

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



Barbora Malecova, David Sala, Garineh Mary Melikian, Nathan Delos Santos, Gulin Erdogan, Rachel Johns, Maryam Jordan, Marc Hartmann, Danny Arias, Arvind Battacharya, Ramana Doppalapudi, Hanhua Huang, Michael Flanagan, Arthur Levin

Avidity Biosciences, Inc. 10578 Science Center Dr., Suite 125 San Diego, CA 92121

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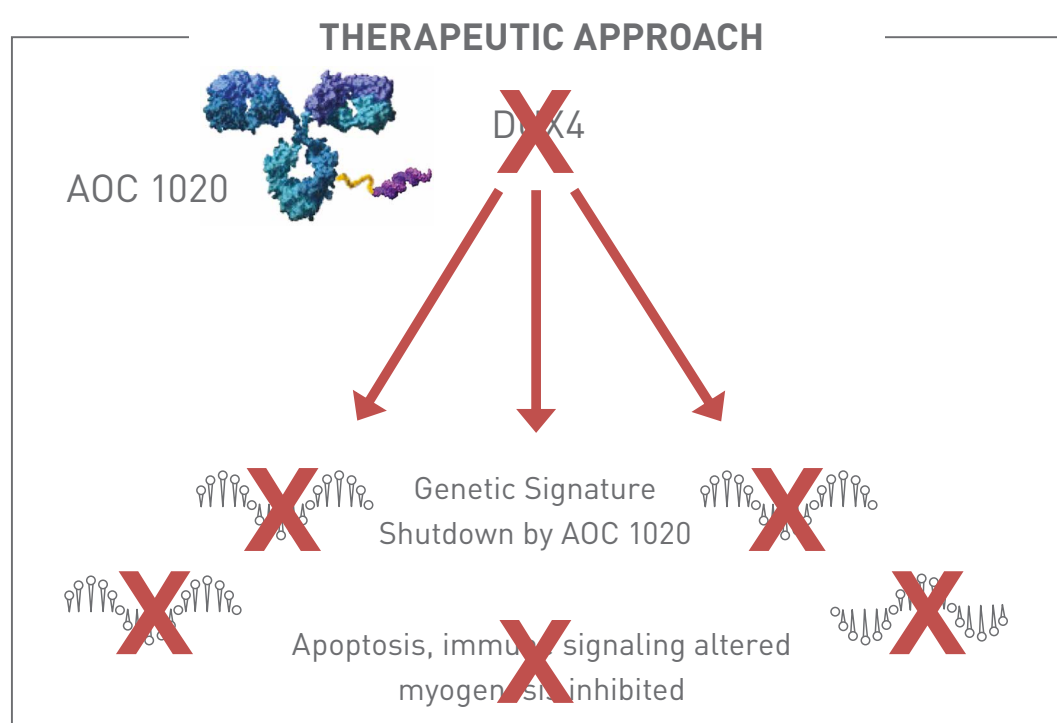


