SGT-003 Gene Therapy Stabilizes the DAPC and Improves Muscle Integrity in Duchenne Muscular Dystrophy

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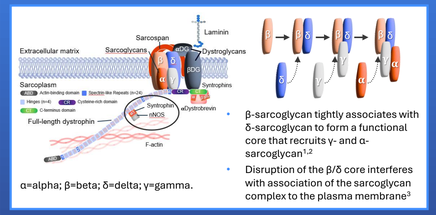
INTRODUCTION

Introduction: Duchenne muscular dystrophy is caused by loss of functional dystrophin, which results in destabilization of the dystrophin-associated protein complex (DAPC).[1,2] Disruption of the DAPC weakens sarcolemmal integrity, leading to membrane fragility, chronic myofiber damage, and persistent activation of degeneration–regeneration cycles.[3]

SGT-003 Reconstitutes the DAPC



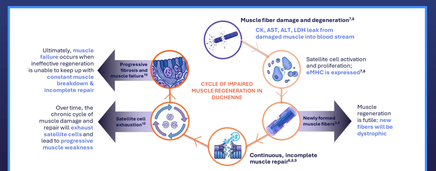
- β-sarcoglycan tightly associates with δ-sarcoglycan to form a functional core that recruits γ- and α-sarcoglycan[1,2]
- Disruption of the β/δ core interferes with association of the sarcoglycan complex to the plasma membrane[3]

α=alpha; β=beta; δ=delta; γ=gamma.

The DAPC anchors nNOS to the sarcolemma. Loss of dystrophin results in mislocalization of nNOS to the cytosol, leading to impaired activity-dependent nitric oxide signaling and associated vasodilation. This contributes to functional ischemia and increased susceptibility to contraction-induced injury.

In Duchenne, chronic muscle injury drives repeated degeneration–regeneration cycles, leading to elevated proportions of eMHC-positive regenerating fibers relative to healthy muscle.[5,6]

Overview of Membrane Damage and Regeneration



eMHC is significantly upregulated in dystrophic muscle fibers.[5,6] Muscle stem cells (satellite cells) are activated to repair and replace damaged muscle fibers–during this process, newly formed muscle fibers transiently express embryonic myosin heavy chain (eMHC).[3,5]

Restoring expression and localization of the entire protein complex, especially the sarcoglycans and nNOS, is a critical therapeutic goal for re-establishing DAPC function and preventing severe muscle disease in Duchenne.

Objective: To evaluate whether SGT-003, Solid's next-generation adeno-associated virus (AAV) microdystrophin gene therapy, restores the DAPC to the sarcolemma, improves sarcolemmal integrity, and normalizes the degeneration–regeneration process.

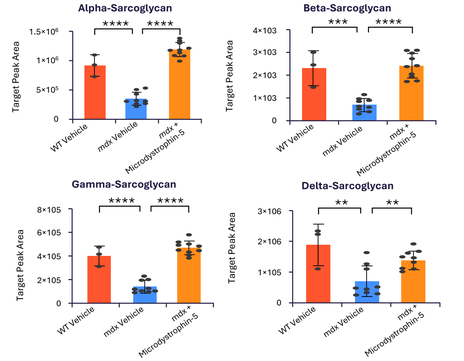
Methods: Sarcolemmal localization of DAPC components (sarcoglycans, dystrobrevin, nNOS) were assessed in muscle samples from *mdx* mice and SGT-003-101 clinical trial participants with Duchenne collected pre- and post-SGT-003 administration. Serum creatine kinase (CK) and titin fragments were quantified as biomarkers of sarcolemmal damage. eMHC expression was measured as a marker of active degeneration–regeneration.

RESULTS

SGT-003 RESTORES THE DAPC

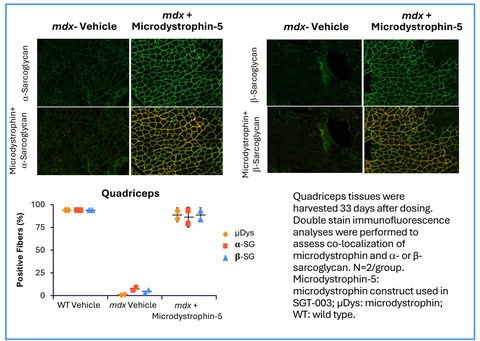
SGT-003 STABILIZES α-, β-, γ-, δ-SARCOGLYCANS; CRITICAL DAPC COMPONENTS

Figure 1. Microdystrophin-mediated reassembly of the sarcoglycan complex in *mdx* mice



Quadriceps tissues were harvested 33 days after dosing. Jess analysis was performed to quantify sarcoglycan protein levels. Mean microdystrophin percent positive fibers are 90% in the *mdx* μDys5 treated animals. WT N=3/group, *mdx* Vehicle N=9/group, *mdx* 7E13 vg/kg N=10/group. One way ANOVA with multiple comparisons performed, asterisk p<0.05. Microdystrophin-5: microdystrophin construct used in SGT-003.

