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ARCUS nuclease-mediated excision of the "Hot Spot" region of the human dystrophin gene for the treatment of Duchenne Muscular Dystrophy (DMD)

American Society of Gene and Cell Therapy
Session: Late-Breaking Abstracts 2
Gary Owens
May 19, 2023

Forward-Looking Statements

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Disclosures

- I am an employee of Precision BioSciences, Inc. (Nasdaq: DTIL)

Duchenne Muscular Dystrophy Currently Lacks a Curative Treatment

Mutation on the X chromosome interferes with dystrophin protein production, which is needed to form and maintain healthy muscle

Affects approximately

1 in 3,500

live male births

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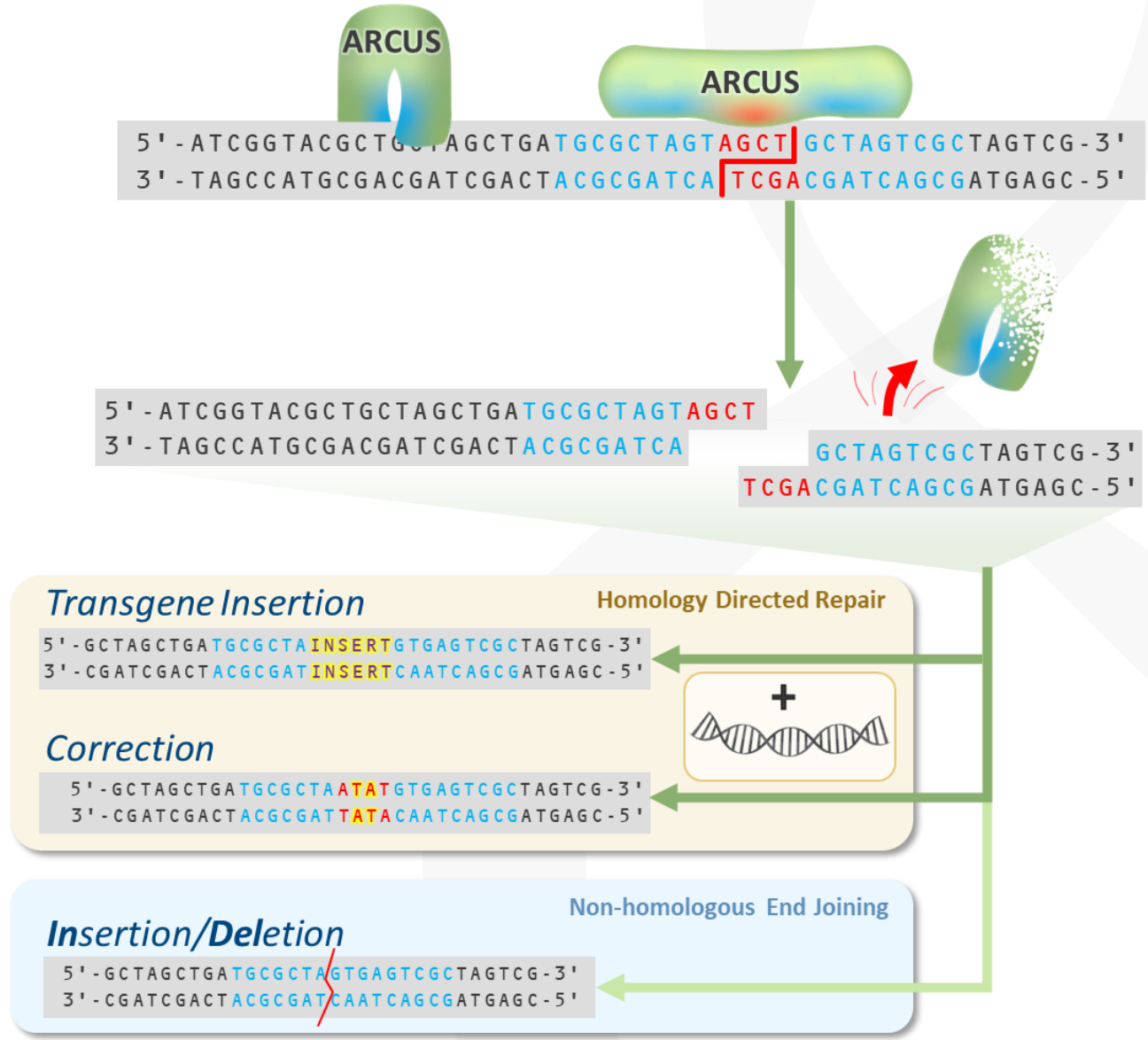
ARCUS: Engineering Nature's Genome Editing System

ARCUS

- Derived from I-CreI, a naturally-occurring green algae homing endonuclease
- Target site recognition and cleavage rely solely on an extensive DNA-protein interface
- DNA cleavage results in 4 bp 3' sticky ends
- Small size (364 aa) facilitates delivery via AAV or LNP