Background

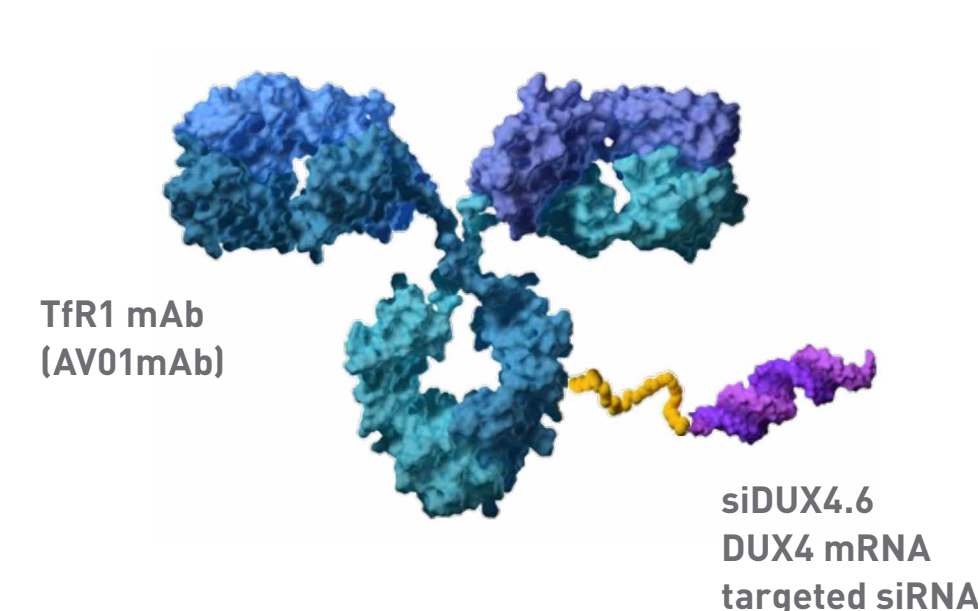
- Facioscapulohumeral dystrophy (FSHD) is a rare genetic muscular disorder, usually presenting with slow-progressing and asymmetric muscle weakness.¹
- The cause of FSHD is aberrant expression of the transcription factor DUX4 in skeletal muscle, leading to a series of downstream events that result in skeletal muscle degeneration and wasting. Strategies aimed at reducing DUX4 expression in the skeletal muscle of FSHD patients are promising therapeutic approaches.²⁻⁴
- Clinical development of oligonucleotide therapeutics for muscle diseases has been limited due to difficulty delivering oligonucleotides into muscle.⁵ Avidity's AOC™ platform combines the specificity of transferrin receptor 1 (TfR1)-directed monoclonal antibodies for muscle delivery with the potency and precision of small interfering RNA (siRNA) in reducing target RNA expression.
- Avidity has conducted a comprehensive *in vitro* screening of a DUX4 siRNA library in a variety of FSHD patient-derived muscle cells, which allowed selection of highly potent siRNA sequences with minimal off-target profile. The selected siDUX4.6 siRNA was conjugated to the murine TfR1 antibody to generate DUX4 AOC. A robust, dose-dependent response was observed for 8 weeks following a single intravenous (IV) dose of DUX4 AOC, with 75% or higher reduction of DUX4-regulated genes in skeletal muscle of the ACTA1-MCM; FLEXDUX4 mouse model of FSHD.
- Data presented herein provide rationale and support for entering the clinic with AOC 1020 for the treatment of FSHD.

Avidity's Approach

Reducing DUX4 expression in the muscle of FSHD patients may limit downstream expression of toxic genes



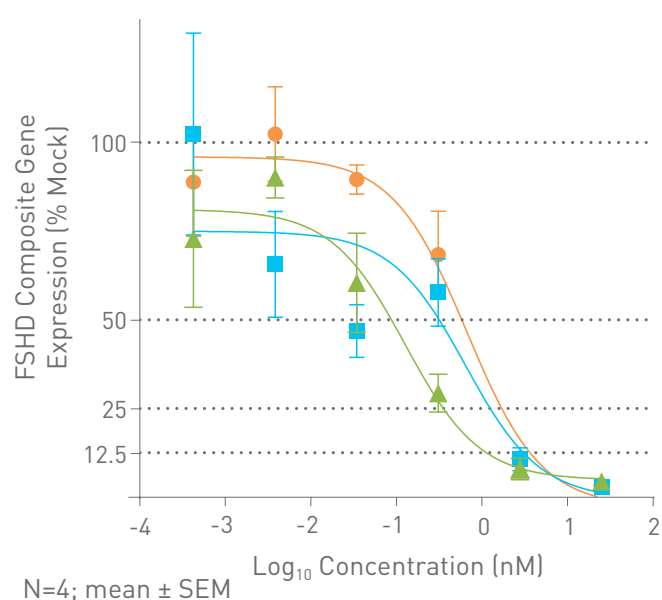
Avidity's AOC 1020 Targets DUX4 mRNA for Degradation, thus Reducing the Expression of the Disease-causing Protein



