The mitochondria-targeting peptide elamipretide potentiates dystrophin expression induced by an exon-skipping morpholino in mdx mice

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Stealth BIOTHERAPEUTICS

Leading Mitochondrial Medicine

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Disclosures

- Dr. David A. Brown is a full-time employee of Stealth BioTherapeutics, which is publicly traded under the NASDAQ symbol “MITO”

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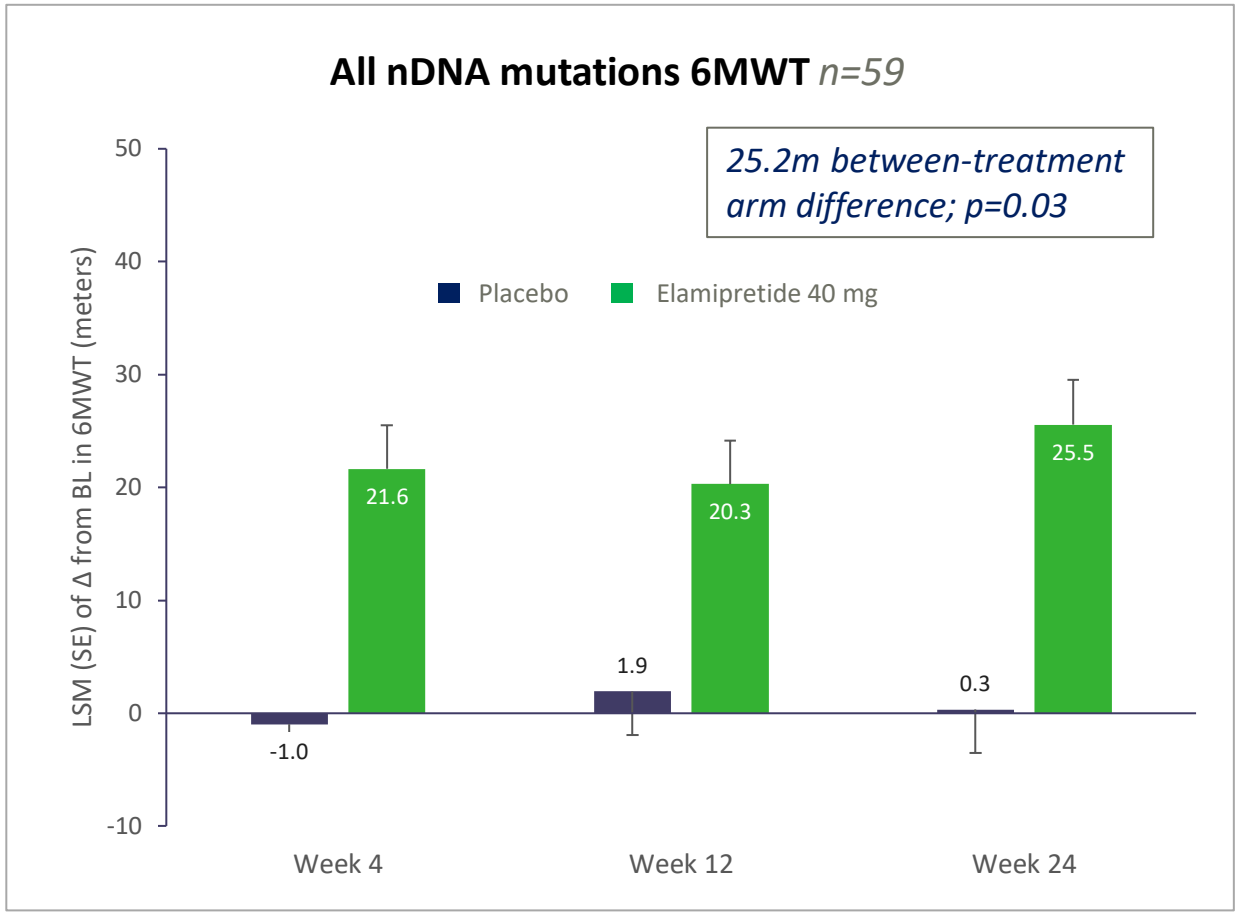
- This presentation contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Stealth BioTherapeutics' expectations for preclinical data in models of ophthalmic diseases and its clinical trial of elamipretide for GA associated with dry AMD. Statements that are not historical facts, including statements about Stealth BioTherapeutics' beliefs, plans and expectations, are forward-looking statements. The words "anticipate," "expect," "hope," "plan," "potential," "possible," "will," "believe," "estimate," "intend," "may," "predict," "project," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Stealth BioTherapeutics may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements as a result of known and unknown risks, uncertainties and other important factors, including: Stealth BioTherapeutics' ability to obtain additional funding and to continue as a going concern; the impact of the COVID-19 pandemic; the ability to successfully demonstrate the efficacy and safety of Stealth BioTherapeutics' product candidates and future product candidates; the preclinical and clinical results for Stealth BioTherapeutics' product candidates, which may not support further development and marketing approval; the potential advantages of Stealth BioTherapeutics' product candidates; the content and timing of decisions made by the FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies, which may affect the initiation, timing and progress of preclinical studies and clinical trials of Stealth BioTherapeutics product candidates; Stealth BioTherapeutics' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Stealth BioTherapeutics' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in the Stealth BioTherapeutics' most recent Annual Report on Form 20-F filed with the Securities and Exchange Commission ("SEC"), as well as in any future filings with the SEC. Forward-looking statements represent management's current expectations and are inherently uncertain. Except as required by law, Stealth BioTherapeutics does not undertake any obligation to update forward-looking statements made by us to reflect subsequent events or circumstances.

