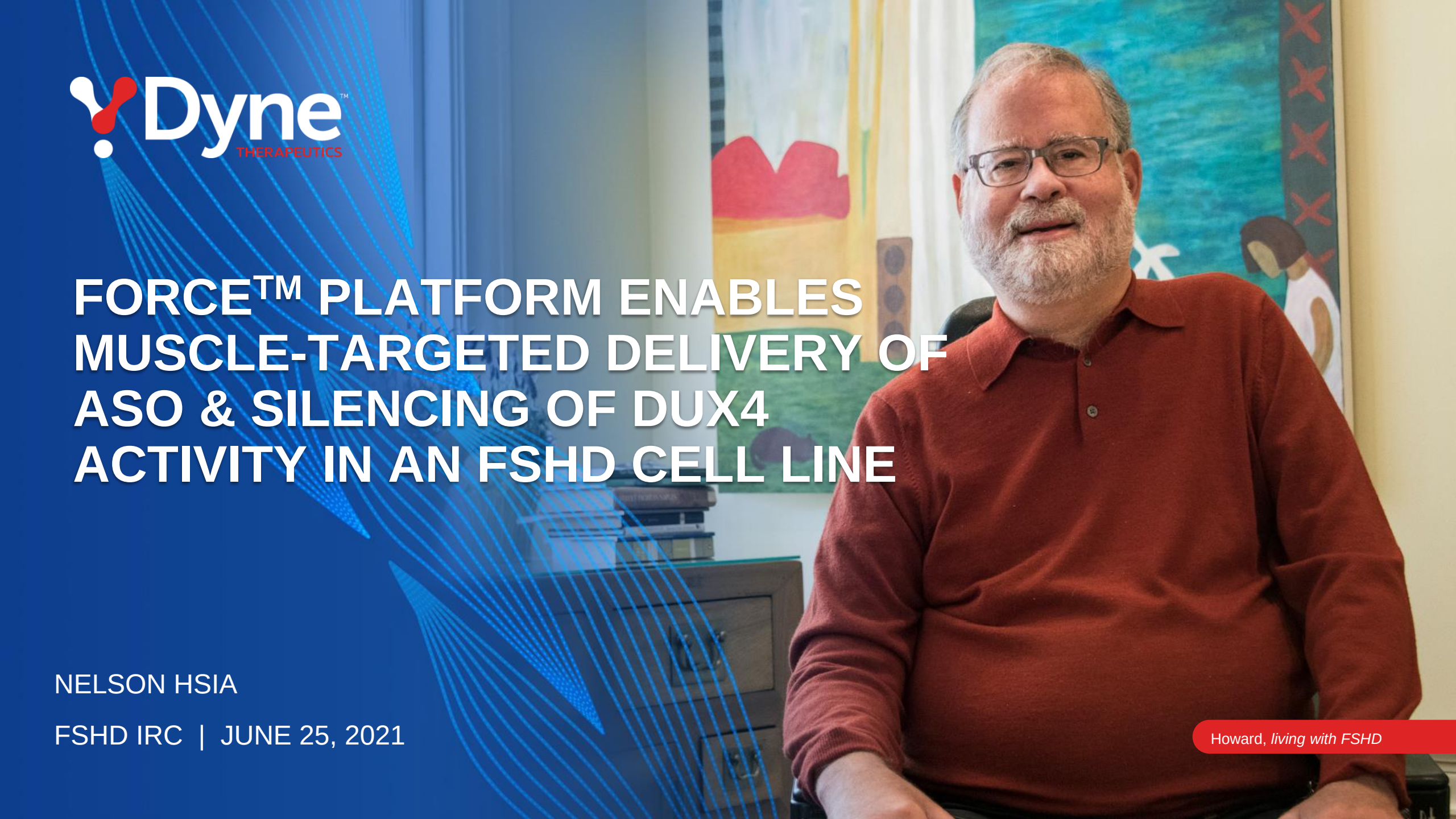
FORCE™ PLATFORM ENABLES MUSCLE-TARGETED DELIVERY OF ASO & SILENCING OF DUX4 ACTIVITY IN AN FSHD CELL LINE