Figure 2. Microdystrophin restores and co-localizes with sarcoglycans in mdx mice



Quadriceps tissues were harvested 33 days after dosing. Double stain immunofluorescence analyses were performed to assess co-localization of microdystrophin and α- or β-sarcoglycan. N=2/group. Microdystrophin-5: microdystrophin construct used in SGT-003; μDys: microdystrophin; WT: wild type.

REFERENCES

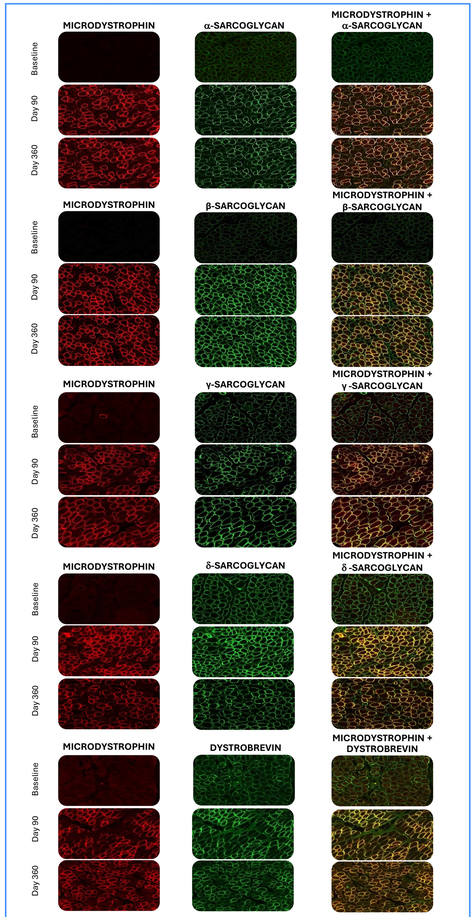
1. Gao QQ, McNally EM. *Compr Physiol.* 2015;5(3):1223-39. 2. Tarakci H, Berger J. *Front Biosci (Landmark Ed).* 2016;21(4):744-756. 3. Shi W, et al. *Muscle Nerve.* 2004;29(3):409-419. 4. Sears et al. *Circ Res.* 2003;92(5): e52-9. 5. Schiaffino S, et al. *Skelet Muscle.* 2015;5:22. 6. Guiraud S, et al. *Hum Mol Genet.* 2019;28(2):307-319. 7. Dubuisson N, et al. *Int J Mol Sci.* 2022;23(24):16080. 8. Cardone N, et al. *Acta Neuropathol Commun.* 2023; 11(1):167. 9. Forcina L, et al. *Cells.* 2020;9(5):1297. 10. Abdel-Sama E, et al. *Acta Myol.* 2009;28(3):94-100. 10. Data on file. Data cutoff September 29, 2025. Solid Biosciences.

ACKNOWLEDGMENTS

This study was sponsored by Solid Biosciences Inc. (Charlestown, MA, USA).

SGT-003 CLINICAL DATA: DAPC RESTORATION

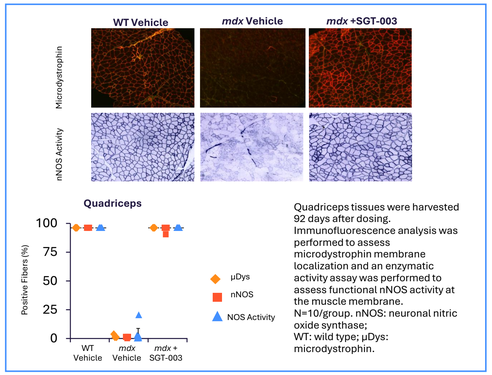
Figure 3. In SGT-003 Treated Participants, microdystrophin appropriately localizes to the sarcolemma where it restores the DAPC, including sarcoglycans and dystrobrevin [10]



Double stain immunofluorescence analyses were performed to assess co-localization of microdystrophin and α, β, γ, δ -sarcoglycan or dystrobrevin. Representative images from the same participant are shown.