Leading Mitochondrial Medicine

- **Stealth BioTherapeutics:**
  - >**15 years** in development of mitochondrial targeted compounds
  - ~**20 Clinical trials** completed or in progress
  - >**500 publications** in partnership with **leading experts** in their respective fields
- **Mitochondrial Platform:**
  - Elamipretide (ELAM):rare cardiomyopathies, mitochondrial myopathy, geographic atrophy
  - Pipeline (SBT-272, SBT-550): neurology
- **Lead Compound ELAM:**
  - **>1,000** subjects dosed systemically
  - >**4 years** of exposure systemically

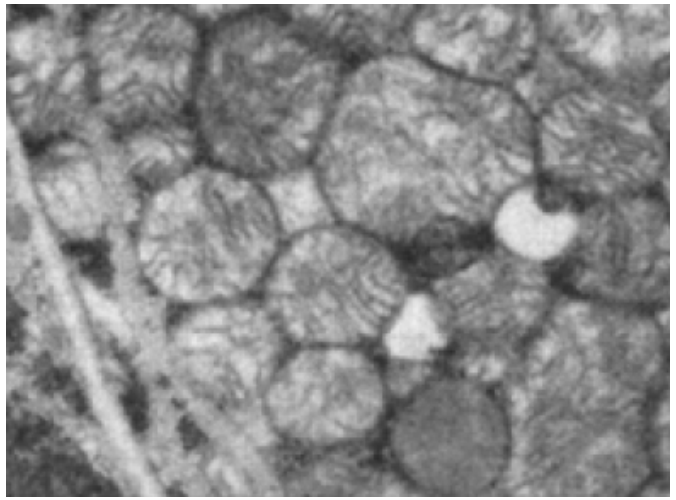
SPIMM-301 Primary Mitochondrial Myopathy
Change in 6MWT: nDNA Subgroup Analysis (pre-specified)



Karaa et al., *in review* 2022

Mitochondrial Dysfunction in Muscular Dystrophies

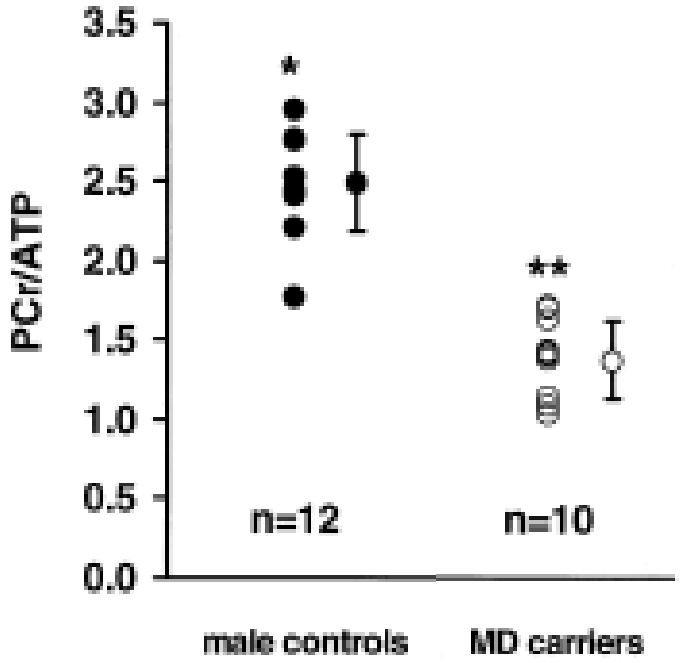
Electron microscopy of biopsied cardiac muscle in DMD Patient