NELSON HSIA

FSHD IRC | JUNE 25, 2021



Howard, *living with FSHD*

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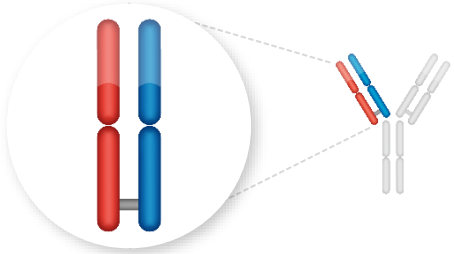
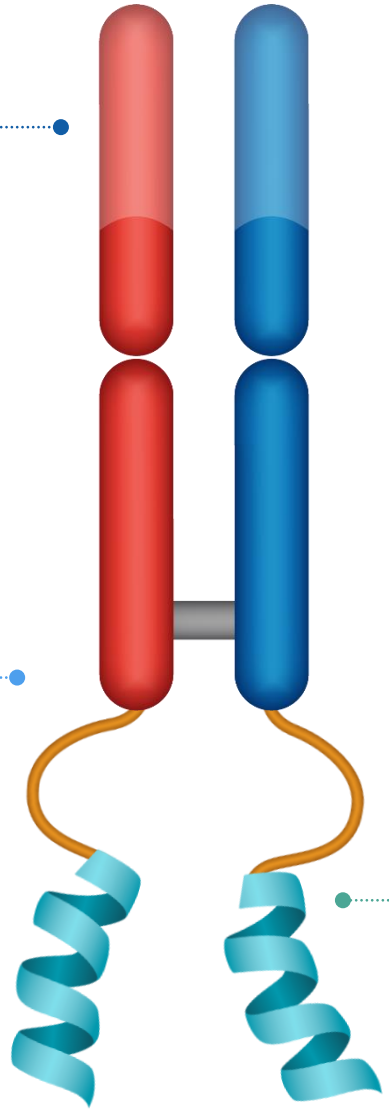
Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



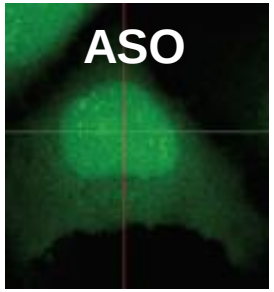


LINKER

Clinically validated, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

Modularity enables rational selection of payload to target the genetic basis of disease



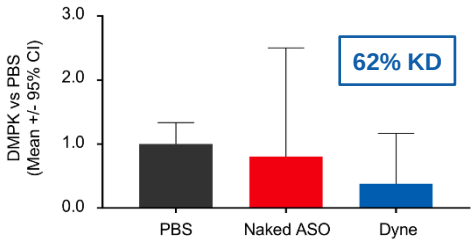
Nuclear localization

Cytoplasmic localization

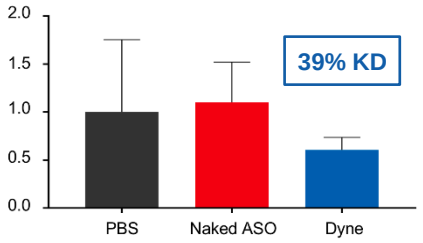
Adapted from: Ohrt et al: NAR , 2006, v.34, p.1369

FORCE™ Platform Achieved Enhanced Distribution and WT *DMPK* KD Across NHP Skeletal, Cardiac and Smooth Muscles

