AOC 1020: An Antibody Oligonucleotide Conjugate (AOC) in Development for the Treatment of FSHD

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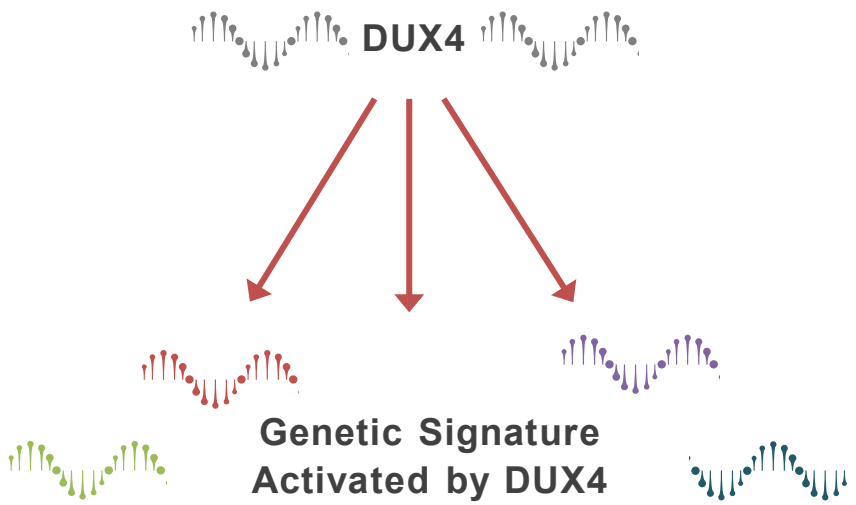
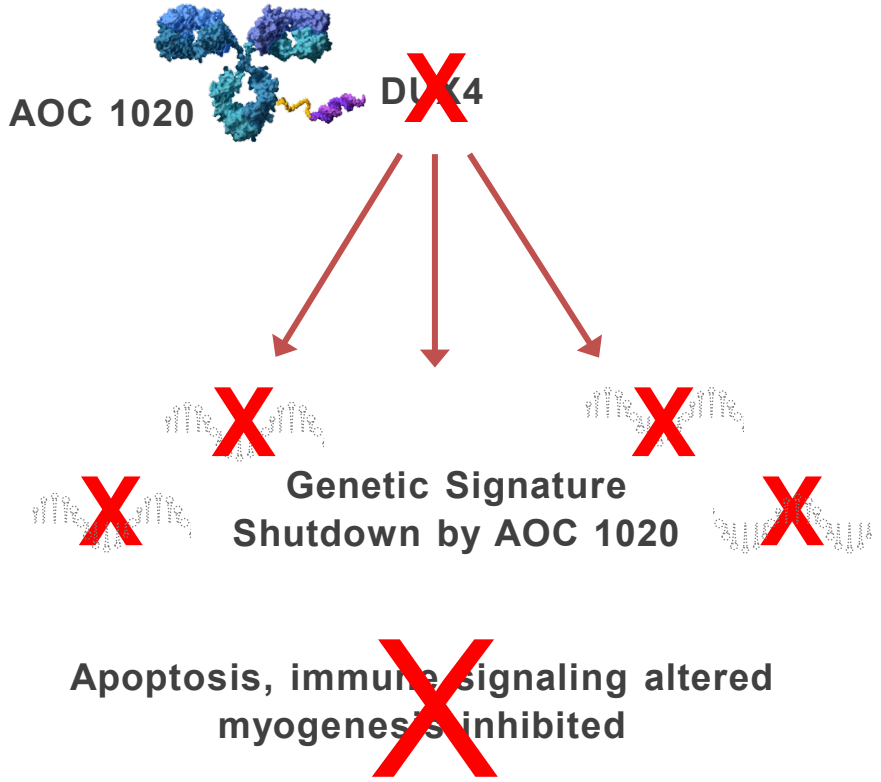
FSHD is Caused by Aberrant Expression of DUX4 in Muscle

DUX4 activates genes that are toxic to muscle cells

MECHANISM OF DISEASE[1,2]



THERAPEUTIC APPROACH[3,4]



1. Lemmers RJLF, et al. *Science.* 2010;329(5999):1650–1653; 2. Snider L, et al. *PLoS Genet*. 2010;6(10):e1001181;
3. Ansseau E, et al. *Genes (Basel)*. 2017;8(3):93; 4. Jiang S, et al. *PLoS Genet*. 2020;16(5):e1008754.

