Antibody-Oligonucleotide Conjugates (AOCs) Demonstrate Potent and Durable Exon Skipping and Dystrophin Restoration in a Mouse Model of Duchenne Muscular Dystrophy

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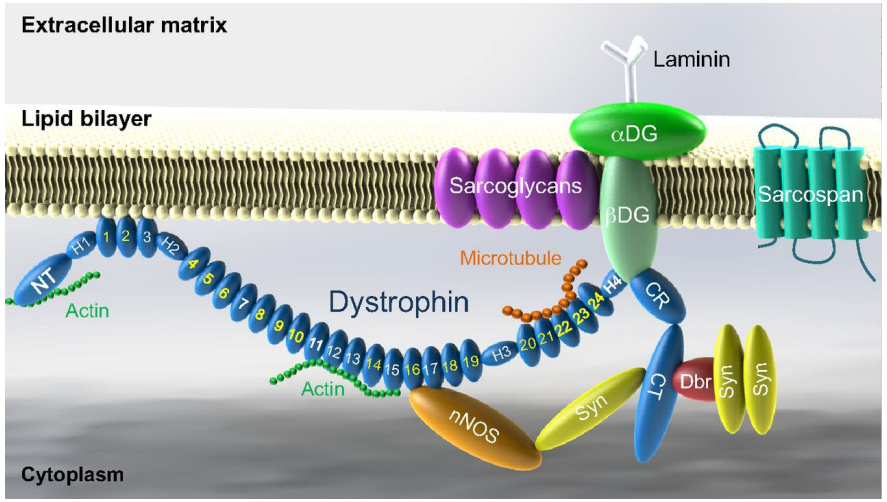
DISCLOSURES:

- Dr. Karamanlidis is an employee of Avidity Biosciences
- He has received stock or an ownership interest from Avidity Biosciences

DMD is a Rare and Severe Genetic Disorder With Unmet Medical Need

- DMD is an X-linked neuromuscular disorder that affects ~1:5,000 male births, equivalent to ~300,000 worldwide[1,2]
- Progressive muscle degeneration, wasting, and paralysis generally leads to death via respiratory and/or cardiac failure in the third-to-fourth decade of life[3]
- DMD is caused by no-to-minimal production of dystrophin protein due to frameshift mutations in the *DMD* gene; one or more missing exons[4]