6 year old boy, EF 58

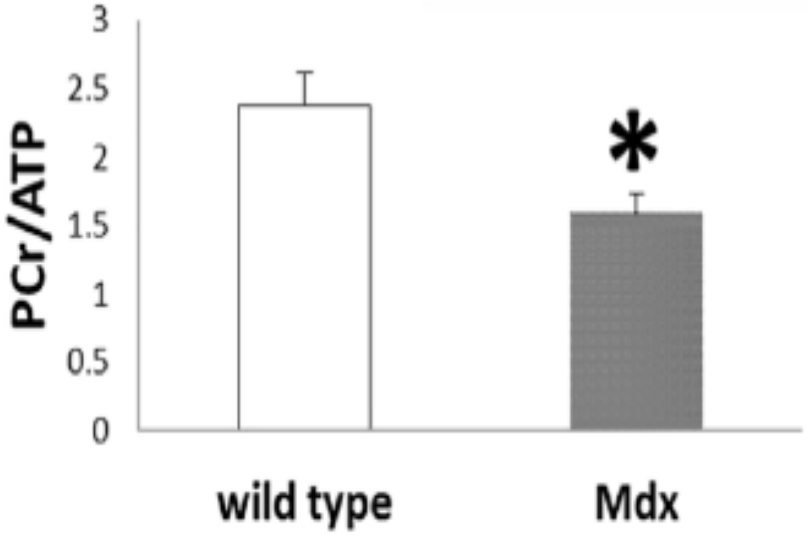
Wakai et al., *1988*

Human Heart



Adapted from Crilley et al., *JACC* 2000

Animal Models



Cui et al., *PLOS One* 2015

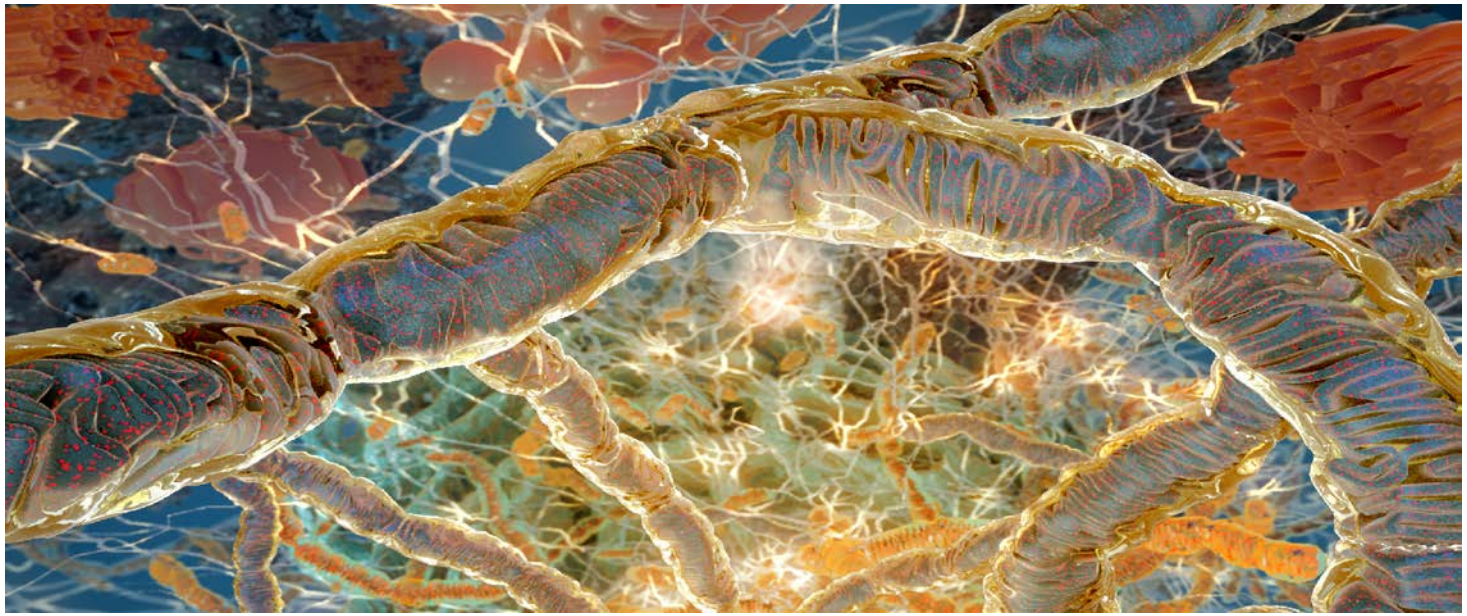
- In humans and animal models, impaired energetics *before* declines in muscle function
- Mitochondrial energy production is limited *early* in the disease process

Addressing Mitochondrial Dysfunction in DMD

Establishes energy (ATP) gradients

Buffers Calcium

Hone to site(s) of membrane injury



Oxidize metabolic substrates (demand)