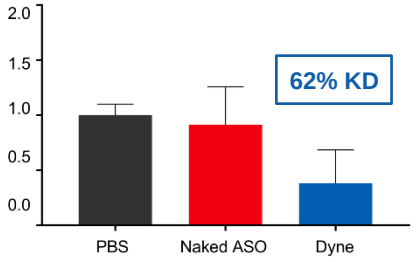
Gastrocnemius



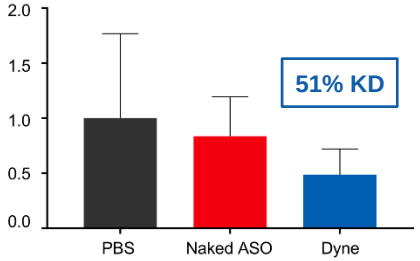
Soleus



Deep Flexor

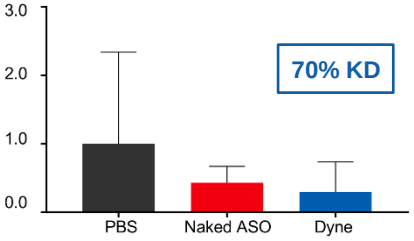


Bicep

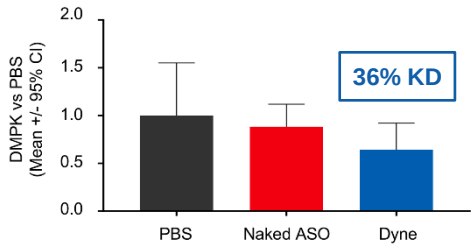


Ileum

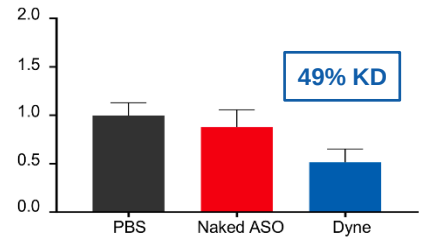
(Near Cecum)



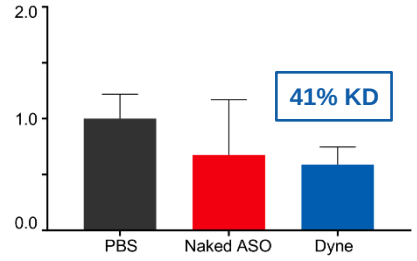
Heart-left Ventricle



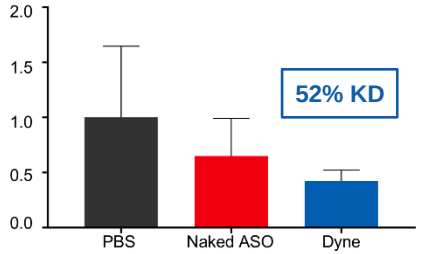
Diaphragm



Masseter

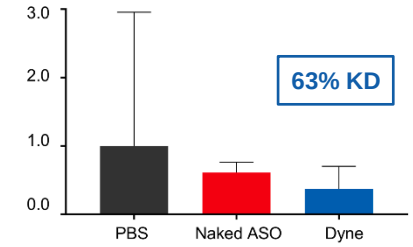


Quadricep



Jejunum

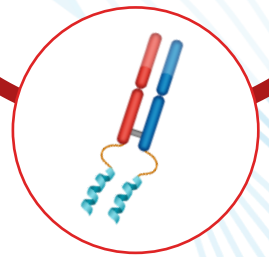
(Duodenum Ends)



Note: WT NHP with WT *DMPK* expression, n=3 per group, single dose IV at 10mg per kg for ASO, 14-day study.

