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

Barbora Malecova
Avidity Biosciences, Inc.
FSHD is Caused by Aberrant Expression of DUX4 in Muscle

**MECHANISM OF DISEASE**

- DUX4 activates genes that are toxic to muscle cells
- Apoptosis, immune signaling altered
- Myogenesis inhibited

**THERAPEUTIC APPROACH**

- Genetic Signature Activated by DUX4
- Genetic Signature Shutdown by AOC 1020
- Apoptosis, immune signaling altered
- Myogenesis inhibited

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

- 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 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

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

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.
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

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

Study design

N = 9-12; males; mean ± SEM

Treadmill Running

In Vivo Force

Compound Muscle Action Potential

Study Day: -14

Day: 0 1 7 10 13 14 15 16

DUX4 AOC or PBS

TMX or Vehicle

Treadmill Force CMAP Necropsy

0 10 30 50 80 100 120 150

0.0 0.5 1.0 1.5 2.0

Normalized Torque (Nm/g)

0 10 30 50 80 100 120 150

0 20 40 60 80 100

Amplitude (mV)

Study Day

Total Running Distance (m)

0 100 200 300 400 500 600

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

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.
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.
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

Avidity Biosciences, Inc: Barbora Malecova, David Sala, Garineh Melikian, Gulin Erdogan, Rachel Johns, Arthur A. Levin, Michael Flanagan

CYTOO: Joanne Young, Erwann Ventre

The Jackson Laboratory: Orsolya Kiraly

Monoceros Biosystems LLC: Sole Gatto, Matthew Onorato

LGC Axolabs GmbH: Martin Koegler, Philipp Hadwiger, Lukas Perkams

Acknowledgements

Avidity Biosciences, Inc: Oliver Dansereau, Samuel Beppler, Eileen Blasi, Varun Goel, Danny Arias, Arvind Bhattacharya, Theresa Falls, Maryam Jordan, Marc Hartmann, Giuseppe Dello Iacono, Subbarao Nallagatla, Karla Schramm, Hanhua Huang

Altasciences: Vivienne Bunker, Satoru Oneda

Monoceros Biosystems LLC: David Nickle, Adam Pavlicek