Support in nascent phospholipid synthesis

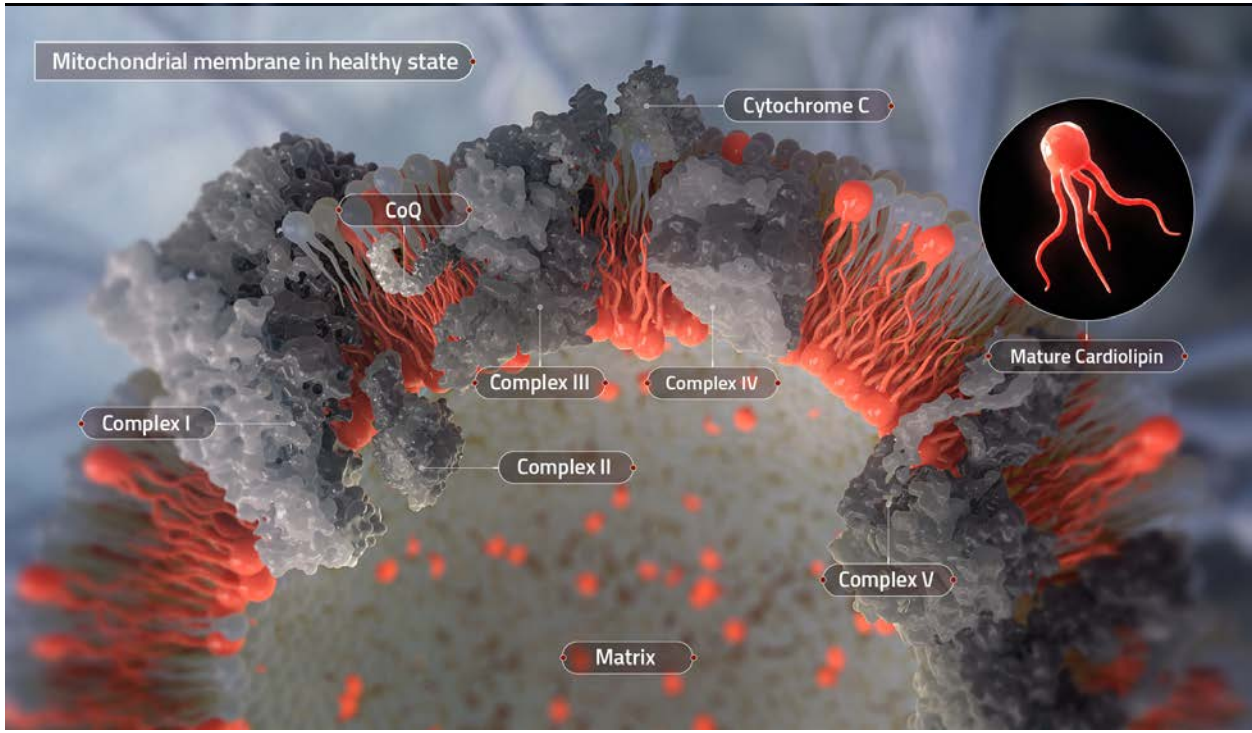
Influence inflammatory signaling

Guide cell fate decisions

Maintain redox/ROS balance

Elamipretide and Cardiolipin

- Cell-permeable mitochondria-targeting peptide, cytoprotective across scores of pre-clinical models
- Interacts with the inner mitochondrial membrane phospholipid *cardiolipin* to restore mitochondrial structure and function
- Reduction of mitochondrial ROS, improved mitochondrial ultrastructure, restoration of cellular bioenergetics (all known to be altered in DMD)



Cardiolipin: signature mitochondrial phospholipid that influences nearly every aspect of mitochondrial physiology

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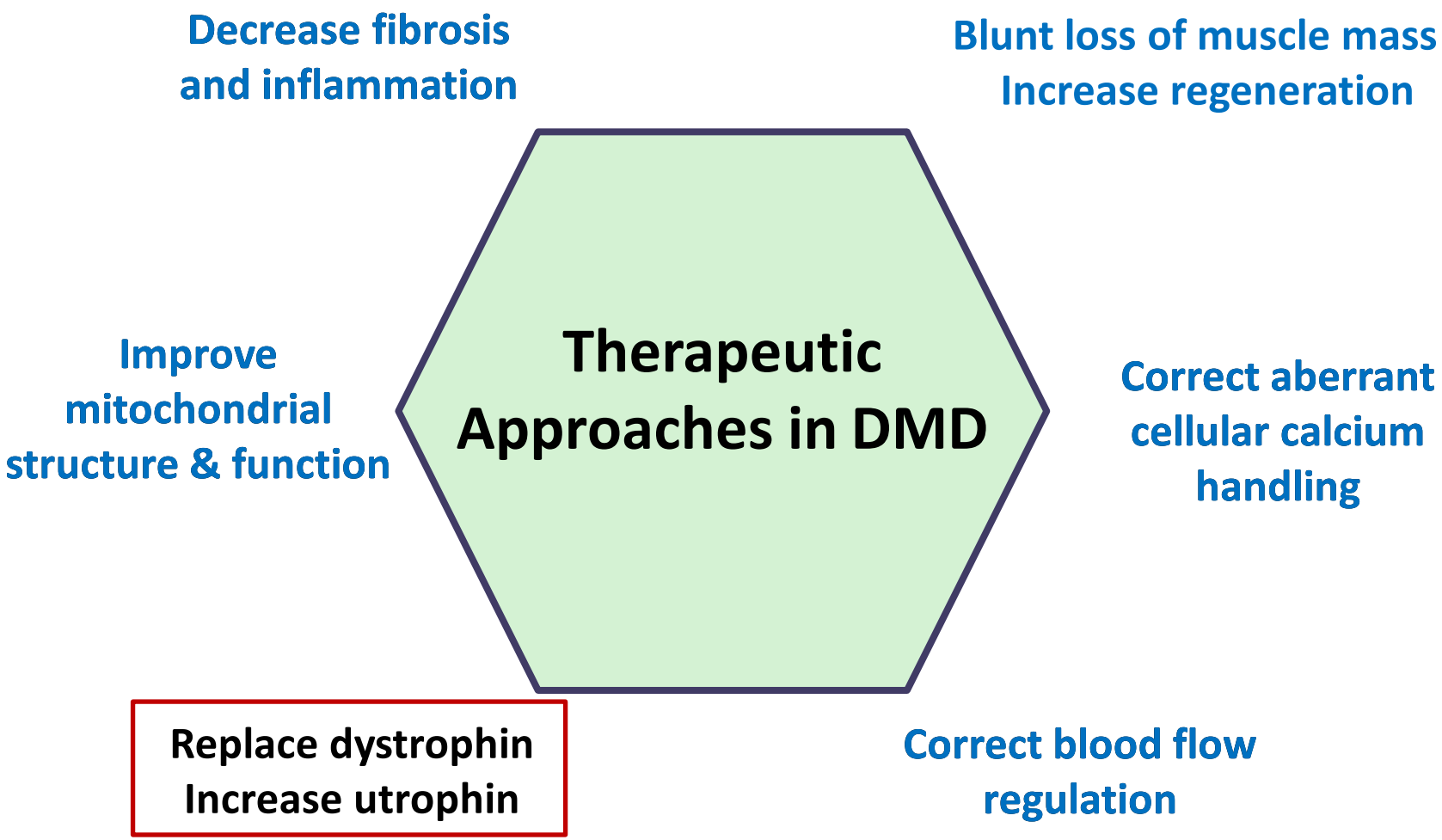
Elamipretide Potential in DMD

Blue font: Benefit with ELAM across pre-clinical models



Can elamipretide augment existing PMO therapies?