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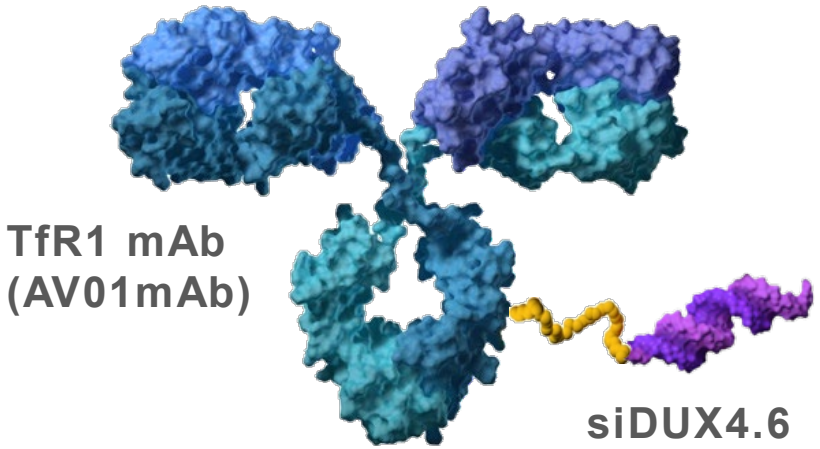
Avidity's AOC 1020 Targets DUX4 mRNA for Degradation and Eliminates the Cause of FSHD

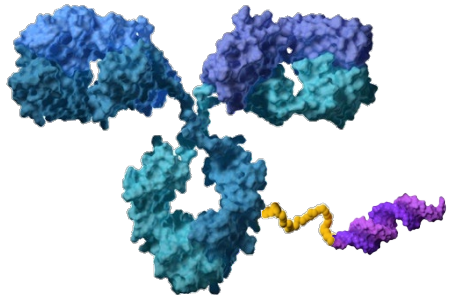
AOC 1020 - ANTIBODY OLIGONUCLEOTIDE CONJUGATE



- AOCs represent a new class of therapeutics allowing delivery of oligonucleotides to target tissues
- Avidity's AOCs combine proven technologies of monoclonal antibodies and oligonucleotides
  - Specificity of targeting
  - Potency & precision of oligonucleotides
  - Targets tissues with potent and durable agents
- We optimized each of component of AOCs and engineered the molecules to maximize activity, durability, and safety
  - **TfR1 mAb:** monoclonal antibody directed to human transferrin receptor 1 (TfR1), optimized through engineering to be effector function null, epitope selection for optimal activity, highly efficient delivery to muscle
  - **Linker:** non-cleavable, enhanced for safety and durability, optimized ratio of oligonucleotides to antibodies
  - **siDUX4.6:** DUX4 mRNA targeting siRNA; engineered and stabilized to withstand lysosomal enzymes, selected for potency and specificity and modified to diminish off-target effects