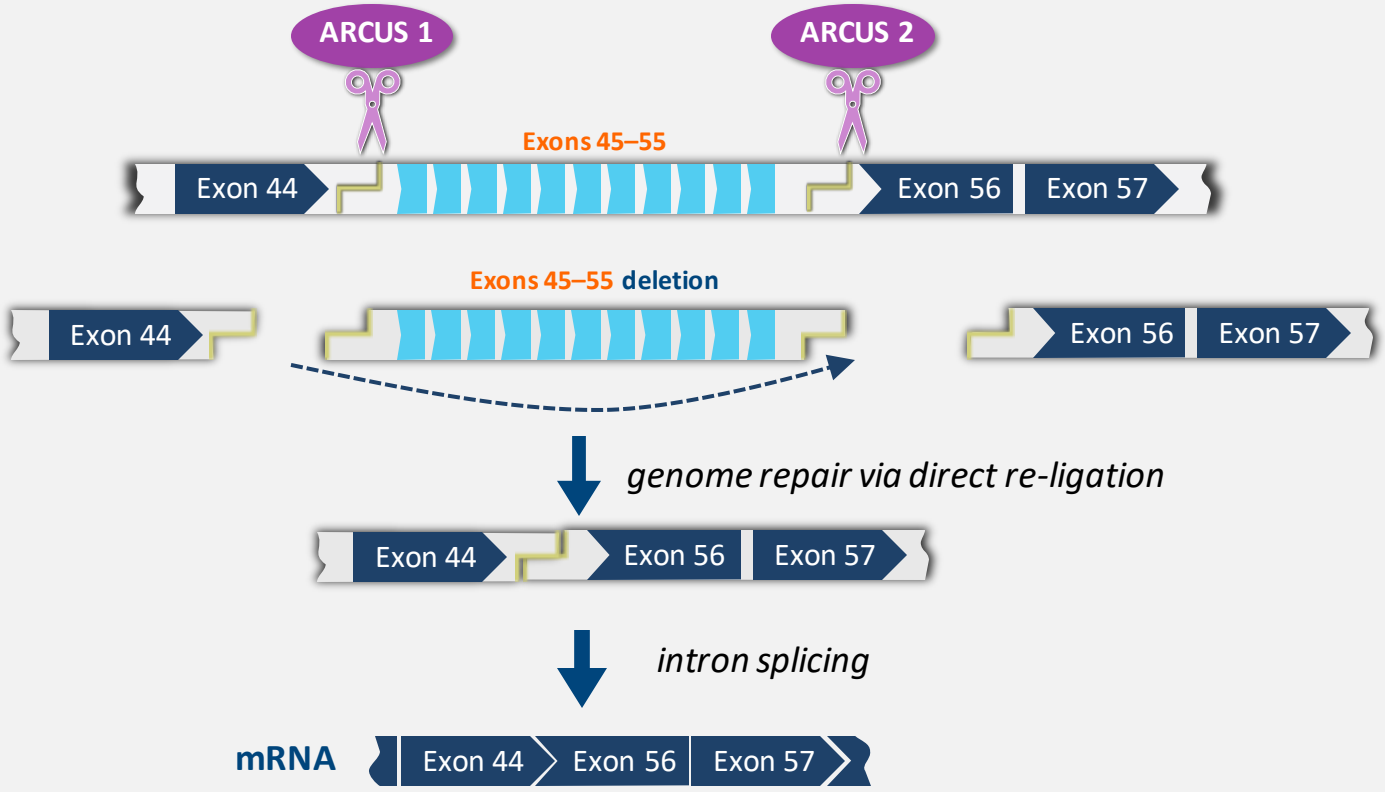
Utilizing ARCUS Nucleases to Restore Dystrophin Expression for DMD

Strategy to restore dystrophin expression

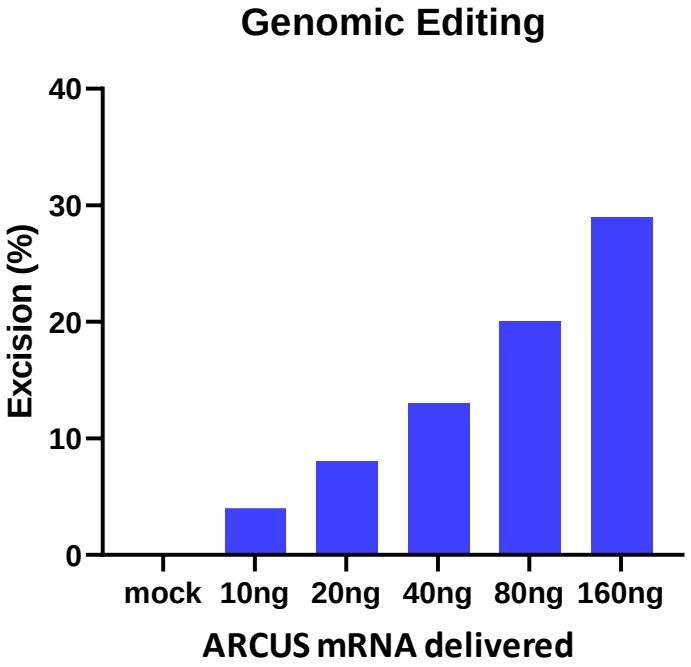
Delete exons 45-55 using a pair of ARCUS nucleases intended to remove a mutation hotspot responsible for approximately 50% of DMD cases