Results

1. 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

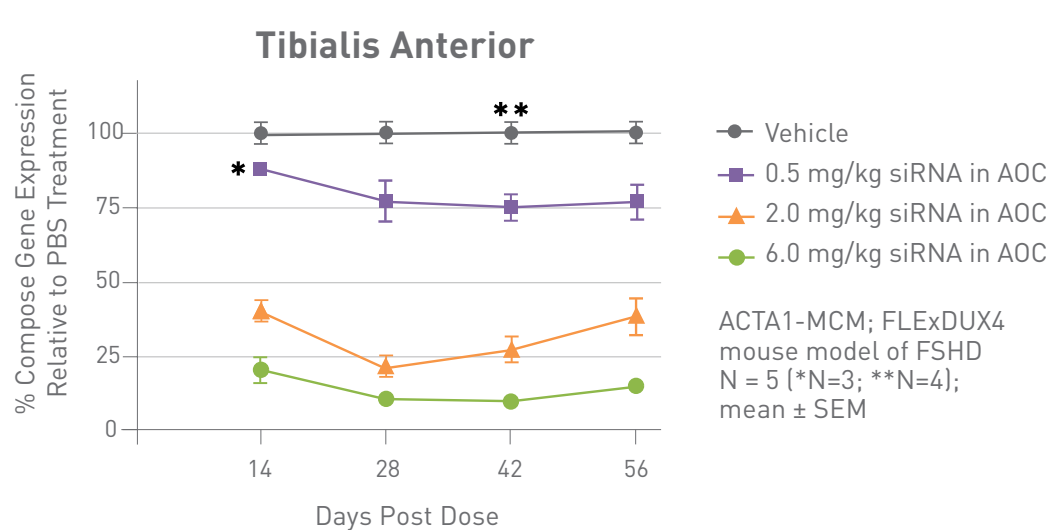


	IC ₅₀ (nM)	E _{max} (%)
MB02	0.639	100
MB05	0.127	95
MB06	0.665	100

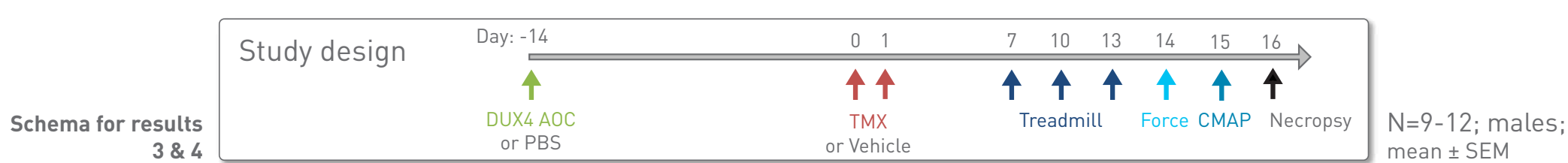
- Robust reduction of DUX4-regulated genes was observed with the lead siDUX4.6 siRNAs in FSHD donor myotubes *in vitro*
- FSHD Composite is a mean expression of DUX4-regulated genes KHDC1L, LEUTX, MBD3L2, ZSCAN4⁸

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

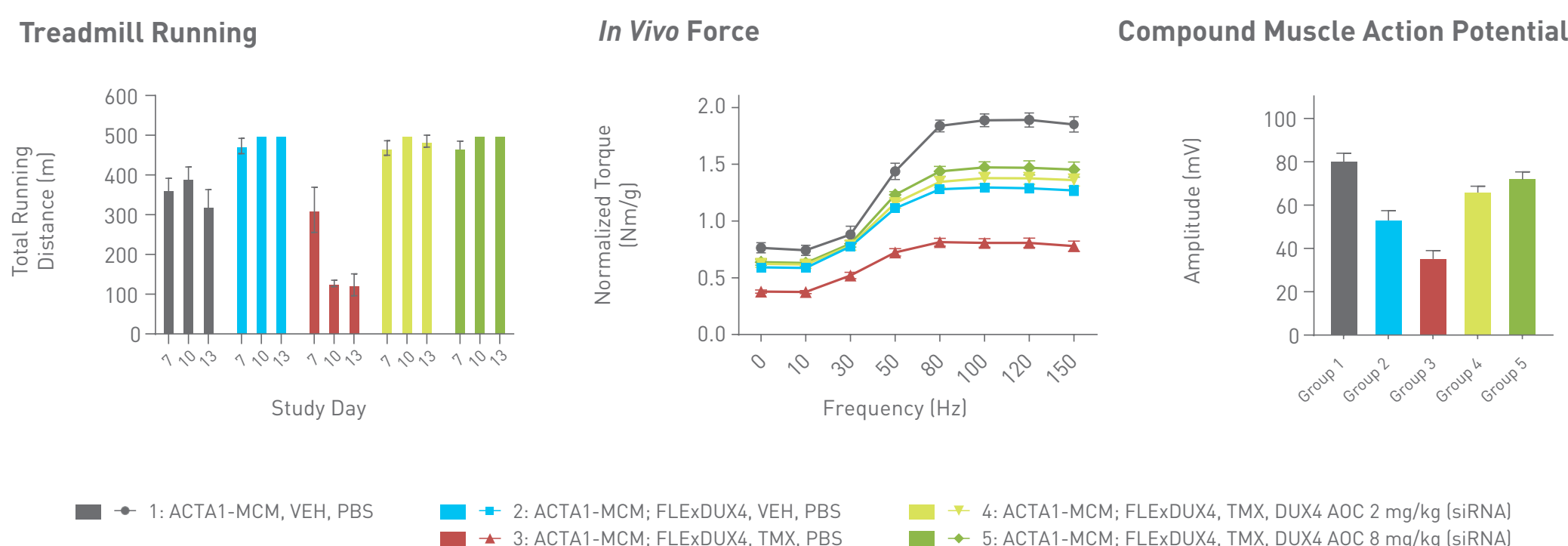
Dose-dependent inhibition of DUX4-regulated genes in skeletal muscles