Improved PMO uptake, retention, efficacy by improving mitochondrial health?

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Elamipretide + PMO Study

Can a mitochondria-protecting peptide improve the efficacy of PMOs at restoring dystrophin?

Study Duration: 7 weeks

AGADA BIOSCIENCES

4-5 weeks of age → 11-12 weeks

WT (n=15)

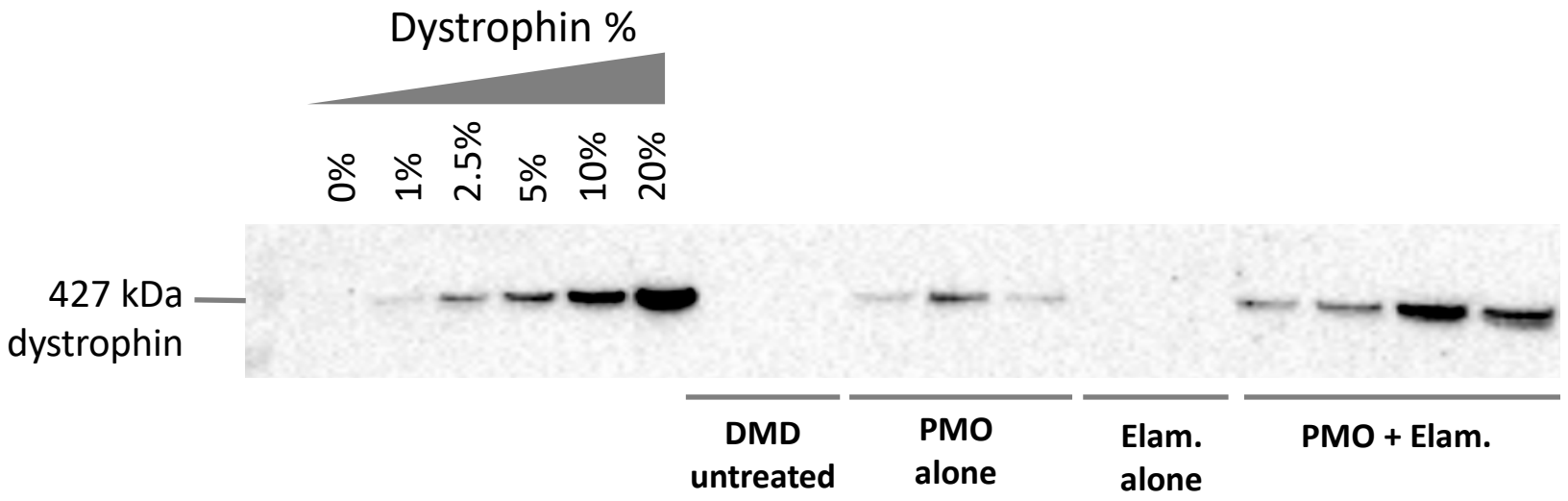
MDX mouse + saline (n=15)

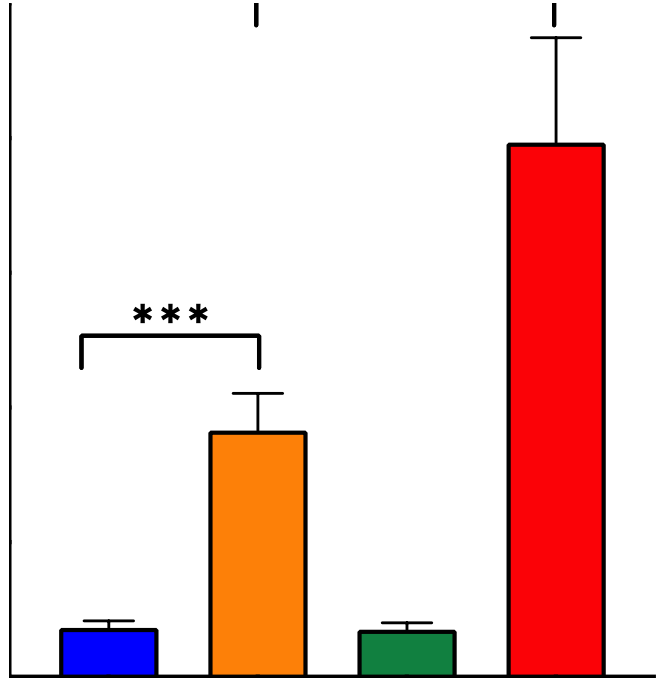
MDX mouse + PMO *125mg/kg/wk retro-orbital injection* **(n=15)**