FORCE Platform Designed to Deliver Significant Advantages

Stop or Reverse Disease Progression



Targeted Muscle Delivery

Leverages TfR1 expression on skeletal, cardiac and smooth muscle

Targets Genetic Basis of Disease

Rationally select payloads to match target biology

Redosable Administration

Potential for individualized patient titration and longer-term efficacy

Enhanced Tolerability

Targeted delivery limits systemic drug exposure

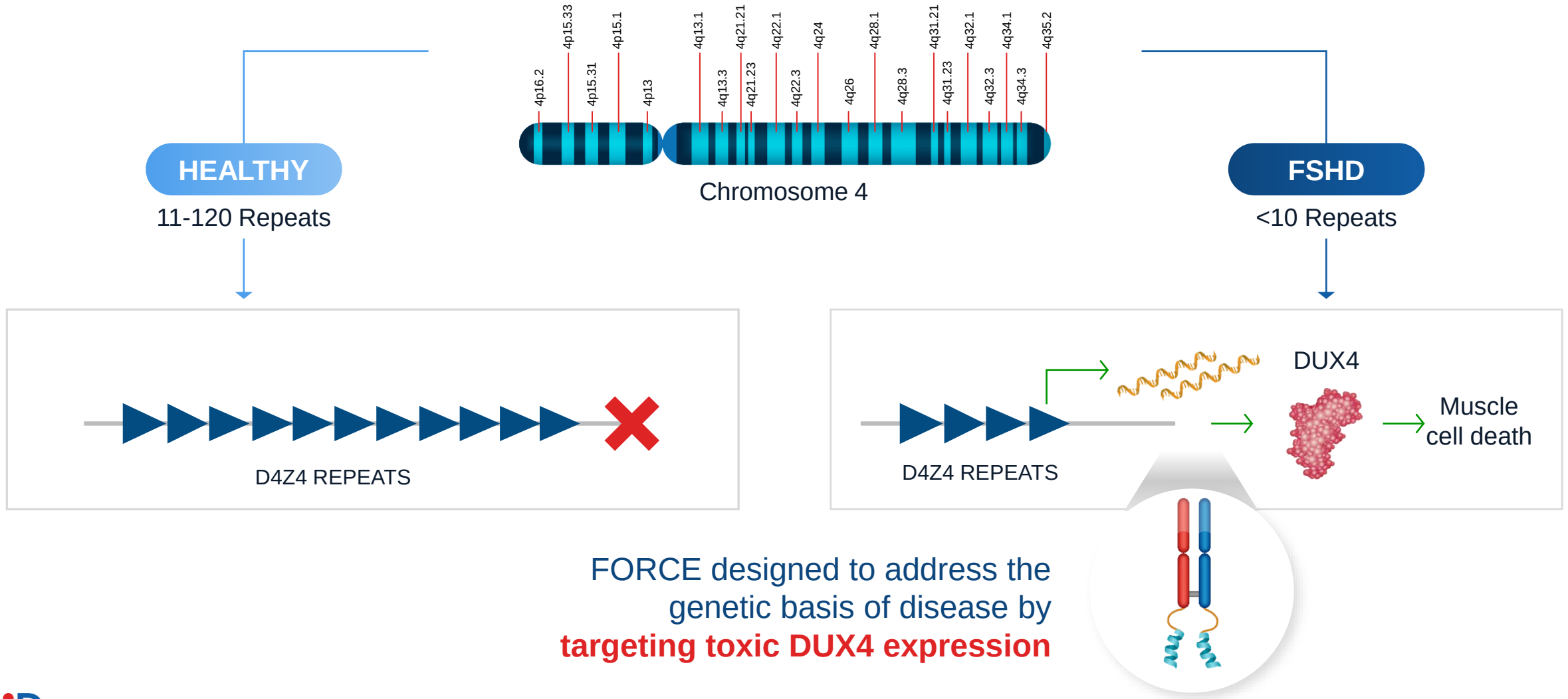
Extended Durability

Potential for prolonged disease-modifying effects, enabling less frequent dosing

Reduced Development and Manufacturing Costs