- 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^{9,10}
- 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)

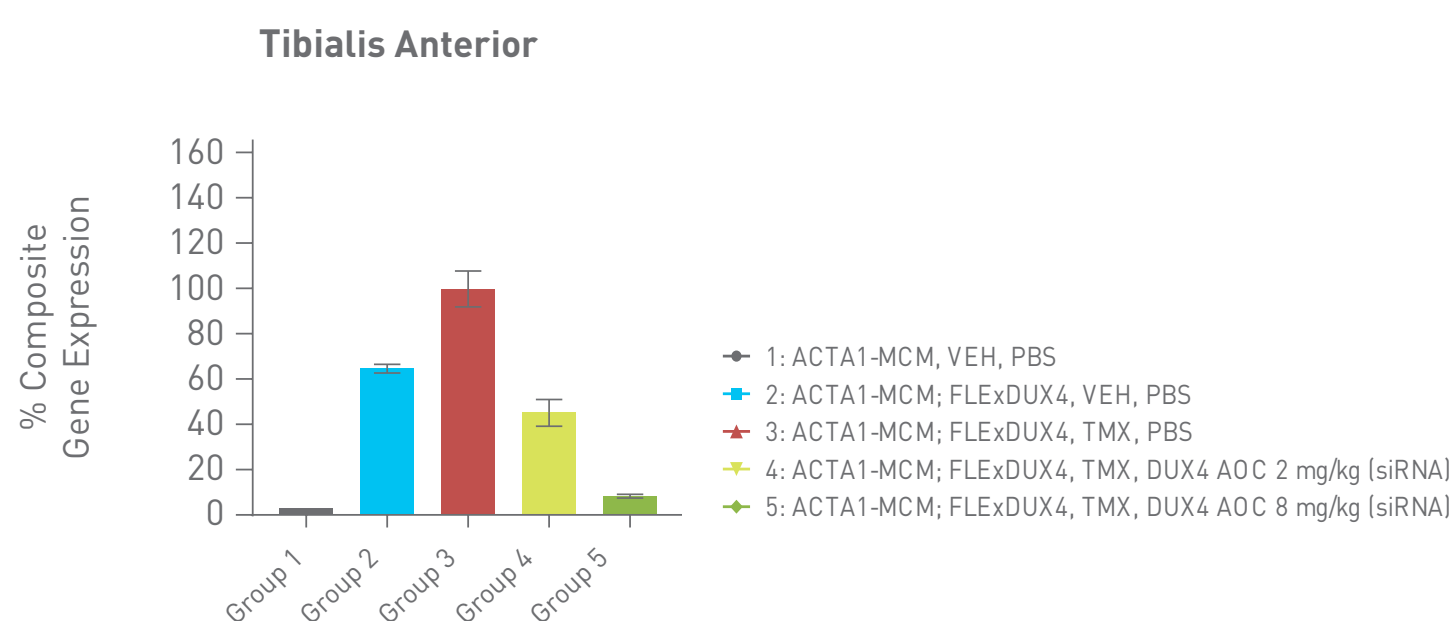


3. Single Intravenous Treatment with DUX4 AOC Prevents Disease Phenotype Development in FSHD Mouse Model



Results

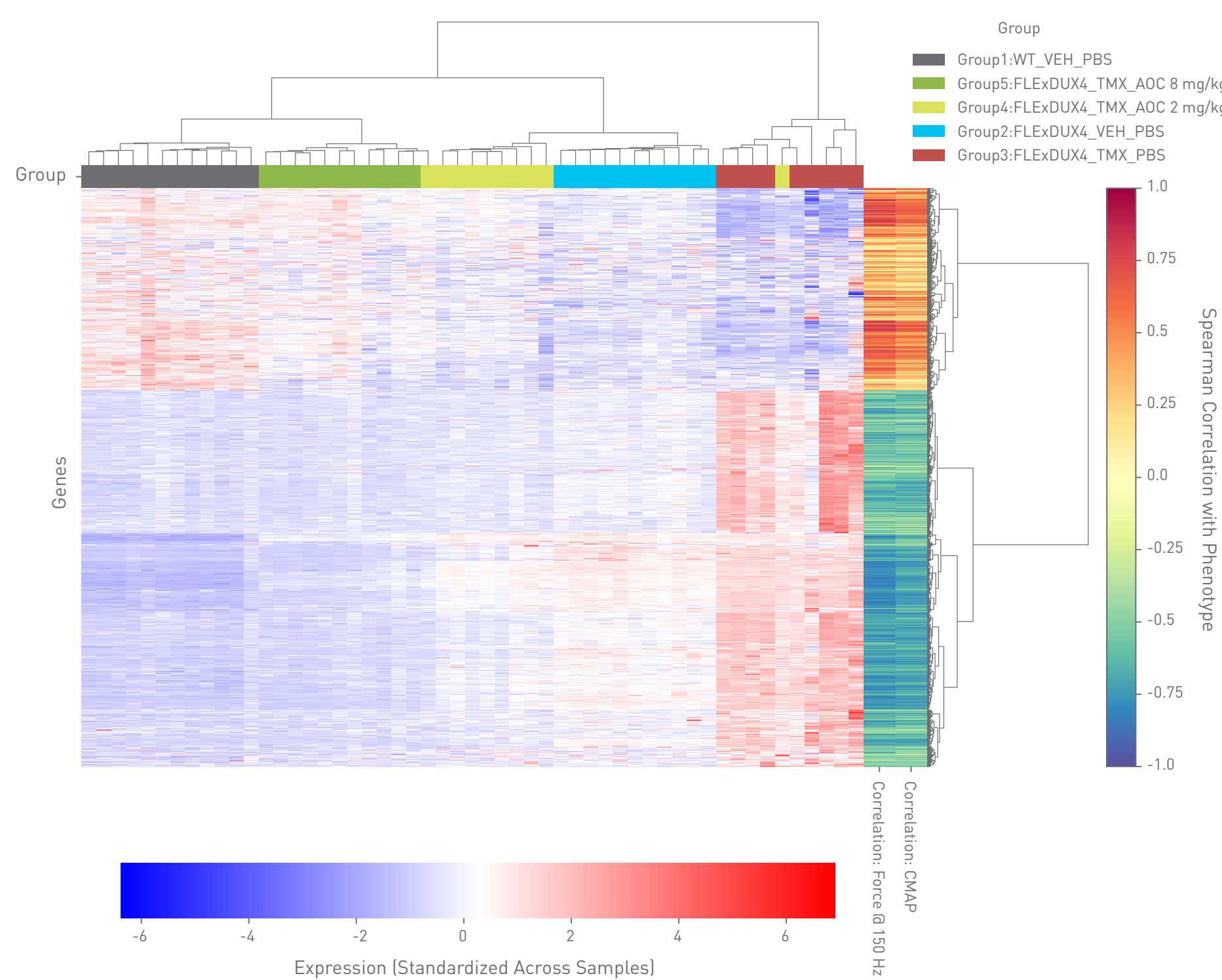
4. Single Dose of DUX4 AOC Inhibits DUX4-Regulated Gene Expression in Muscle of Tamoxifen-Induced FSHD Mouse Mode



- The siRNA clinical candidate siDUX4.6 robustly inhibits expression of DUX4-regulated mouse genes (Wfdc3, Ilvbl, Slc15a2, Sord)^{9,10} in skeletal muscle 1 month after single IV administration at therapeutically relevant doses