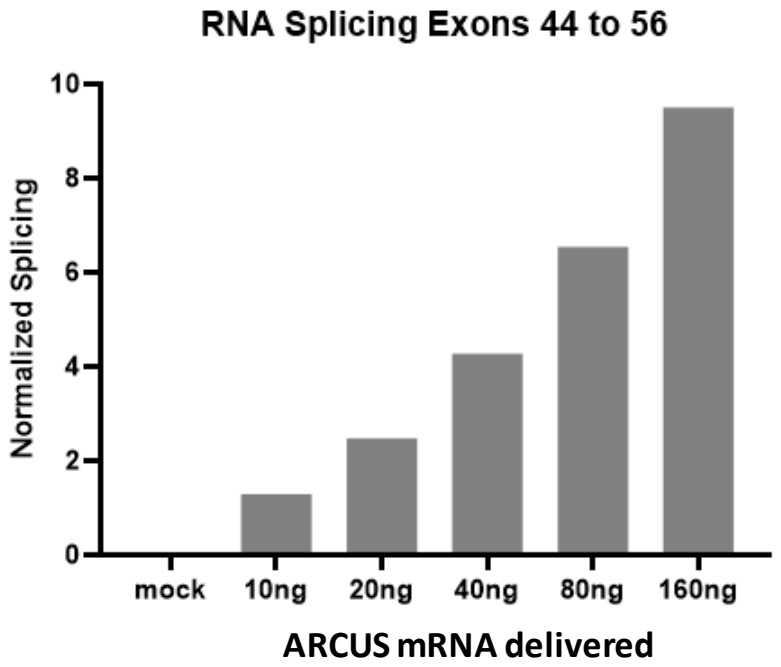
GOAL

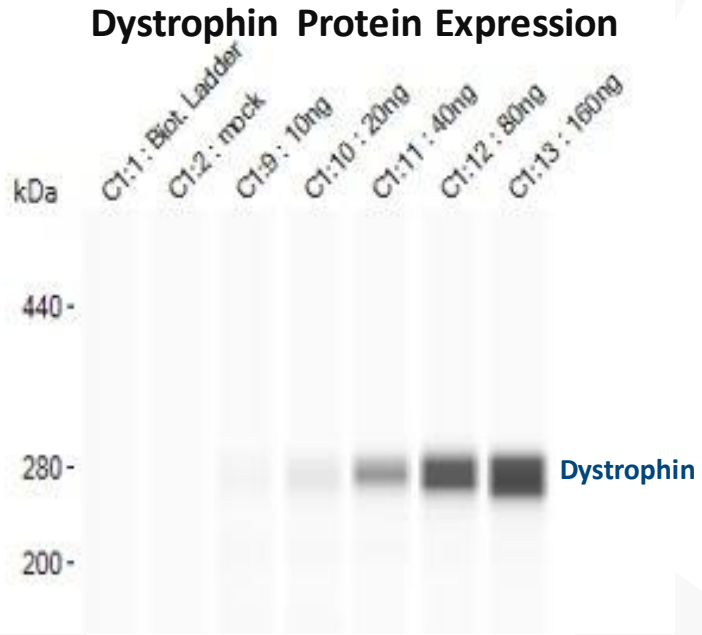
Two complementary ARCUS nucleases delivered in a single AAV are used to make a complex edit of the genome which results in the generation of a "Becker's like," functionally competent variant of the dystrophin protein



Dystrophin Gene Correction Observed in DMD Patient Myoblasts







Exons 45-55 deleted

Exon 44 spliced to Exon 56

Dystrophin protein expressed

Truncated variant

In Vivo POC Study Design

- **Objective:** Assess muscle function in a humanized, murine model of DMD
- **Test Article:** A single AAV with 2 early generation ARCUS nucleases, expression driven by a muscle specific promoter
- **Mouse Models:**
  - hDMD/mdx *
    - Contains human dystrophin gene and mouse dystrophin gene with mdx mutation
    - Expresses human dystrophin and no mouse dystrophin
  - hDMDdel52/mdx **
    - Mutated human and mouse dystrophin gene
    - Does not express functional human or mouse dystrophin
- **Readouts:**
  - Excision of exons 45-55
  - Dystrophin restoration
  - Force frequency
  - Histology for dystrophin^{+} muscle fibers and BaseScope for editing in Pax7^{+} cells