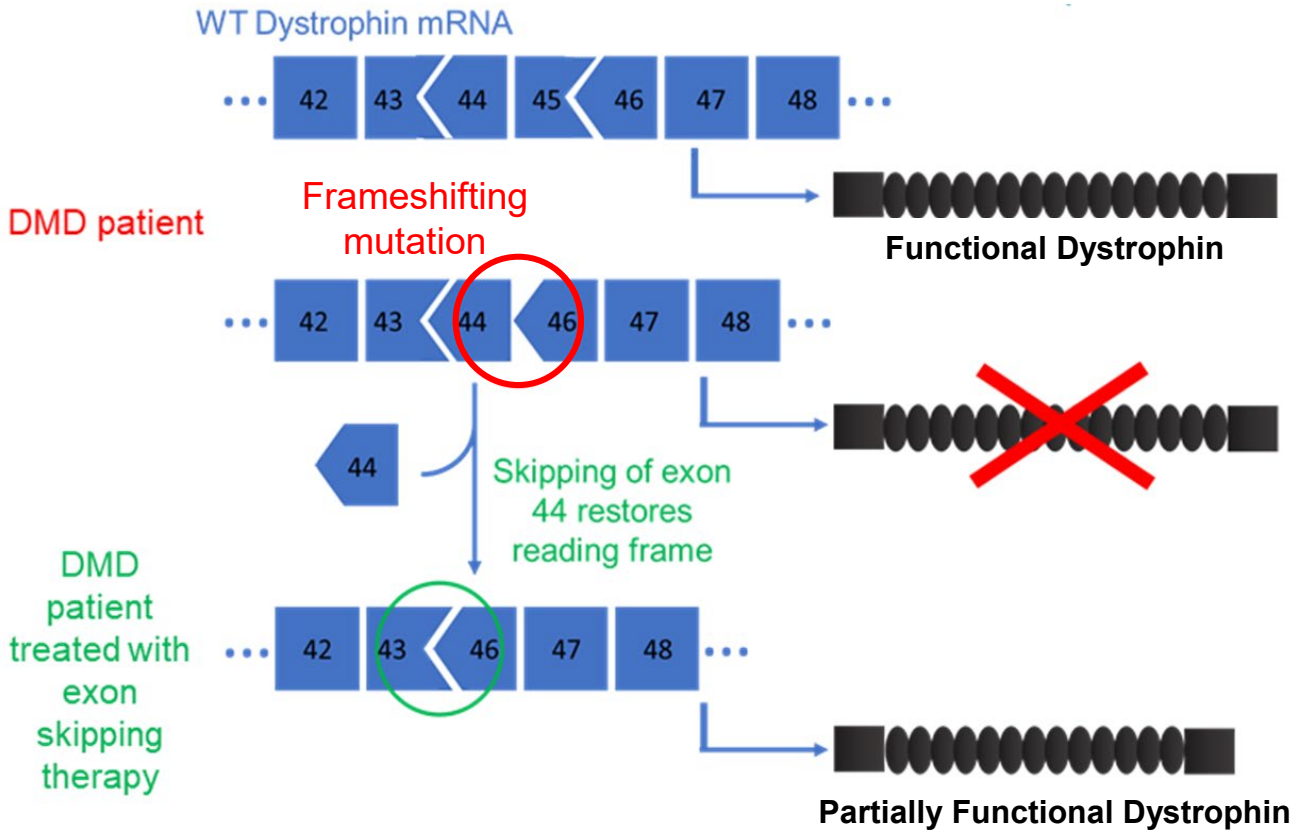


DMD, Duchenne muscular dystrophy.

1. Bushby K, et al. *Lancet Neurol*. 2010;9(1):77–93; 2. Parad RB, et al. *Int J neonatal Screen.* 2021;7(4):77;
3. Koeks Z, et al. *J Neuromuscul* Dis. 2017;4(4):293–306; 4. de los Angeles Beytía M, et al. *Acta Myol*. 2012;31(1):4–8;
5. CureDuchenne™. What is Duchenne? https://www.cureduchenne.org/about/what-is-duchenne/ [Last accessed March 2022].

Restoration of Dystrophin Protein by Oligonucleotide-Mediated Exon Skipping

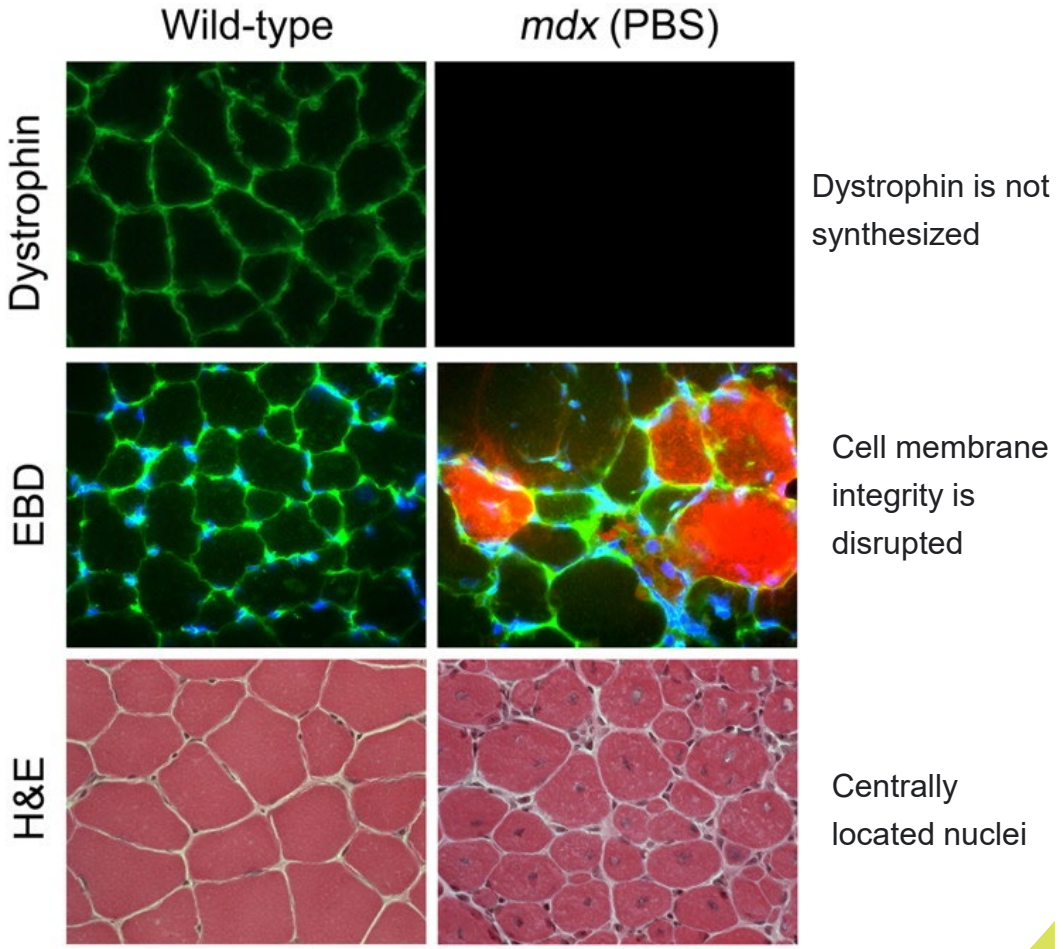
Example of exon 44 skipping in DMD patients with Δ45