MDX mouse + elamipretide *5mg/kg/day intraperitoneal* **(n=15)**

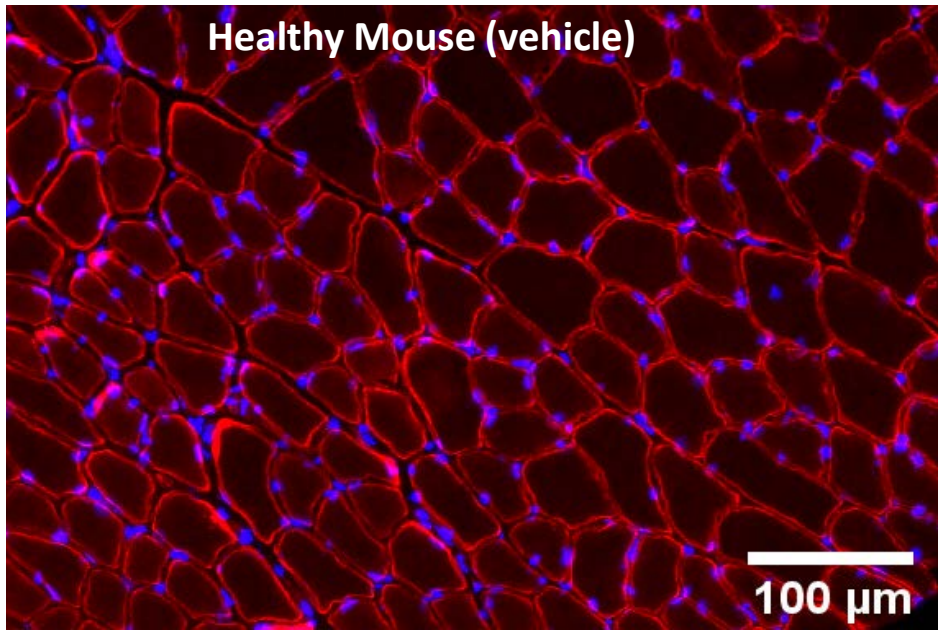
MDX mouse + PMO + elamipretide (n=15)

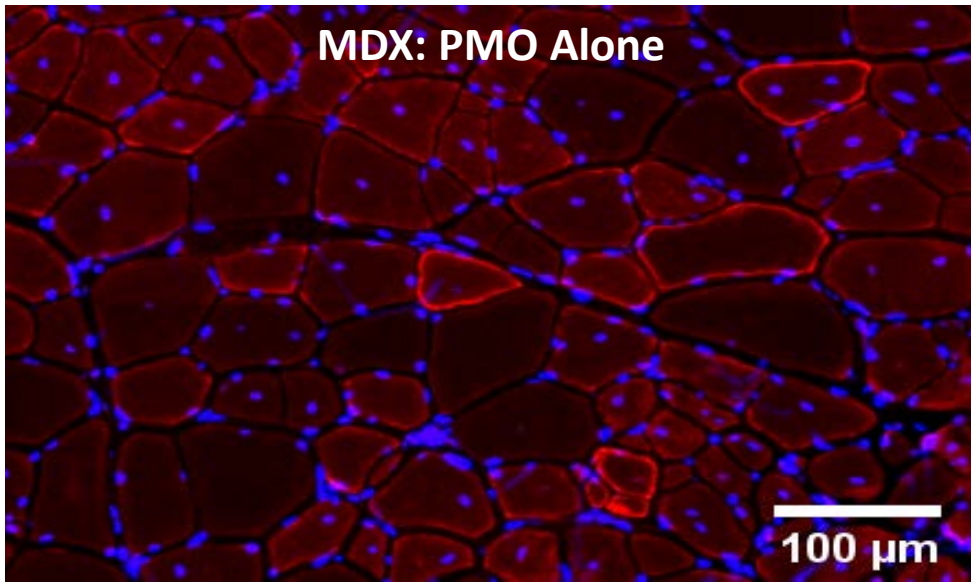
Elamipretide Augmented PMO-mediated Dystrophin Expression