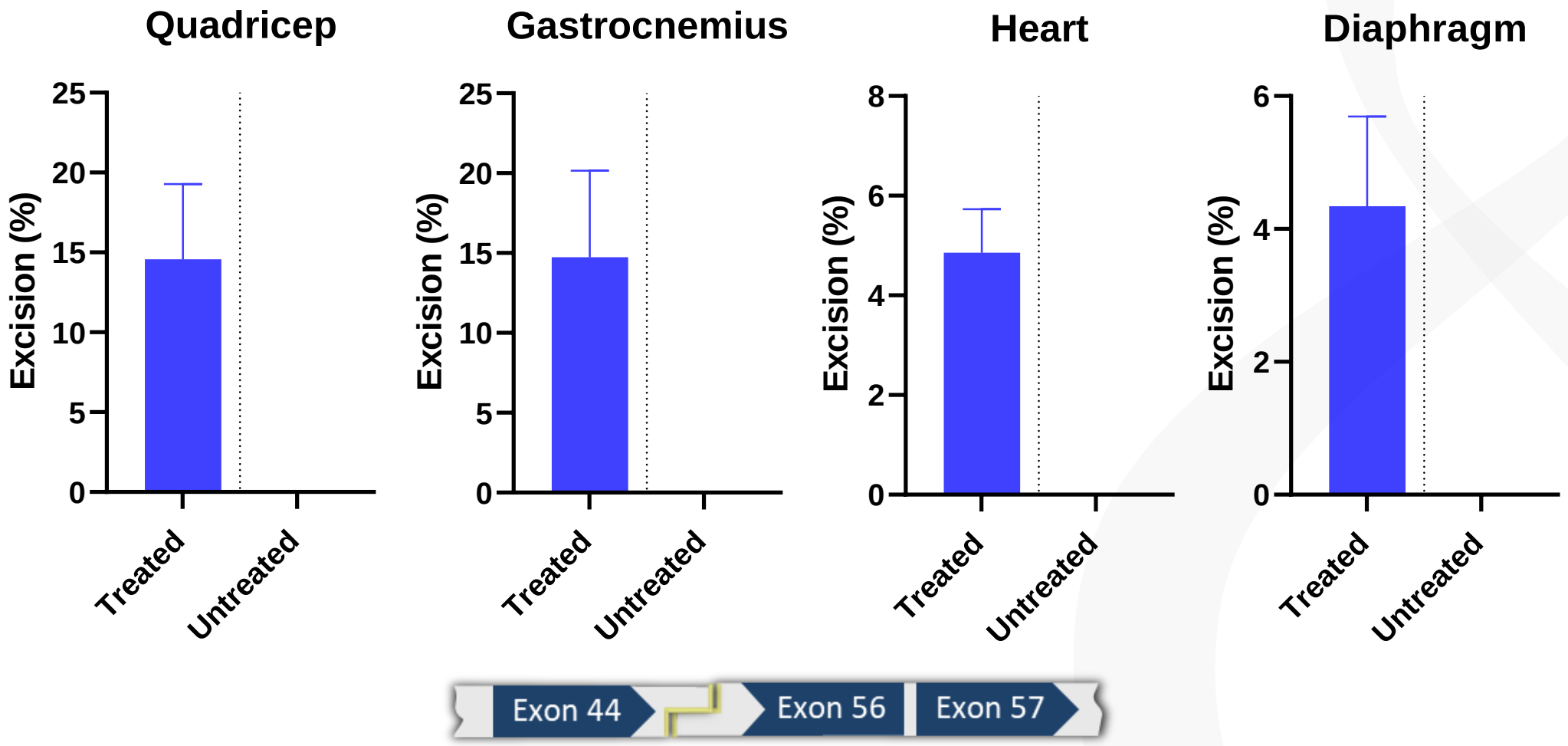
8 Weeks

Group	Mouse Strain	N
ARCUS-treated	hDMDdel52/mdx	10
Untreated	hDMDdel52/mdx	10
Untreated	hDMD/mdx	10

*'t Hoen PA, de Meijer EJ, Boer JM, Vossen RH, Turk R, Maatman RG, et al. Generation and characterization of transgenic mice with the full-length human DMD gene. J Biol Chem. 2008; 283(9):5899–907. Epub 2007/12/18. https://doi.org/10.1074/jbc.M709410200 PMID: 18083704

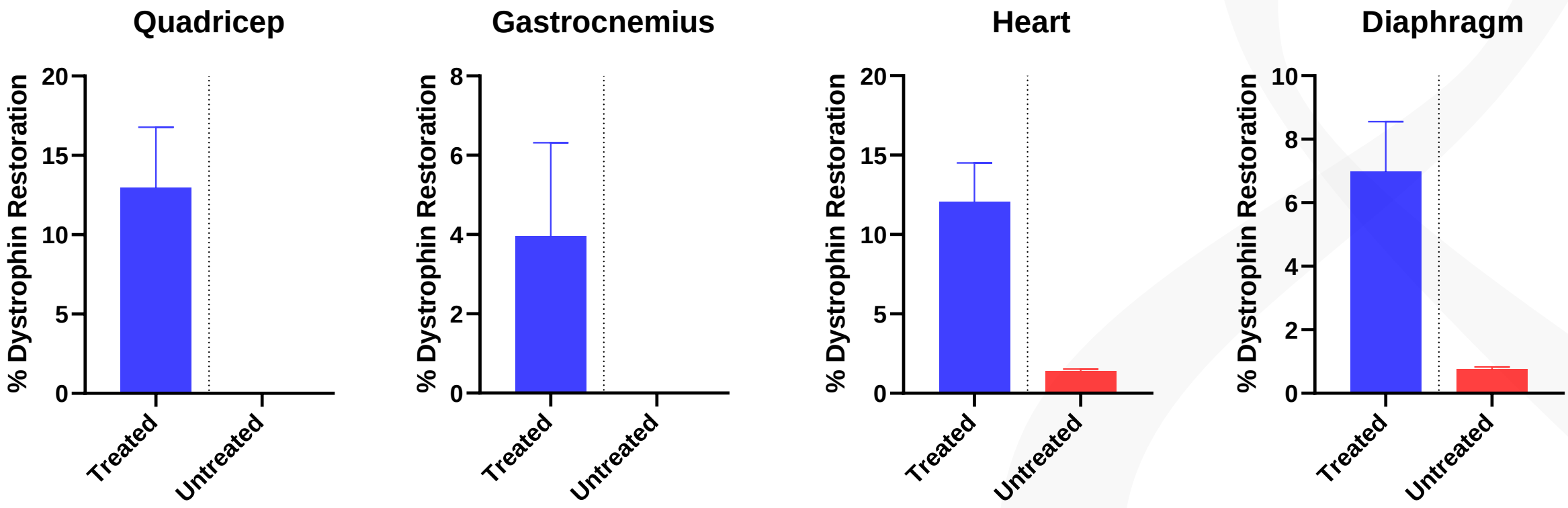
**Yavas A, Weij R, van Putten M, Kourkouta E, Beekman C, Puoliväli J, Bragge T, Ahtoniemi T, Knijnenburg J, Hoogenboom ME, Ariyurek Y, Aartsma-Rus A, van Deutekom J, Datson N. Detailed genetic and functional analysis of the hDMDdel52/mdx mouse model. PLoS One. 2020 Dec 23;15(12):e0244215. doi: 10.1371/journal.pone.0244215. PMID: 33362201; PMCID: PMC7757897.