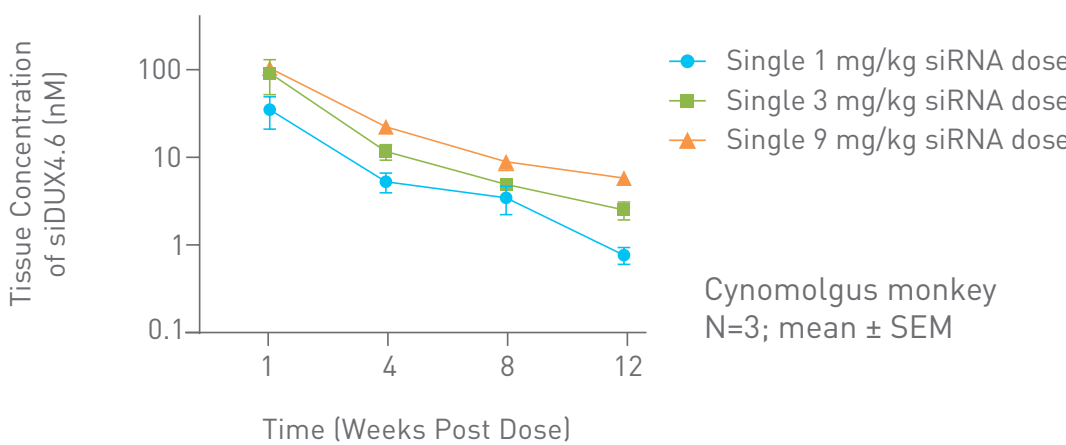
5. DUX4 AOC Treatment Prevents Global FSHD Disease-related Gene Expression Response in Muscle of FSHD Mouse Model

Clustermap: All Differentially Expressed Genes from Comparing TMX_PBS vs. WT_VEH_PBS (Absolute logFC > 1.0, Adjusted *p* Value < 0.01, 3,961 Genes)



- RNA-seq analysis of TA muscle identifies 3,961 genes with significant responses in a tamoxifen-induced FSHD mouse model, many of which correlate with functional outcomes (force and CMAP measurements)
- Treatment with DUX4 AOC prevents this disease gene expression response, reflected by treated samples clustering with normal control

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



- 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

Conclusion

- 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
- Avidity is evaluating AOC 1020 in the Phase 1/2 FORTITUDE clinical trial in adults with FSHD

Acknowledgements

- Avidity Biosciences, Inc.: Eileen Blasi, Varun Goel, Theresa Falls, Giuseppe Dello Iacono, Subbarao Nallagatla, Karla Schramm, Oliver Dansereau, Samuel Beppler
- CYT00: Joanne Young, Erwann Ventre
- The Jackson Laboratory: Orsolya Kiraly
- Monoceros Biosystems LLC: Sole Gatto, Matthew Onorato, David Nickle, Adam Pavlicek
- LGC Axolabs GmbH: Martin Koeqler, Philipp Hadwiger, Lukas Perkams
- Altasciences: Vivienne Bunker, Satoru Oneda

Abbreviations and References

AOC, antibody oligonucleotide conjugate; FSHD, facioscapulohumeral dystrophy; IV, intravenous; mRNA, messenger RNA; PBS, phosphate-buffered saline; RNA, ribonucleic acid; RT-qPCR, quantitative reverse transcription polymerase chain reaction; SEM, standard error of the mean; siRNA, small interfering RNA; TfR1, transferrin receptor 1.

¹Tawil R, et al. *Neuromuscul Disord.* 2010;20(7):471-5; ²Bouwmann LF, et al. *Curr Opin Neurol.* 2020;33(5):635-40; ³Anseau et al. *Genes.* 2017;88(3):93; ⁴Le Gall et al. *J Clin Med.* 2020; 7(9):2886; ⁵Roberts TC, et al. *Nat Rev Drug Discov.* 2020;19(10):673-94; ⁶Lemmers RJLF, et al. *Science.* 2010;329(5999):1650-3; ⁷Snider L, et al. *PLoS Genet.* 2010;6(10):e1001181; ⁸Yao et al. *Hum Mol Genet.* 2014;23(20):5342-52; ⁹Whiddon et al. *Nat Genet.* 2017; 49(6): 935-940; ¹⁰Jones T and Jones PL. *PLoS One.* 2018;13(2):e0192657.