DMD, Duchenne muscular dystrophy; mRNA, messenger ribonucleic acid; WT, wild type.
Aartsma-Rus A, et al. *BMC Medical Genetics*. 2007;8(43);2.

The *mdx* Mouse is the Most Widely Used Animal Model for DMD Research

The *mdx* mouse has a stop codon mutation in exon 23 on the DMD gene that disrupts full-length dystrophin expression

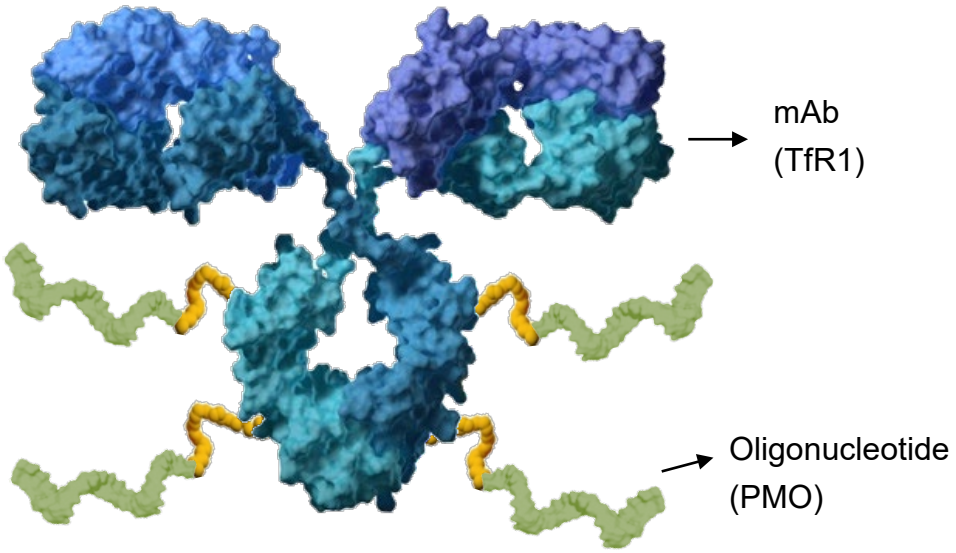


DMD, Duchenne muscular dystrophy; EBD, Evans blue dye; H&E, hematoxylin and eosin; PBS, phosphate buffered saline.

