotic remodeling, and failed muscle regeneration, we hypothesize that our Biologic can modulate the VML injury microenvironment to support skeletal muscle repair.

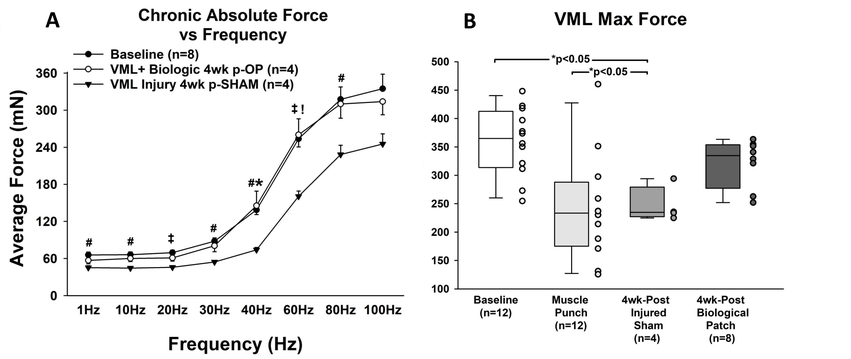
Methods

- **Human satellite cell model:** Pax7+ satellite cells isolated from human deltoid biopsies were used to assess Biologic-mediated muscle repair.
- **VML models:** Biopsy-punch injuries were created in the gastrocnemius muscles of C57BL/6 mice. Chronic injuries progressed for 4 weeks before Biologic implantation or SHAM surgery; acute injuries received immediate Biologic treatment. Repair was assessed by intact footplate mechanics, MRI, histology, and proteomics.



Results

Chronic Treatment



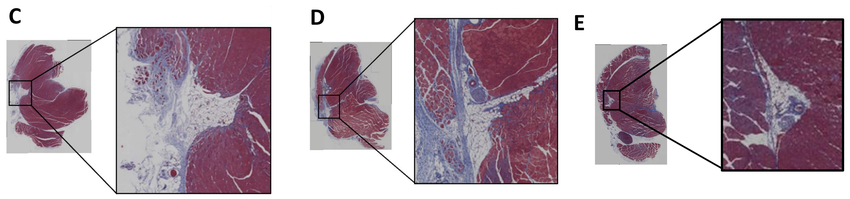
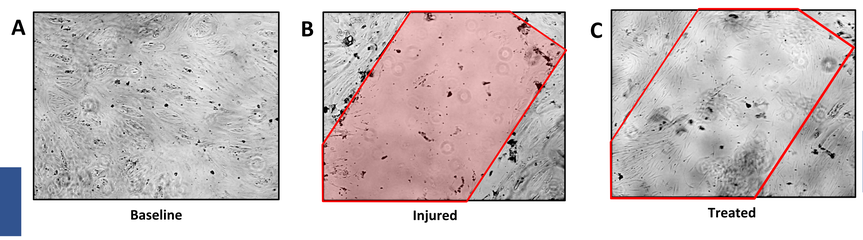


Figure 4: Footplate mechanics and Histology following chronic VML injury and delayed treatment in mice (n = 4/group). Force Frequency curves (**A**) and maximum force (**B**) are shown. Representative Masson's trichrome stained sections are displayed below: **C**, VML injury with sham surgery at week 3; **D**, VML injury with fibroblast-only construct implantation; and **E**, VML injury with Biologic implantation containing fibroblasts and cardiomyocytes. (^#p < 0.05 and ^‡p < 0.01, baseline vs. VML injury; *p < 0.05 and ^!p < 0.01, VML + biologic vs. VML injury.)