Development of AOC 1020 as a Potent and Specific Inhibitor of DUX4 Expression

AOC 1020



Transferrin receptor 1 mAb

Screen DUX4 siRNAs in FSHD donor cells using gene signature

Off-target analysis by RNA-seq

Select potent siRNAs with minimal off-target profile

Target candidate profile met

Evaluate in FSHD mouse model & GLP studies

COMPLETED

ONGOING

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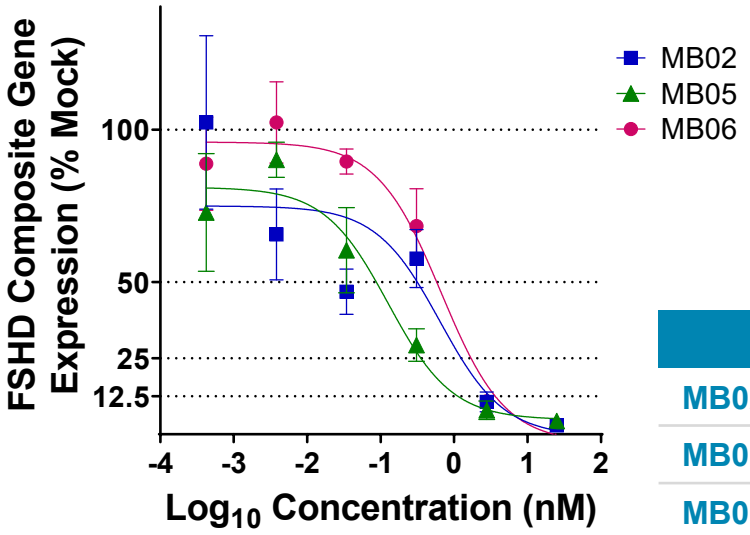
Lead siRNA Sequence siDUX4.6 Inhibits DUX4-Regulated Genes in FSHD Patient-Derived Muscle Cells

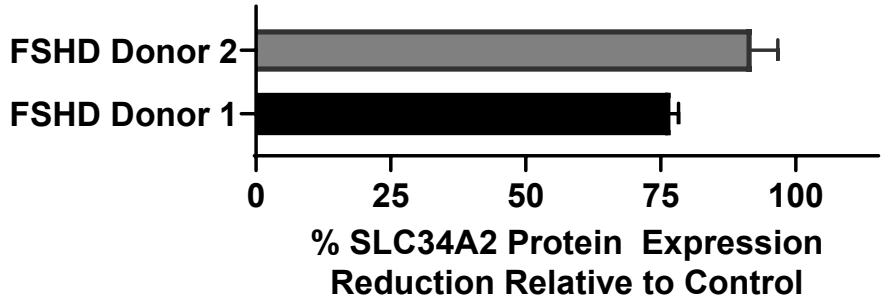
Sub-Nanomolar Potency of the siDUX4.6 Sequence *In Vitro* in FSHD Primary Patient-Derived Myotubes



	IC_{50} (nM)	E_{max} (%)
MB02	0.639	100
MB05	0.127	95
MB06	0.665	100

N=4; mean ± SEM

siDUX4.6 Sequence Inhibits SLC34A2 Protein Expression by >75% in FSHD Donor Myotubes



N=4; mean ± SEM

- Robust downregulation of DUX4-regulated genes was observed with the lead siDUX4.6 siRNAs in FSHD donor myotubes *in vitro*
- FSHD Composite is a mean expression of DUX4-regulated genes KHDC1L, LEUTX, MBD3L2, ZSCAN4

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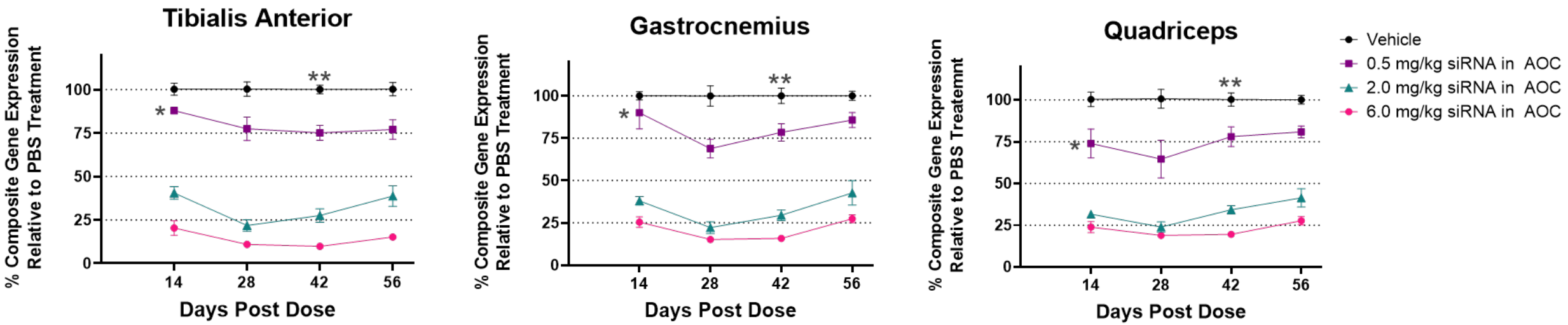
siDUX4.6 Shows Potent Inhibition of DUX4-Regulated Genes in Transgenic Mouse Model of FSHD for 8 Weeks