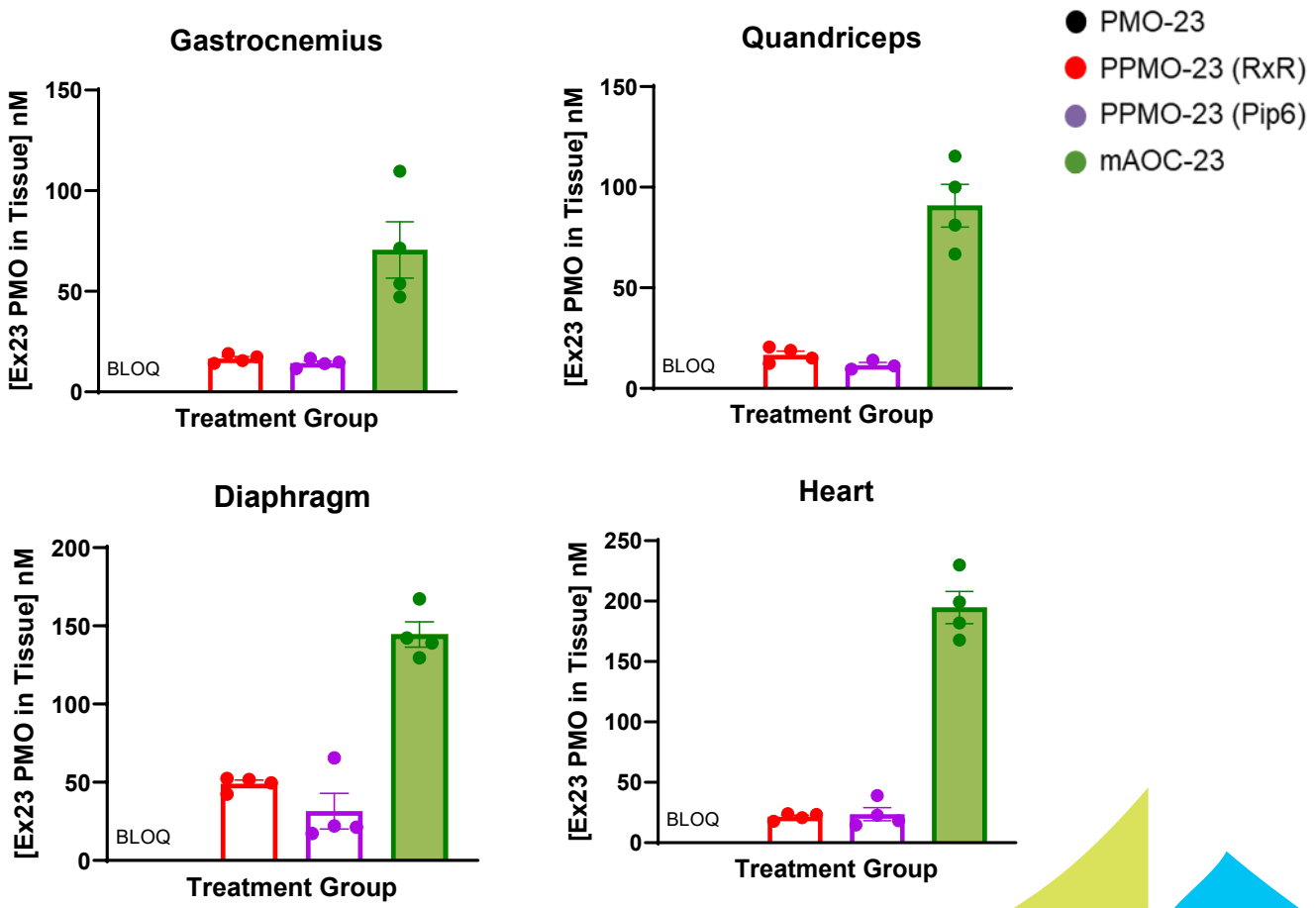
1. Mann CJ, et al. *Proc Natl Acad Sci U S* A. 2001;98(1):42–7; 2. Rooney JE, et al. *Proc Natl Acad Sci U S A*. 2009;106(19):7991–6.

AOCs: A Powerful New Class of Drugs That Efficiently Delivers Oligonucleotides to Striated Muscle

Antibody–Oligonucleotide Conjugate (AOC)



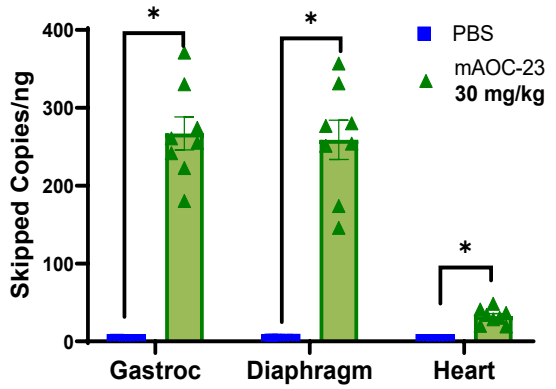
Tissue uptake in *mdx* mice treated with 5 mg/kg PMO