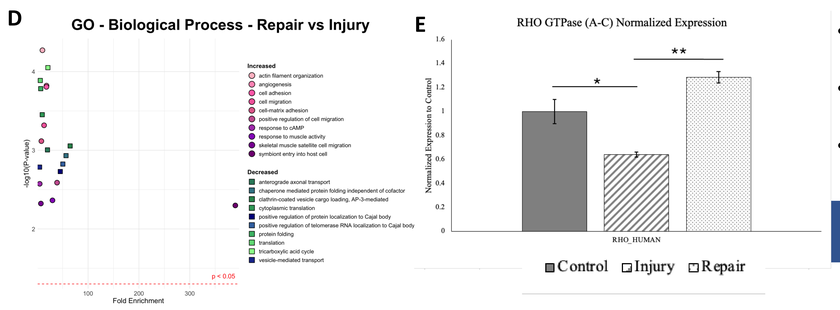
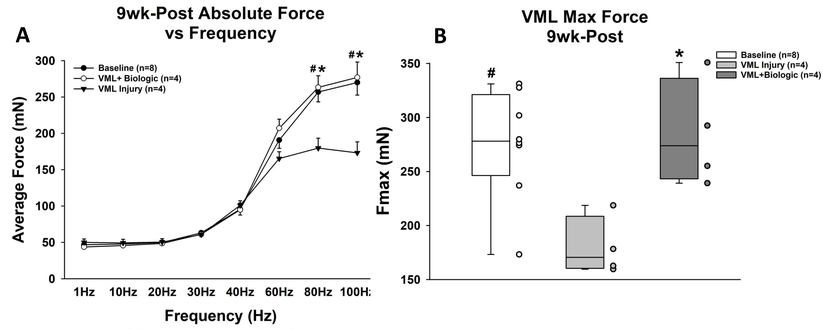


Figure 5: Pax7⁺ human muscle satellite cells were expanded and differentiated into myoblasts and myotubes before cryoinjury (**A**). Injured cells (**B**) were treated with Biologic supernatant (**C**), and proteomic analysis was performed to identify associated biological processes (**D**). Normalized RHO GTPase expression (**E**) was reduced following cryoinjury and increased after Biologic treatment. (^*p < 0.05, control vs. injury; p < 0.01, injury vs repair)

Acute Treatment



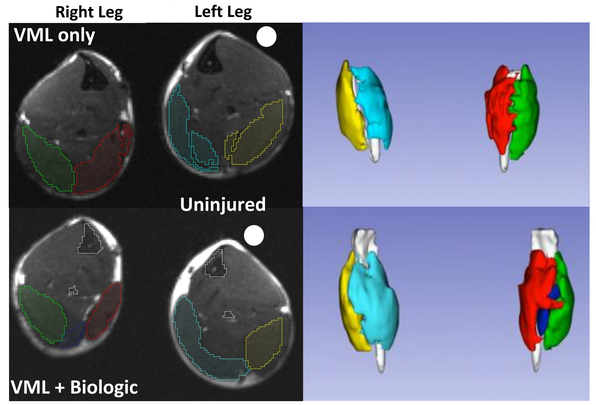


Figure 6: Footplate mechanics following VML injury and acute Biologic treatment in mice (n = 4/group). Force Frequency curves (**A**) and maximum force (**B**) are shown. Representative MRI images with 3D renditions are displayed below; the right limb (left) was injured/treated, and the left limb is identified by a marker placed anterior to the leg. Colors indicate muscle groups, Red – right medial gast., Green – right lateral gast., Teal – left medial gast., Yellow – left lateral gast., Blue - new tissue, White – Bone. (^#p < 0.05, baseline vs. VML injury; *p < 0.05, VML + Biologic vs. VML injury.)

Conclusions

- Our Biologic treatment improved muscle force following VML injury, with treated mice recovering > 90% muscle function.
- Functional improvements were observed after both acute and chronic treatment , demonstrating the potential versatility of the Biologic.
- The findings support our Biologic as a regenerative approach for restoring muscle function and improving outcomes after VML.
- Ongoing studies will evaluate treatment timing, immunomodulatory mechanisms, multi tissue regeneration and translational potential.

Disclosure

Drs. Goldman, Koevary, and Lancaster have disclosed a financial interest in Avery Therapeutics, Inc. to the University of Arizona. In addition, the University of Arizona has a financial interest in Avery Therapeutics, Inc. These interests have been reviewed and are being managed by the University of Arizona in accordance with its policies on outside interests.

Acknowledgements

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