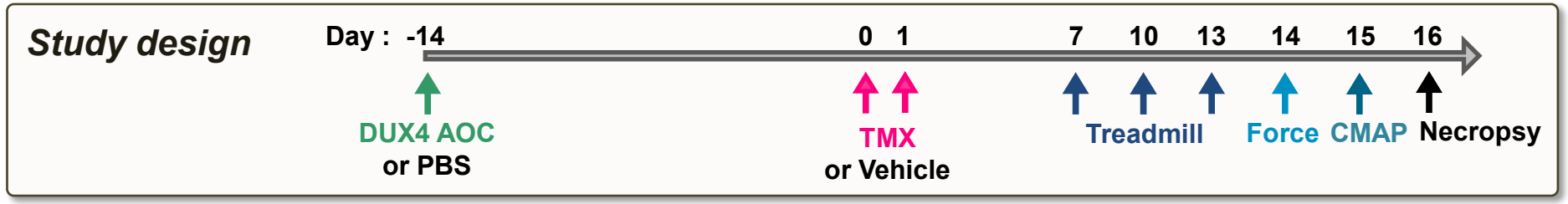
Dose-dependent inhibition of DUX4-regulated genes in skeletal muscles



ACTA1-MCM; FLExDUX4 mouse model of FSHD
N = 5 (*N=3; **N=4); mean ± SEM

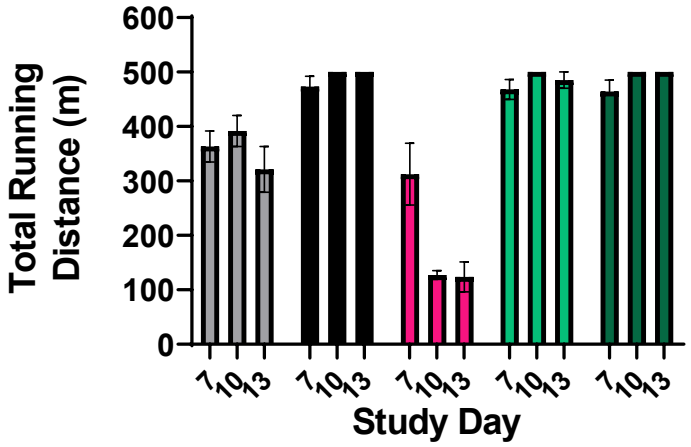
- The siRNA clinical candidate siDUX4.6 demonstrated activity *in vivo* towards the human DUX4 mRNA, measured by downregulation of DUX4-regulated mouse genes Wfdc3, Ilvbl, Slc15a2, Sord.
- Approximately a 75% reduction in DUX4 responsive genes was induced after a single systemic IV administration of 6 mg/kg of siRNA within the AOC (mTfR1-siDUX4.6)

Single Intravenous Treatment with DUX4 AOC Prevents Disease Phenotype Development in FSHD Mouse Model