Excision of the “Hot Spot Region” of the Dystrophin Gene in Target Tissues



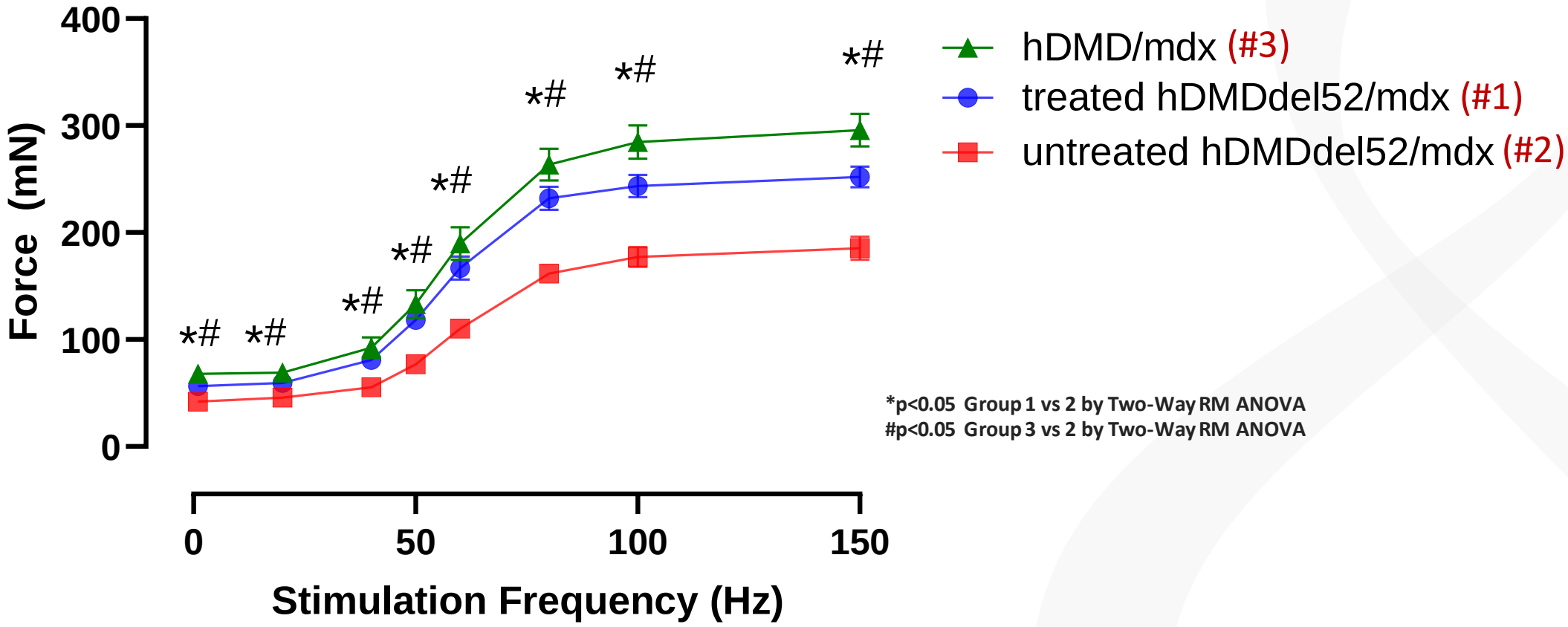
Genomic Excision of Exons 45-55

Edited Dystrophin Protein Variant Expressed in Target Tissues



Truncated dystrophin protein produced from splice edited mRNA

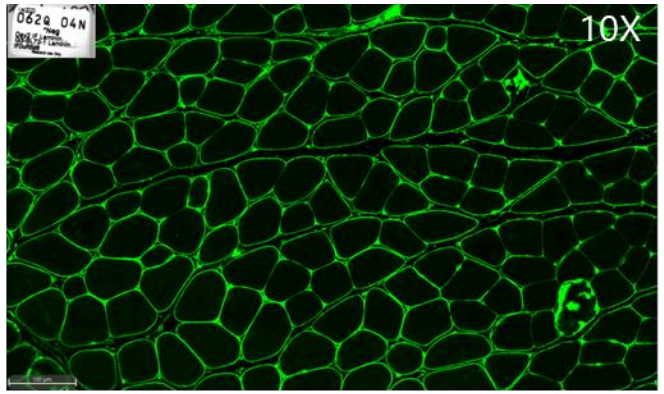
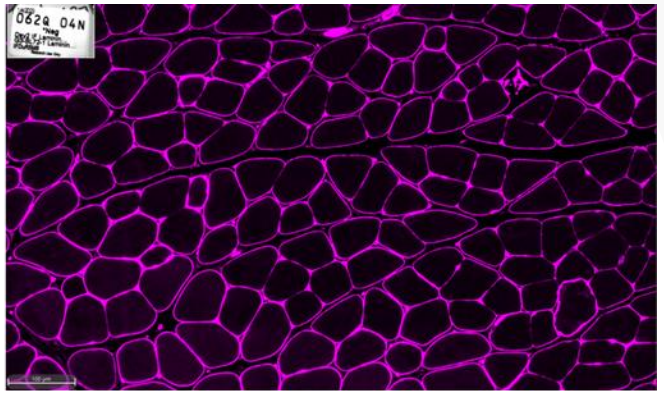
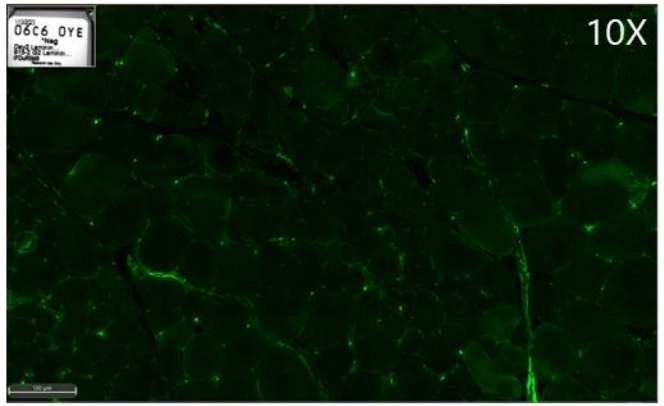
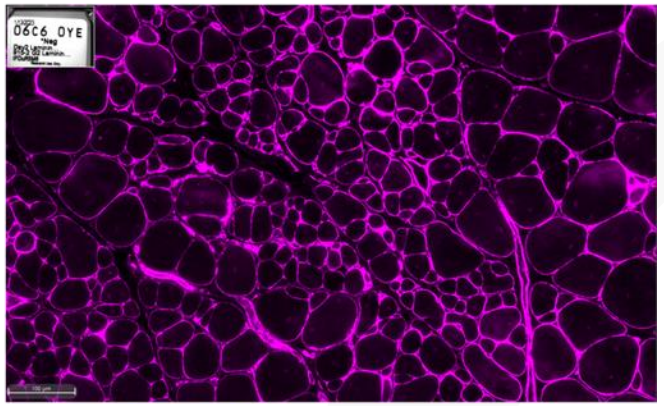
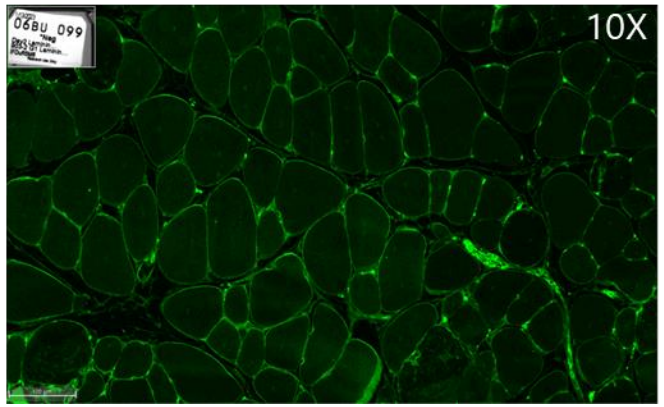
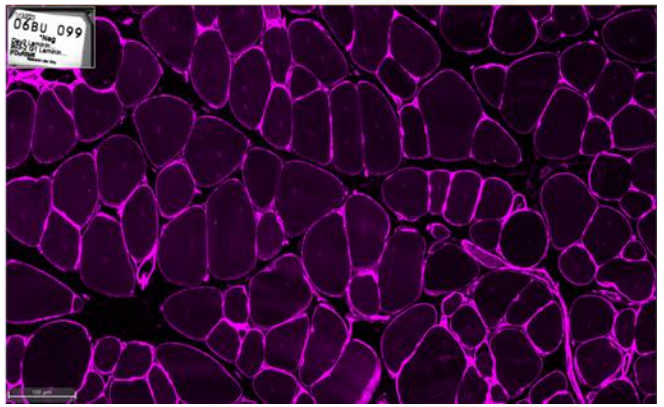
Maximum Force Output of Gastrocnemius Muscle in ARCUS-Treated Mice was Significantly Improved



- hDMDdel52/mdx & hDMD/mdx mice were tested 8 weeks post ARCUS AAV delivery
- Changes in muscle function were measured in the gastrocnemius muscle using electrical stimulation and measurement of muscle force
- **Maximum force output (MFO) of the gastrocnemius muscle in ARCUS-treated hDMDdel52/mdx mice was significantly improved, reaching 86% of the MFO levels observed in non-diseased, control mice**