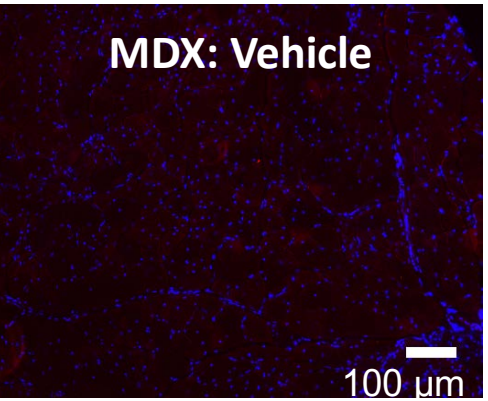


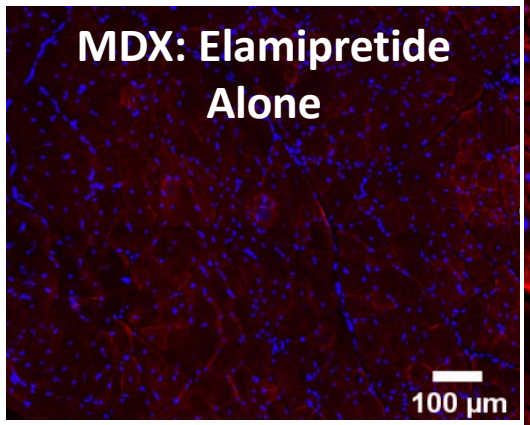


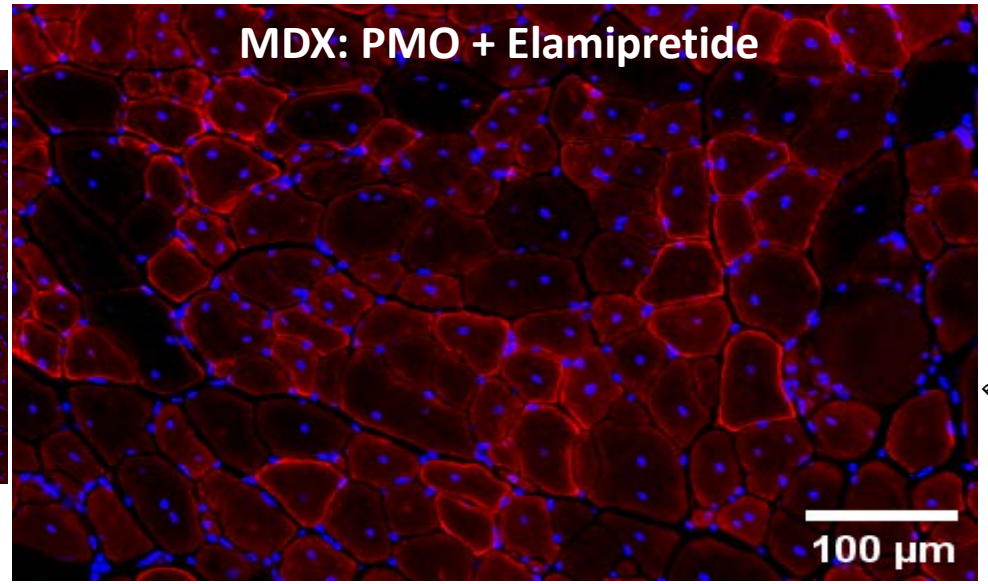
Dystrophin Expression: Immunofluorescence Studies

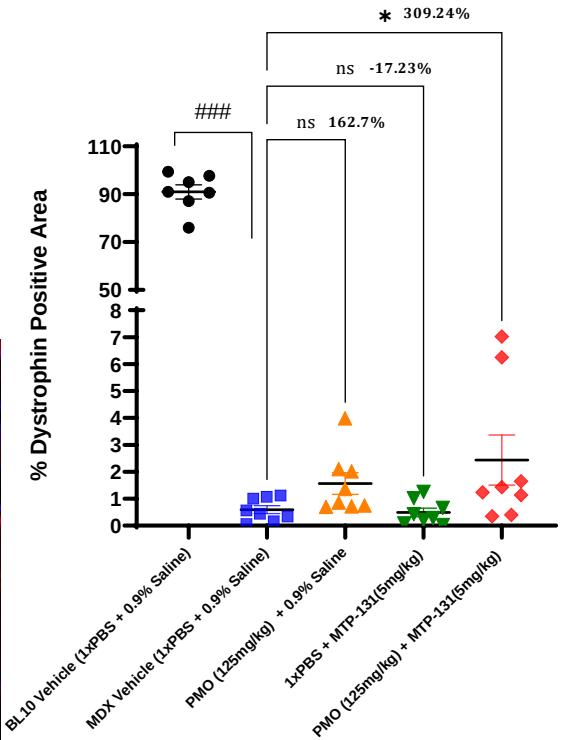












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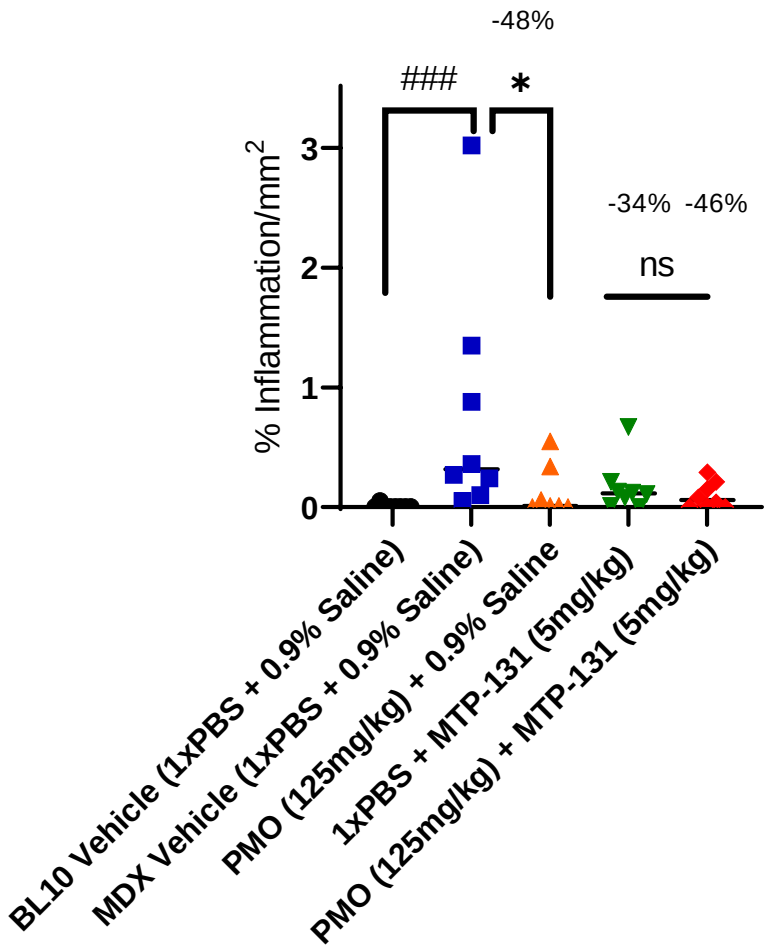
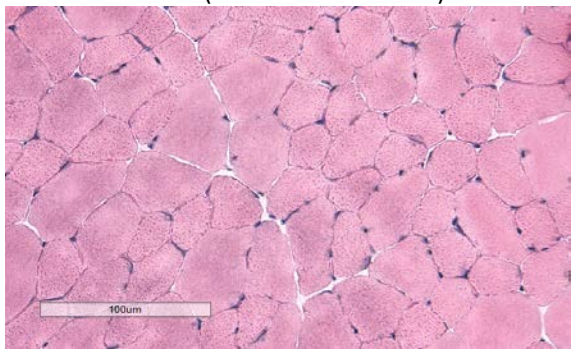
% Inflammation in TA Tissues