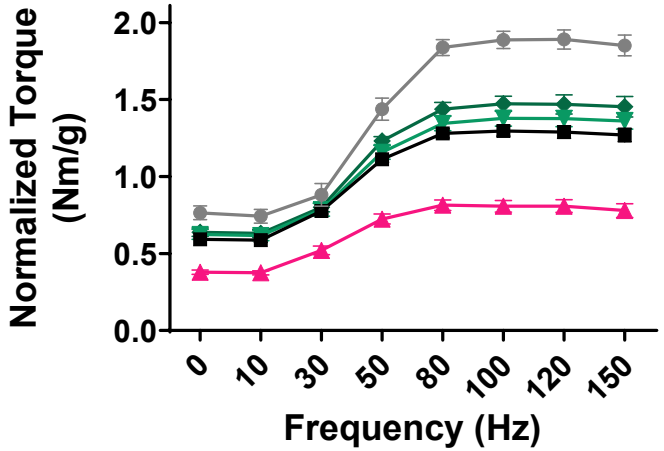


N = 9-12; males;
mean ± SEM

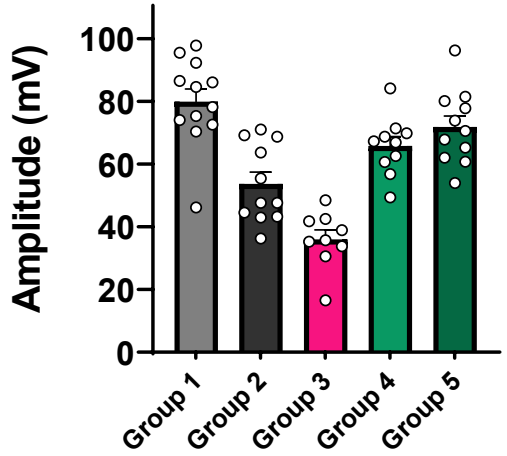
Treadmill Running



In Vivo Force



Compound Muscle Action Potential



1: ACTA1-MCM, VEH, PBS
2: ACTA1-MCM; FLExDUX4, VEH, PBS
3: ACTA1-MCM; FLExDUX4, TMX, PBS
4: ACTA1-MCM; FLExDUX4, TMX, DUX4 AOC 2 mg/kg (siRNA)
5: ACTA1-MCM; FLExDUX4, TMX, DUX4 AOC 8 mg/kg (siRNA)