Restoration of Dystrophin in Gastrocnemius Muscle

Green = Dystrophin
Purple = Laminin

Dystrophin	Laminin	
		Untreated Non-Disease Model (hDMD/mdx)
		Untreated Disease Model (hDMDdel52/mdx)
		Treated Disease Model (hDMDdel52/mdx)

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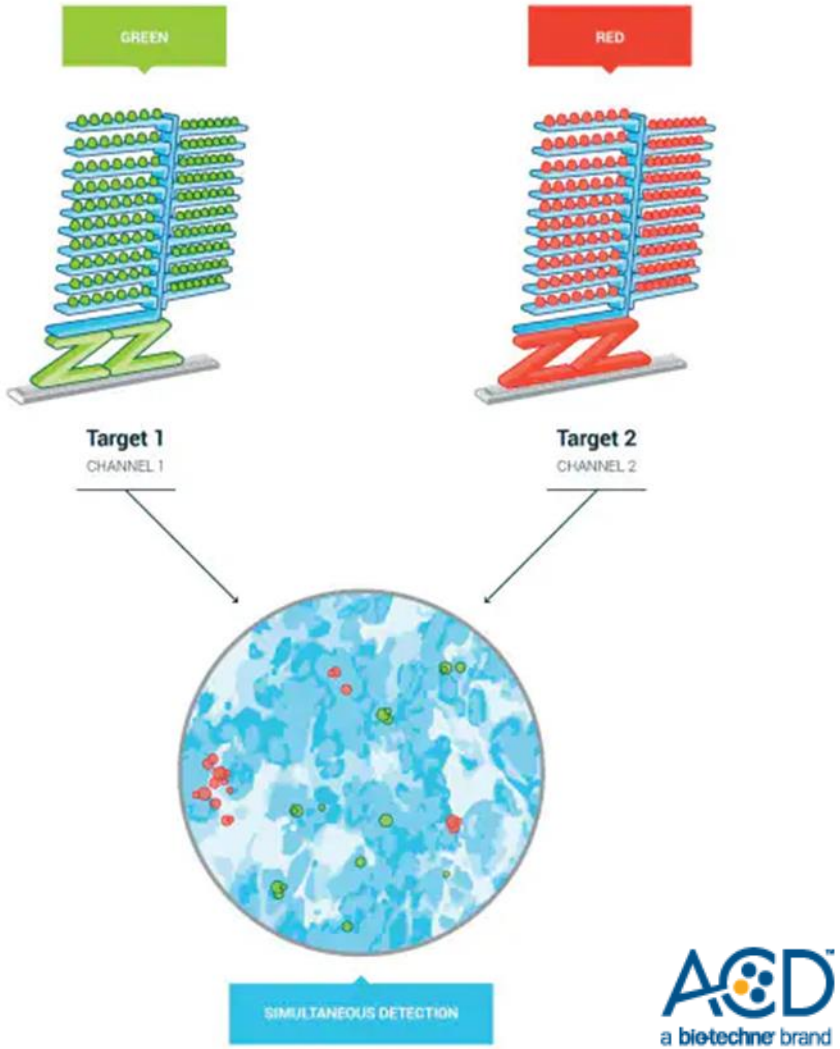
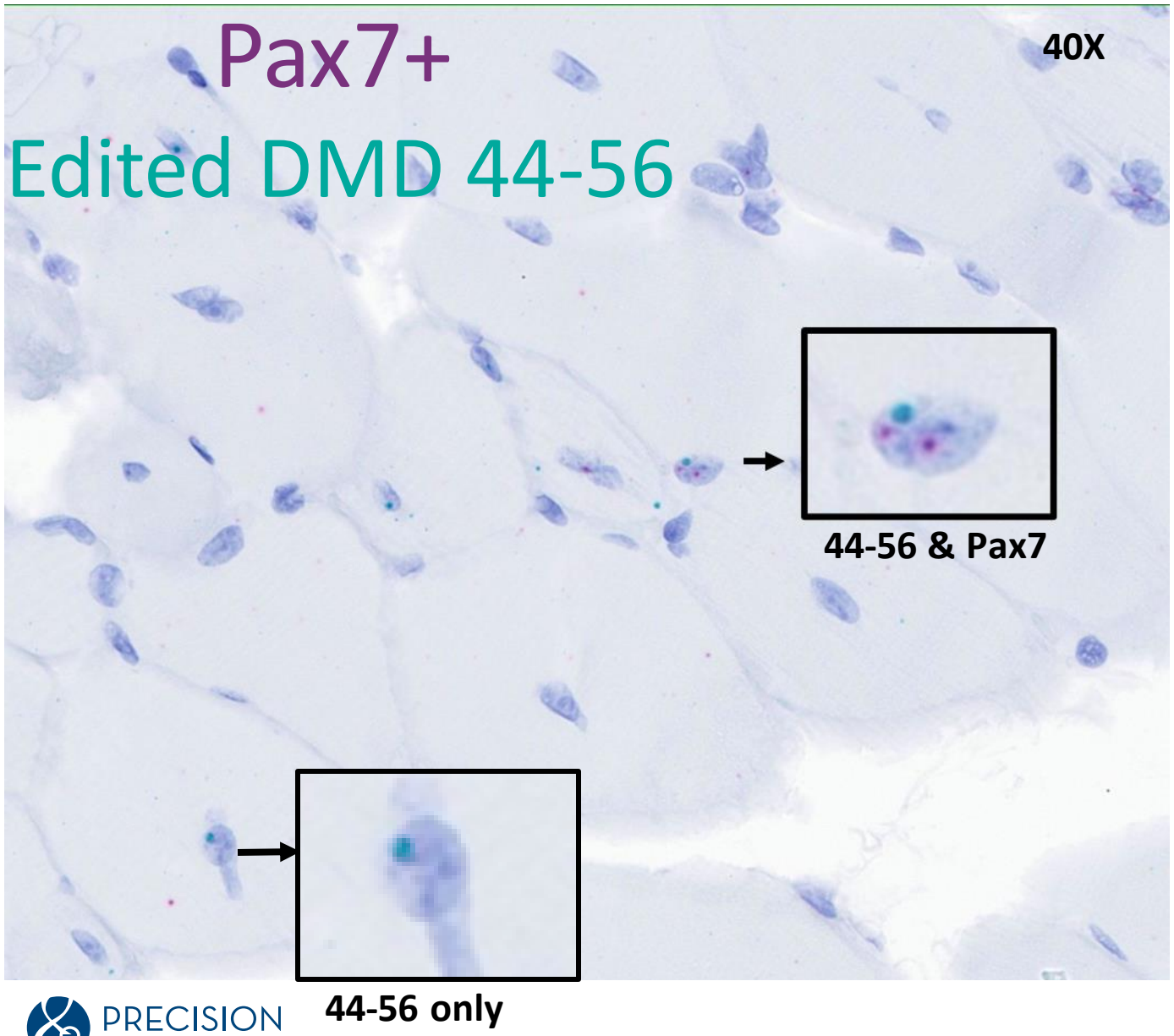
BaseScope™ Duplex Assay