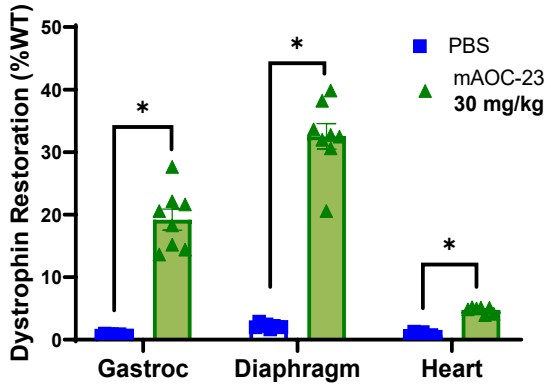
AOC, antibody–oligonucleotide conjugate; BLOQ, below limit of quantification; mAb, monoclonal antibody; PMO, phosphorodiamidate morpholino oligomer; PPMO, peptide-conjugated PMO; RxR, peptide sequence (RXR)4XB; TfR1, transferrin receptor 1.

mAOC-23 Treatment Produces Dose-Dependent and Long-Lasting Dystrophin Restoration in *mdx* Mice

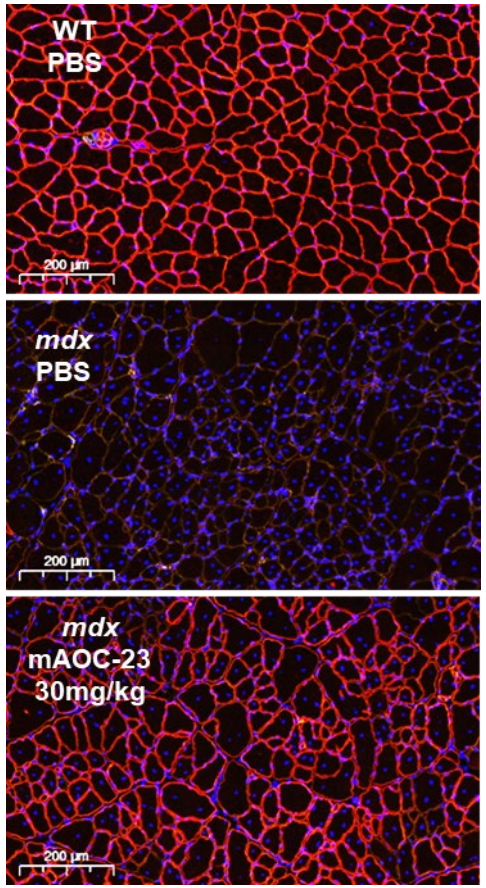
Exon 23 Skipping (RNA)
28 Days Post Dose (*mdx* Mice)



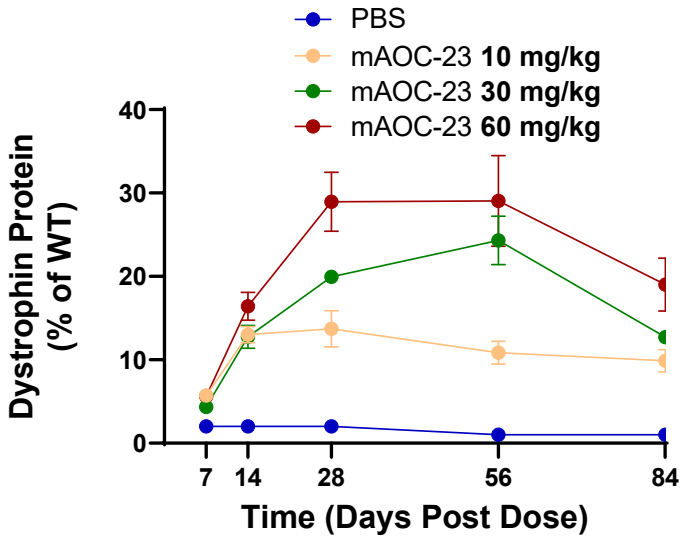
Dystrophin Protein Restoration
28 Days Post Dose (*mdx* Mice)



Homogeneous Dystrophin (Red) Restoration in a Quadriceps Cross-Section (28 Days Post Dose)