A single Fab and linker utilized across all programs

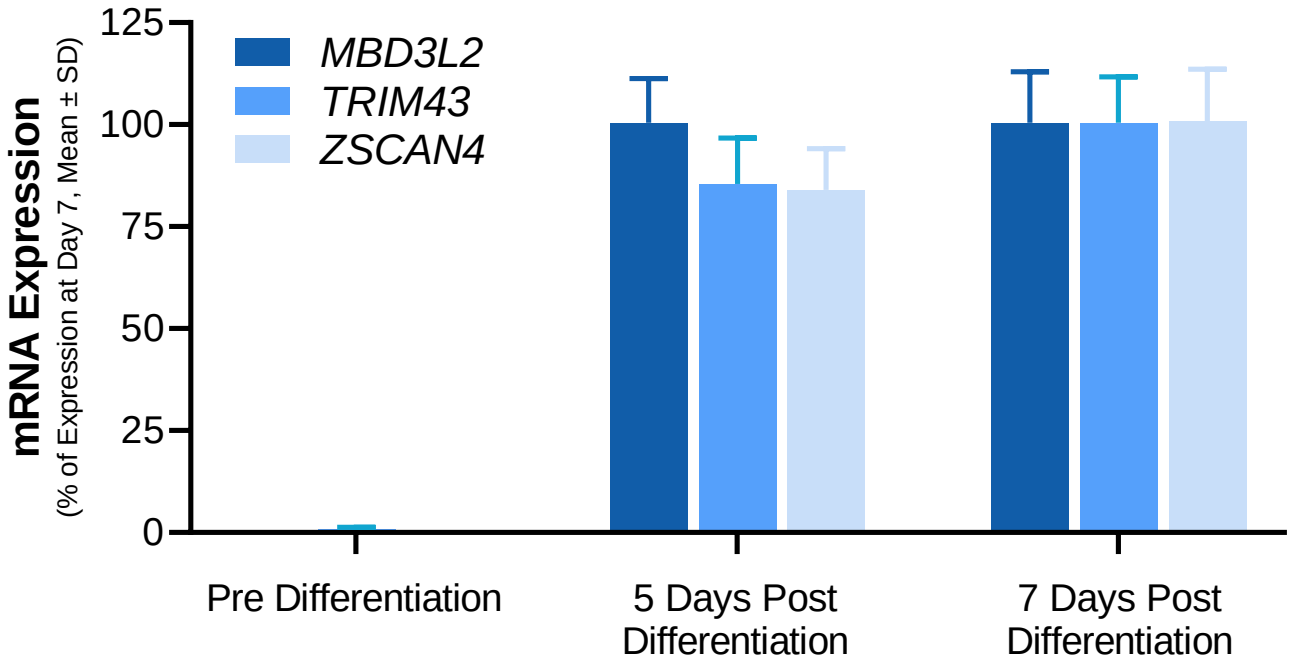
FORCE Targets the Genetic Basis of FSHD



FORCE designed to address the genetic basis of disease by **targeting toxic DUX4 expression**

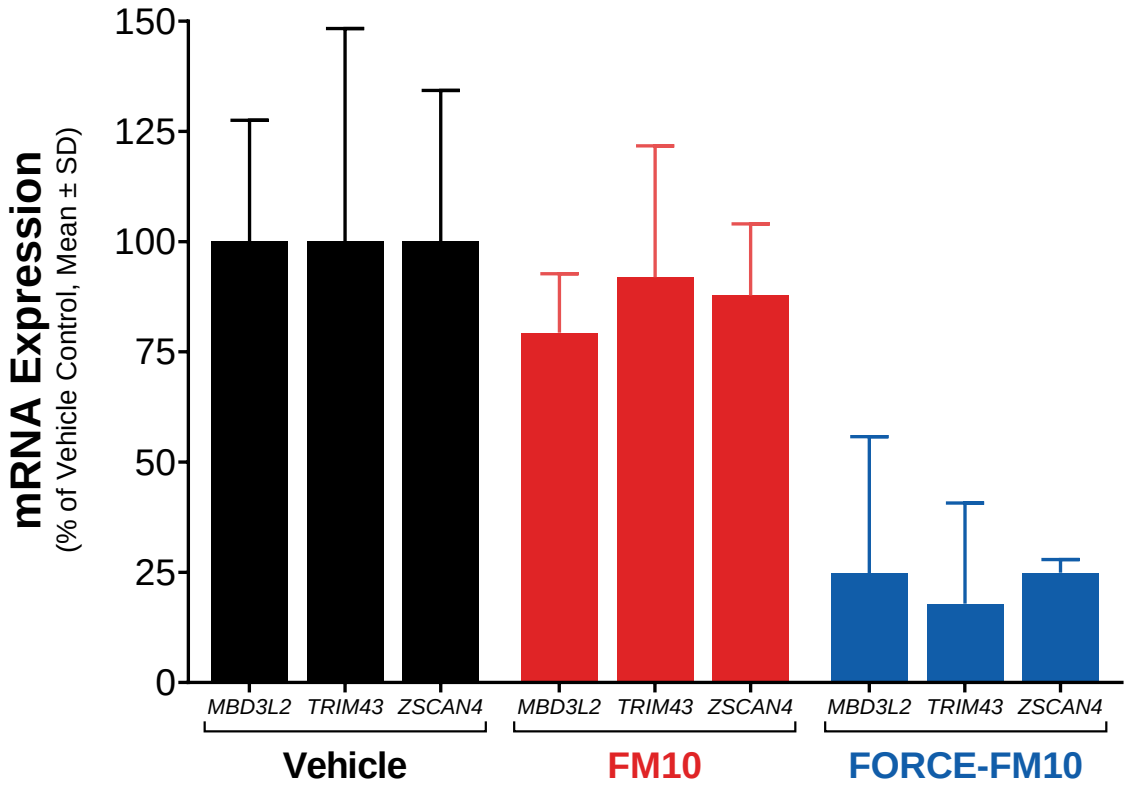
Activation of DUX4 Transcriptome in FSHD Patient Myotubes

- Immortalized FSHD patient cells selected as our *in vitro* model system



- DUX4 transcriptome expression occurs only after differentiation to myotubes
- No significant difference in transcriptome marker expression observed between 5 and 7 days
- 5 days post differentiation selected for subsequent studies that assess our therapeutics