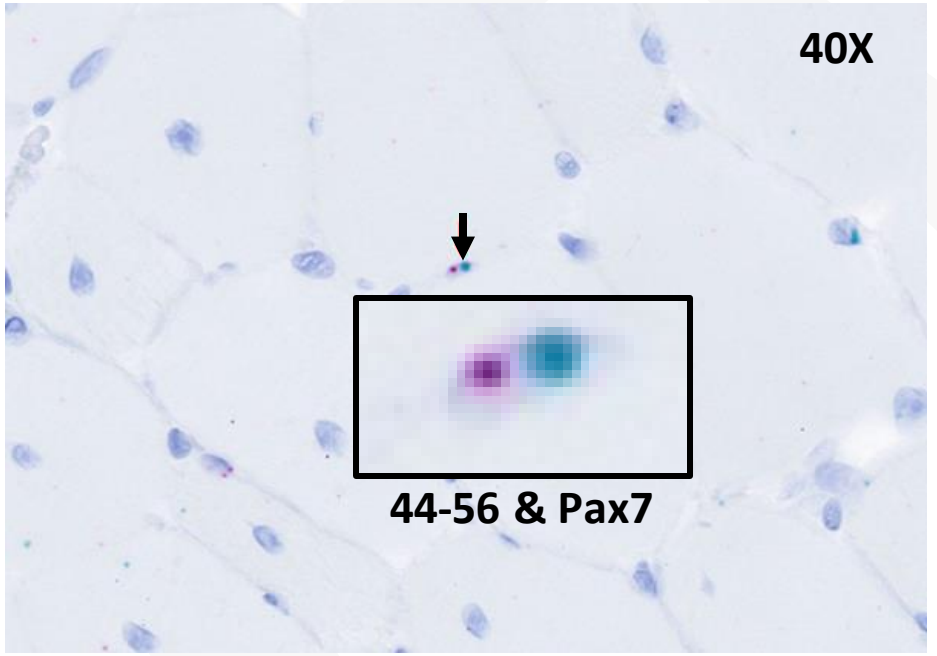


- BaseScope ™ Duplex Assay can be used for simultaneous visualization of two RNA targets while maintaining single cell resolution
- Detection of short RNA target sequences and exon junctions in cells and tissues with morphological context
- Highly specific and sensitive detection of RNA targets with discrimination at the single nucleotide level
- Utilized BaseScope™ with probes to detect the exon 44-56 splice edited message and Pax7 message, a marker of muscle stem cells (satellite cells)

Edited Dystrophin Transcript in PAX7+ cells, a Marker for Muscle Satellite Cells



- 44-56 Dystrophin mRNA splice edit by BaseScope
- Following AAV delivery, we observed evidence of the edited dystrophin transcript in PAX7+ cells, a marker for muscle satellite cells



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Conclusions

- Here, we report in vivo proof of concept of a dual **ARCUS** nuclease approach in a humanized DMD mouse model
- Following AAV delivery, we observed the edited dystrophin protein variant in multiple tissue types including heart, diaphragm, and skeletal muscle
- The maximum force output (MFO) of the gastrocnemius muscle in ARCUS-treated animals was significantly improved, reaching 86% of the MFO levels observed in non-diseased, control mice
- Dystrophin protein was restored to muscle fibers with evidence of the edited dystrophin transcript in $PAX7^{+}$ cells, a marker for muscle satellite cells
- This proof-of-concept study demonstrates therapeutic potential of an ARCUS gene editing approach for the treatment of DMD and supports ongoing development toward clinical candidate nomination

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