a)

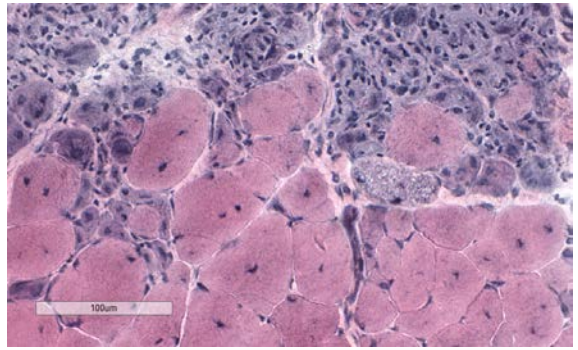


b)

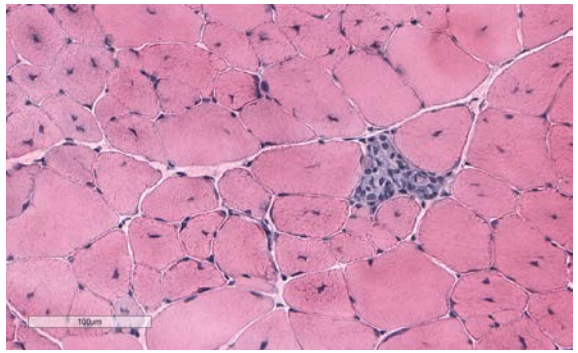
BL10 Vehicle (1xPBS + 0.9% Saline): ID 2797



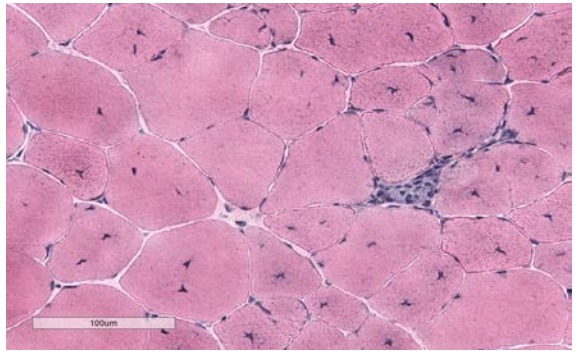
MDX Vehicle (1xPBS + 0.9% Saline): ID 2791



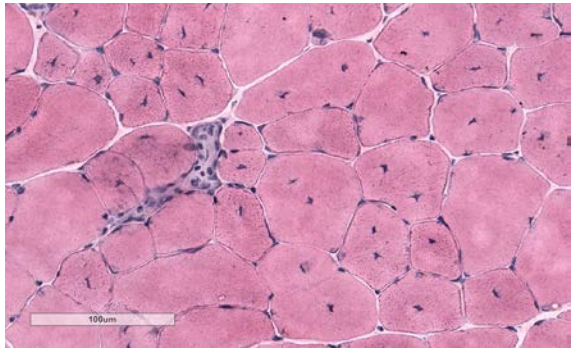
PMO (125 mg/kg) + 0.9% Saline: ID 2726



MTP-131 (5 mg/kg) + 1xPBS: ID 2744



PMO (125mg/kg) + MTP-131 (5mg/kg): ID 2734



Punchlines

- In mdx mice, elamipretide significantly increased dystrophin protein expression evoked by an exon-skipping PMO
  - Dystrophin levels more than doubled as assessed by Western blot and immunofluorescence
  - Trends to reduce inflammation in the mdx model

- Upcoming work:
  - Assessment of dystrophin in additional muscles
  - Mechanistic insights involved in the synergistic effect
  - Additional insights into timing of elamipretide and PMO for efficacy

- Continued exploration of the cardioprotective effect of elamipretide in DMD cardiomyopathy

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- Stealth BioTherapeutics Team

Discussion