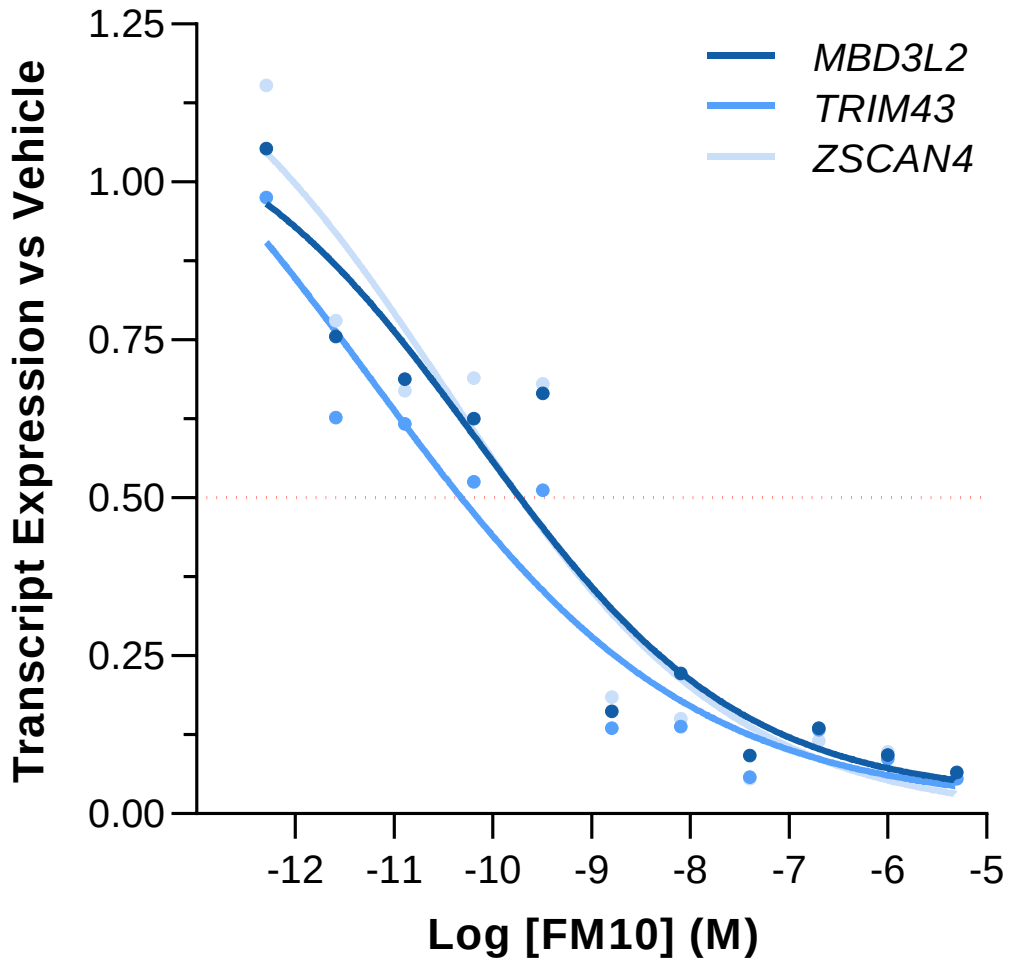
FORCE-FM10 Shows Superior Suppression of DUX4 Transcriptome Relative to Naked FM10 PMO in FSHD Patient Myotubes



- FM10 is a PMO targeting *DUX4* mRNA for degradation
- FSHD patient cells were treated with either 8 nM of naked FM10 PMO or FORCE-FM10
- FORCE-FM10 treatment resulted in a 75% reduction of DUX4 transcriptome markers, whereas naked FM10 showed no significant transcriptome reduction

FORCE-FM10 is Highly Potent in FSHD Patient Myotubes

IC50 is in the Low Nanomolar Range



DUX4 Transcriptome Marker	IC_{50}
MBD3L2	0.2 nM
TRIM43	0.05 nM
ZSCAN4	0.2 nM

Summary

- FORCE platform enables targeted muscle delivery of therapeutic oligonucleotides
- FORCE-FM10 achieves superior suppression of DUX4 transcriptome relative to naked PMO in FSHD patient cells
- Enhanced muscle distribution based on data in multiple NHP studies

FSHD is one of three INDs planned between Q4 2021 - Q4 2022

Acknowledgements