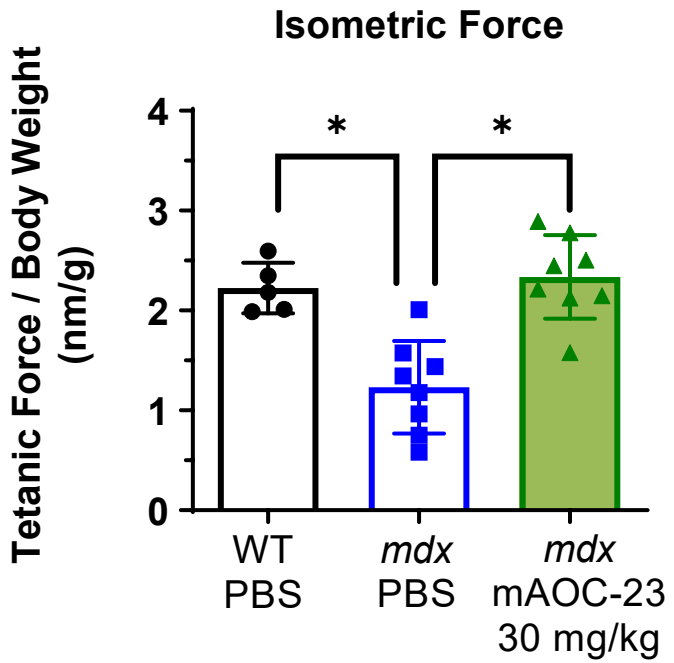
Dystrophin Protein Restoration in *mdx* Mice (Gastrocnemius)

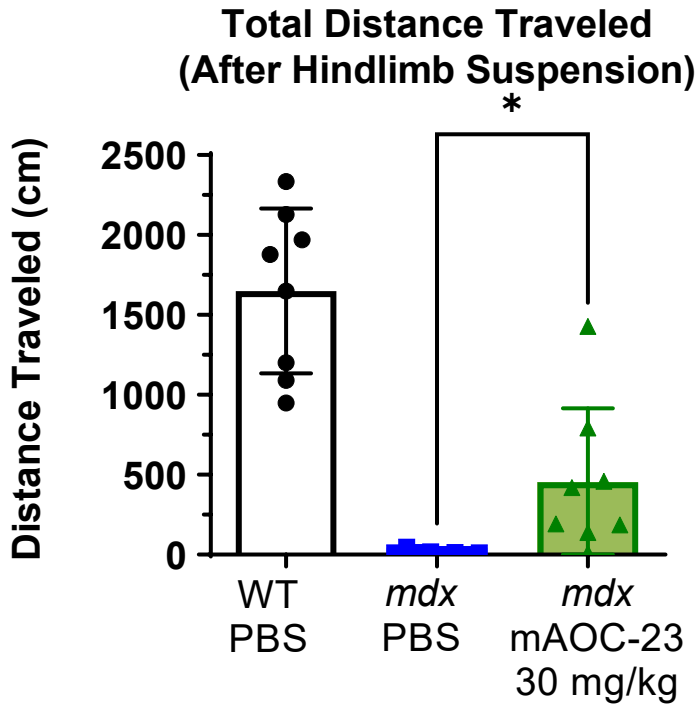


*$p<0.05$
AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; RNA, ribonucleic acid; WT, wild type.

mAOC-23 Improved Muscle Function in *mdx* Mice

mdx mice treated with a single dose of mAOC-23 show functional improvement *in vivo* (28 days post dose)