SGT-003 RESTORES SARCOLEMMAL nNOS SIGNALING – A KEY BIOLOGIC FUNCTIONAL ATTRIBUTE OF DYSTROPHIN

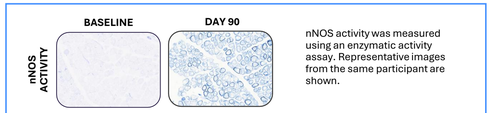
Figure 4. SGT-003 microdystrophin uniquely restores membrane localization of enzymatically active, functional nNOS in mdx mice



Quadriceps tissues were harvested 92 days after dosing. Immunofluorescence analysis was performed to assess microdystrophin membrane localization and an enzymatic activity assay was performed to assess functional nNOS activity at the muscle membrane. N=10/group. nNOS: neuronal nitric oxide synthase; WT: wild type; μDys: microdystrophin.

SGT-003 Clinical Data: Reconstitution of Functional nNOS at Sarcolemma

Figure 5. SGT-003 microdystrophin uniquely restores membrane localization of functional nNOS activity in SGT-003 treated participants[10]

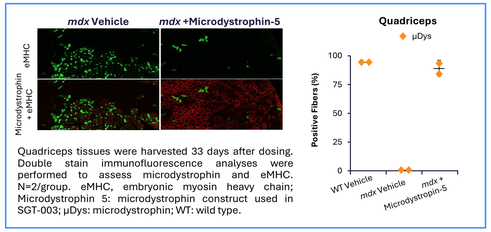


nNOS activity was measured using an enzymatic activity assay. Representative images from the same participant are shown.

SGT-003 PROTECTS MUSCLE FROM INJURY

SGT-003 Restores Sarcolemmal Integrity and Suppresses Myofiber Degeneration Evaluated by eMHC Quantification

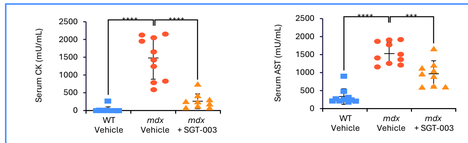
Figure 6. Reduction of ongoing dystrophic myofiber degeneration and regeneration observed after treatment



Quadriceps tissues were harvested 33 days after dosing. Double stain immunofluorescence analyses were performed to assess microdystrophin and eMHC. N=2/group. eMHC, embryonic myosin heavy chain; Microdystrophin 5: microdystrophin construct used in SGT-003; μDys: microdystrophin; WT: wild type.

SGT-003 RESTORES MEMBRANE INTEGRITY

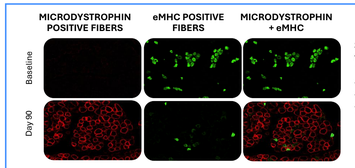
Figure 7. Reduction of serum biomarkers of membrane instability observed after SGT-003 treatment



Serum was collected 91 days after dosing. Serum CK activity and serum AST were measured to assess membrane damage. N=10/group. AAV: adenovirus-associated vector; AST: aspartate aminotransferase; CK: creatine kinase; WT: wild type. Asterisk p<0.05.

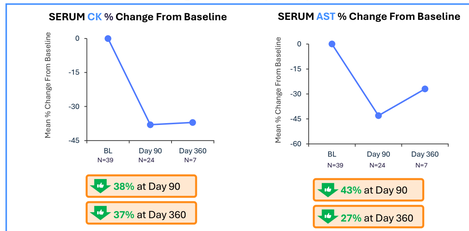
SGT-003 Clinical Data: Reduces Muscle Degeneration

Figure 8. SGT-003 stabilizes the muscle membrane and prevents muscle injury in treated participants[10]



Solid Biosciences data on file. Double stain immunofluorescence analyses were performed to assess microdystrophin and eMHC. Representative images from the same participant are shown.

Figure 9. SGT-003 stabilizes the muscle membrane and reduces serum markers of membrane damage in treated participants[10]



CONCLUSIONS

- SGT-003 produces compelling biological evidence of DAPC restoration, enhanced sarcolemmal resilience, and a measurable reduction in ongoing muscle injury in both mdx mice and boys with Duchenne
- SGT-003 restores sarcolemmal nNOS signaling, a key biological functional attribute of dystrophin
- Critically, the decrease in eMHC suggests that muscle fibers are no longer trapped in a perpetual injury-repair loop — a shift that may enable true structural preservation and improved long-term function for patients with Duchenne

Presented at American Society of Gene & Cell Therapy, May 11-15, 2026, Boston, Ma