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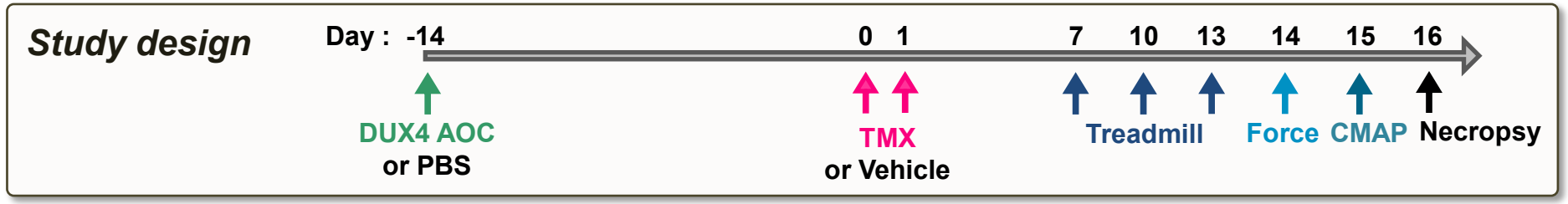
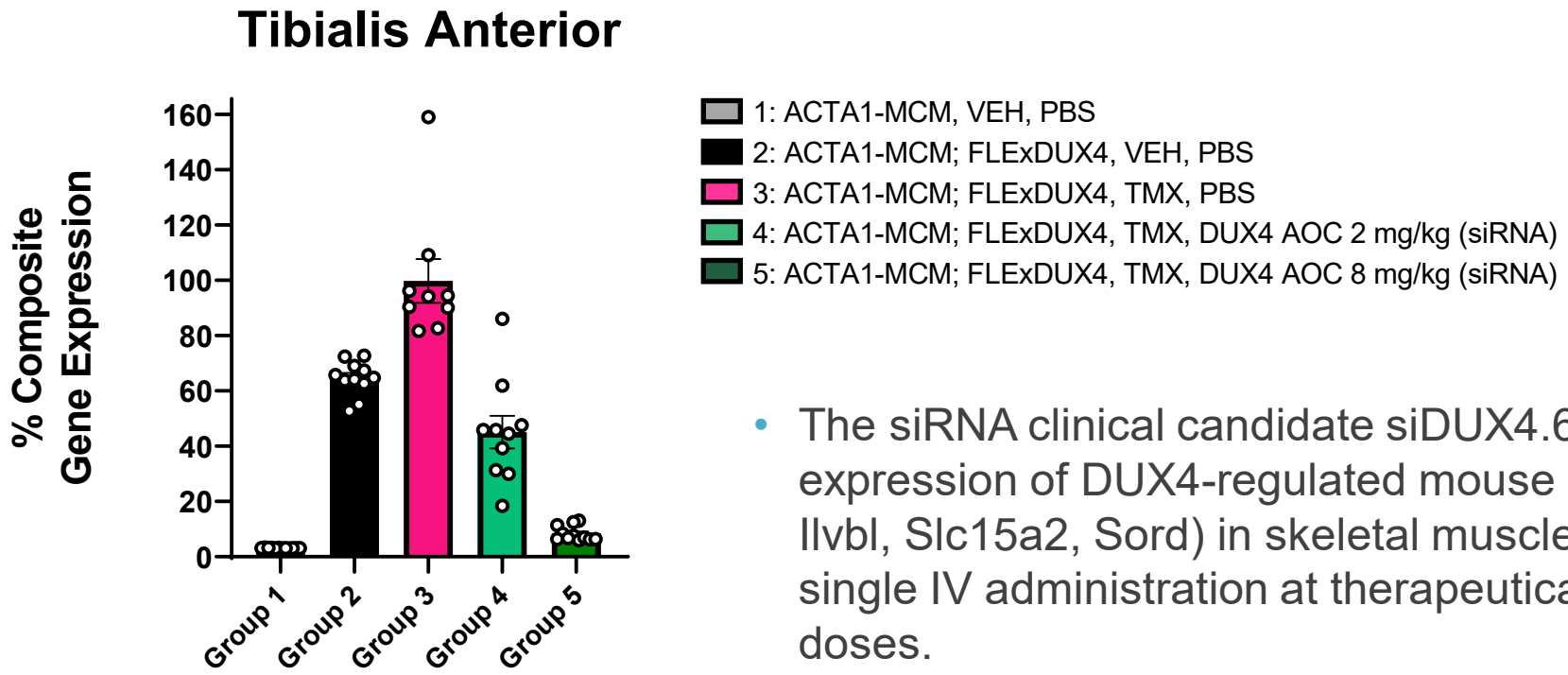
Single Dose of DUX4 AOC Inhibits DUX4-Regulated Gene Expression in Muscle of Tamoxifen-Induced FSHD Mouse Model



N = 9-12; males;
mean ± SEM



- The siRNA clinical candidate siDUX4.6 robustly inhibits expression of DUX4-regulated mouse genes (Wfdc3, Ilvbl, Slc15a2, Sord) in skeletal muscle 1 month after single IV administration at therapeutically relevant doses.