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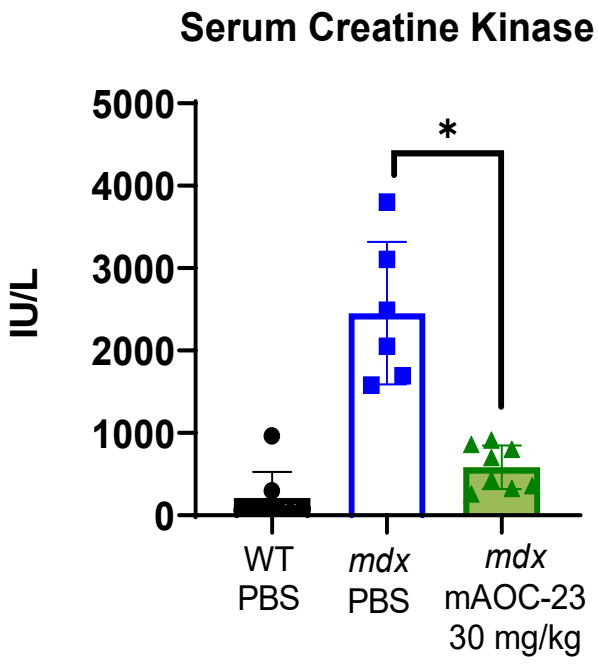
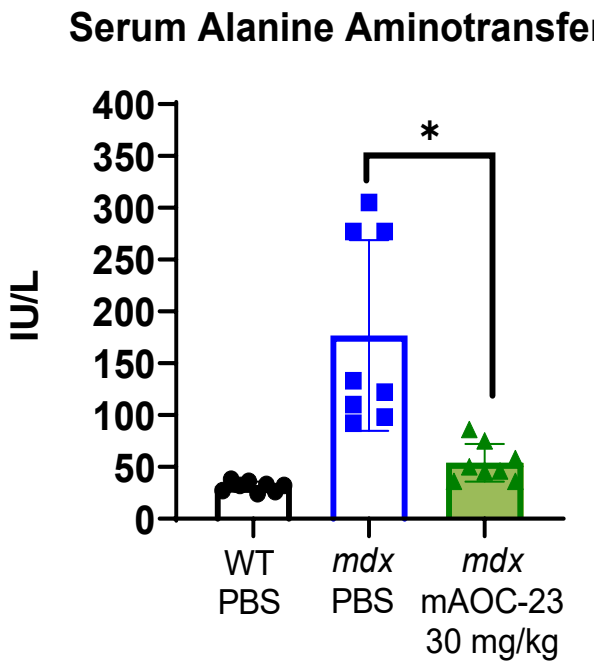
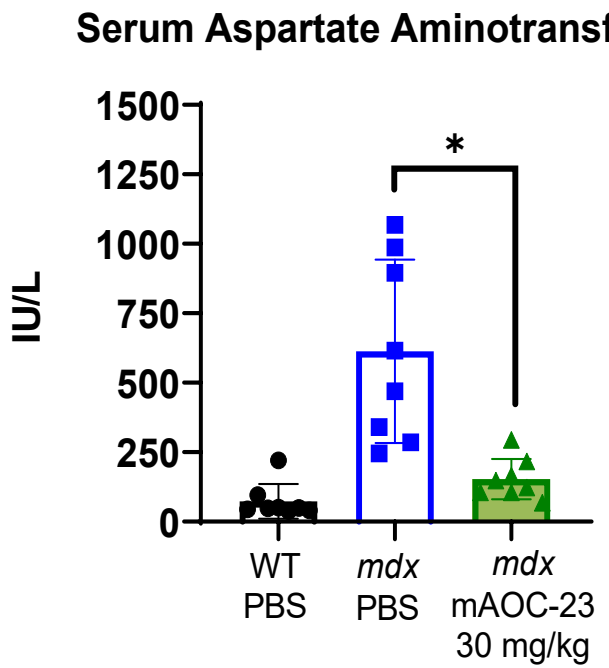
AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; WT, wild type.

mAOC-23 Improved Serum Biomarkers of Muscle Damage in *mdx* Mice, in Addition to Muscle Function







*$p<0.05$
AOC, antibody–oligonucleotide conjugate; PBS, phosphate buffered saline; WT, wild type.

Antibody–Oligonucleotide Conjugates Have the Potential to be Promising Therapeutics for DMD

- AOC technology effectively delivers RNA therapeutics to muscle and heart tissues, primary tissues impacted by DMD
- In a mouse model of DMD, a surrogate AOC demonstrated exon skipping, restoration of dystrophin protein, and subsequent improvement in muscle function
  - The pharmacologic activity was long lasting following a single dose, suggesting the potential for infrequent dose regimens
  - These data support the development of Avidity's three AOC programs in DMD
- Avidity is advancing AOC 1044 targeting exon 44 skipping for the potential treatment of DMD, which is anticipated to be in the clinic by the end of 2022

AOC, antibody–oligonucleotide conjugate; DMD, Duchenne muscular dystrophy; RNA, ribonucleic acid.

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