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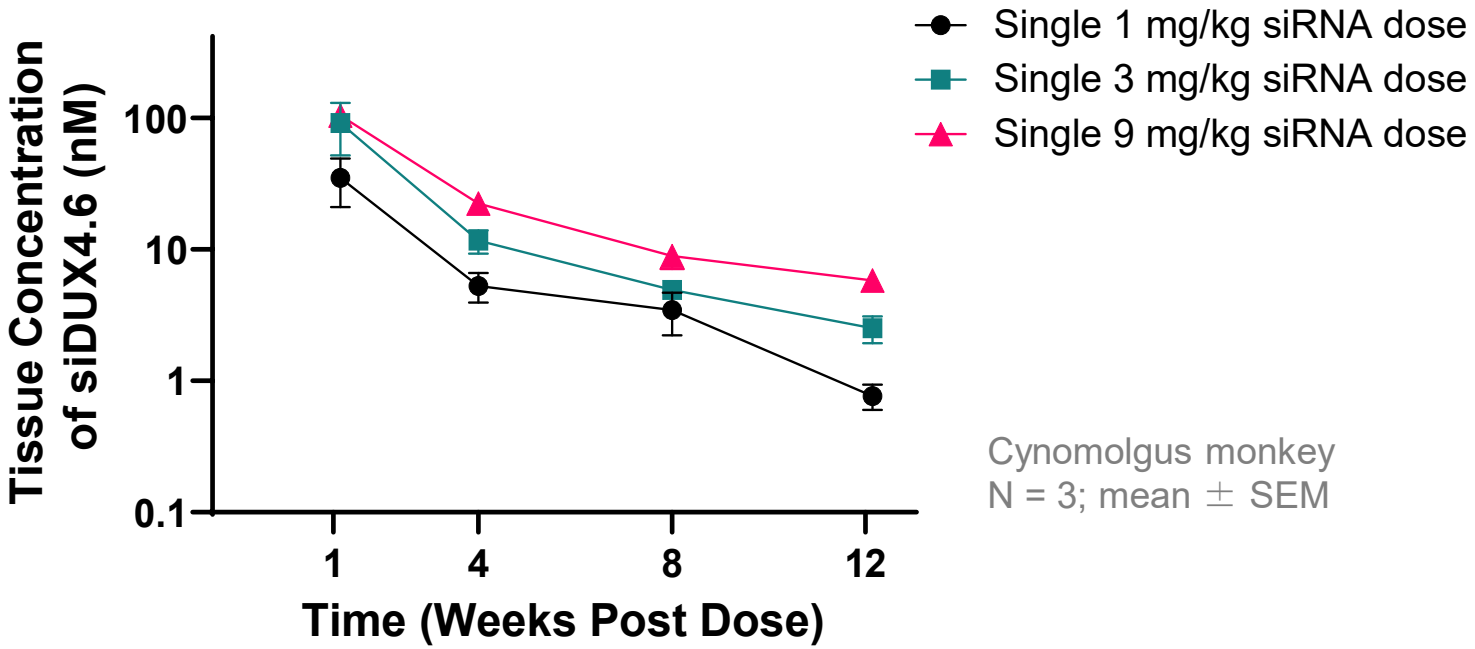
AOC 1020 PK Results in NHP Muscle Tissue Support an Infrequent Dosing Regimen for FSHD Patients



Cynomolgus monkey
N = 3; mean ± SEM

- AOC 1020 produced dose-dependent increase in siRNA tissue exposure in skeletal muscle tissues following single systemic IV doses
- The muscle tissue concentration for siDUX4.6 in NHP at therapeutically relevant doses is above IC50 values that we typically observed for other TfR1-based AOCs
- Based on our data, we anticipate this will allow for an infrequent dose schedule in the clinic

AOC 1020 is On-Track to be in the Clinic by the End of 2022

- siDUX4.6:
  - Was selected as clinical candidate siRNA targeting DUX4 mRNA, having an activity across all tested 11 FSHD patient-derived muscle cell lines, with a sub-nanomolar potency *in vitro*
  - Demonstrates efficacy *in vitro* by downregulating a panel of known DUX4-regulated genes in FSHD patient-derived myotubes
  - Demonstrates a dose-dependent activity and long duration of action (8 weeks) after single systemic IV dose *in vivo* in FSHD mouse model expressing human DUX4
  - Prevents a muscle weakness development after 2 and 8 mg/kg (siRNA within AOC) single systemic IV dose in FSHD mouse model
  - Has minimal seed-mediated off-target profile in human muscle cells
- AOC 1020 is currently in GLP toxicology studies
- Avidity is planning to enter the clinic with AOC 1020 for treatment of FSHD by end of 2022

Authors and Acknowledgements

Authors

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