



DYNE-302 Leads to Functional Improvement and Resolves Muscle Transcriptomic Changes in Mouse Models of FSHD

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RNA Leaders US

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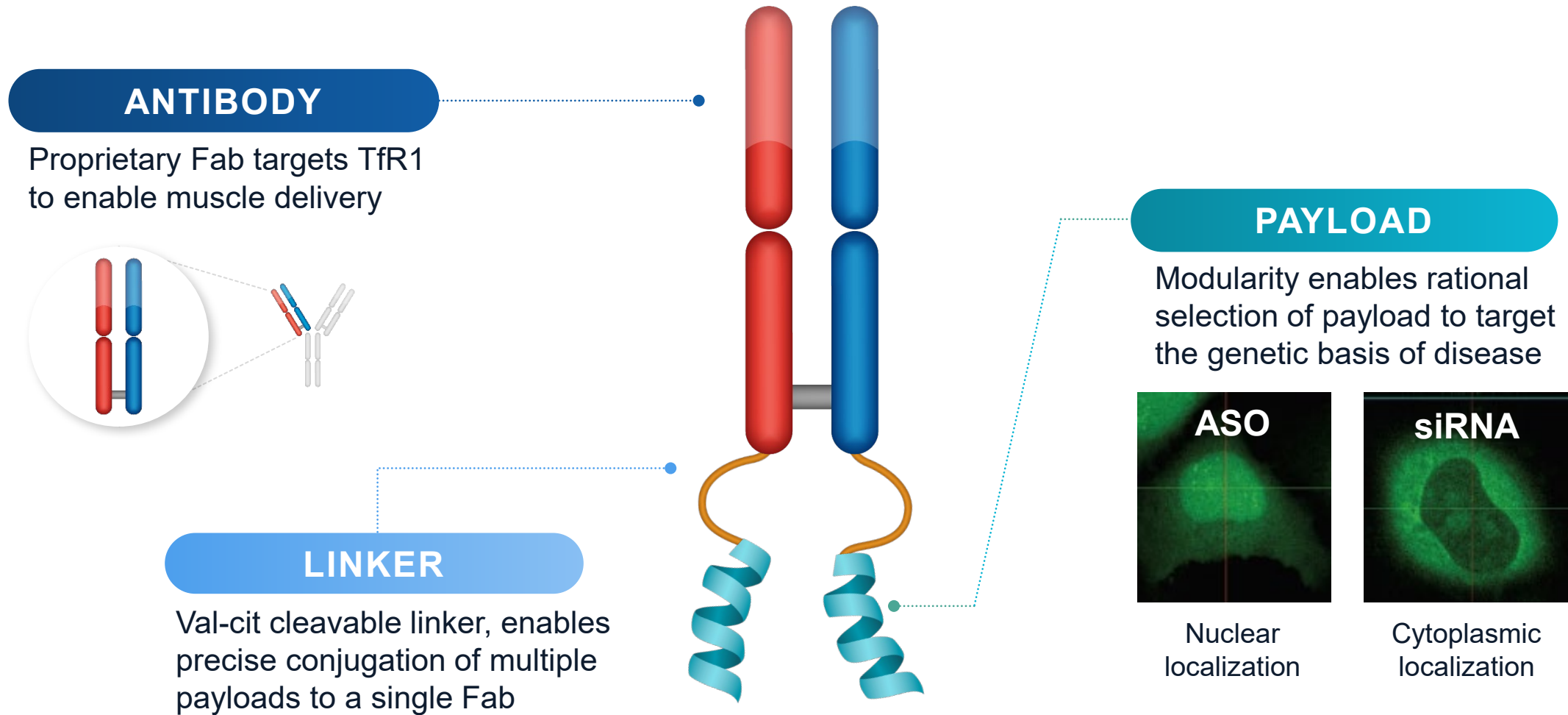
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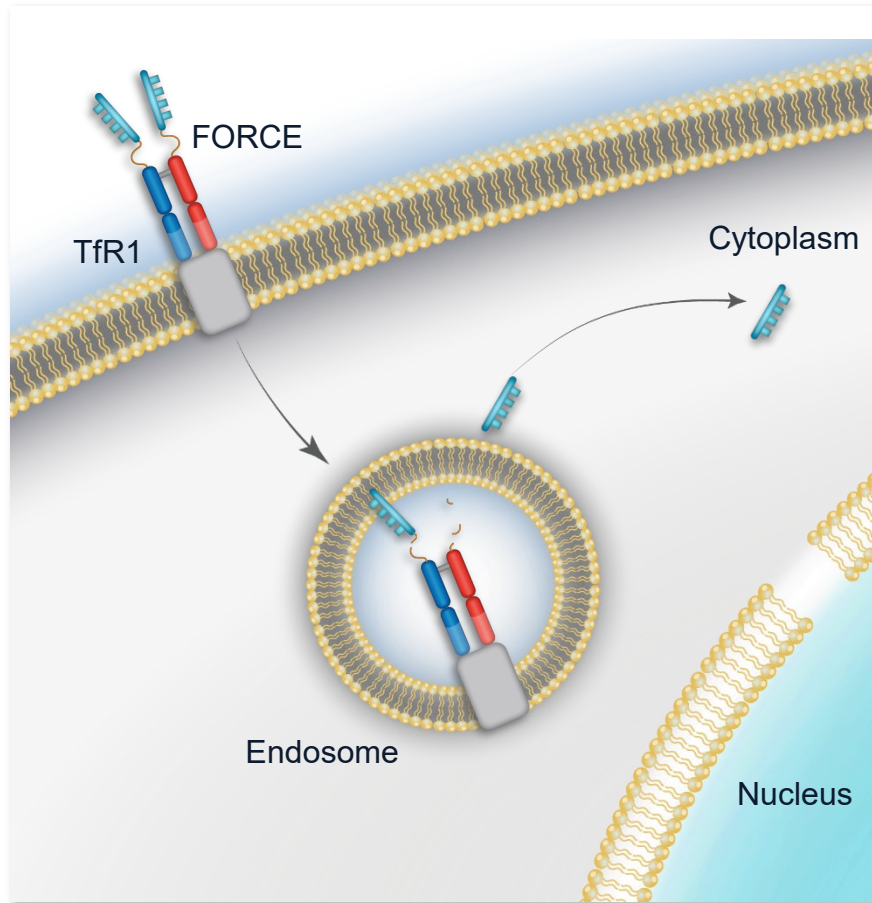
The FORCE™ platform and DYNE-302 are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority.

Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases



Fab and linker are components of FORCE molecules in clinical development for DM1 and DMD

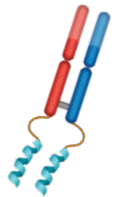
FORCE Platform Harnesses Cell Biology to Modify Disease



- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

FORCE Platform Designed to Deliver Significant Advantages

**Provide
Functional
Improvement**



Targeted Delivery

Leverages TfR1 expression on skeletal, cardiac, and smooth muscle as well as blood-brain-barrier



Targets Genetic Basis of Disease

Rationally select payloads to match target biology



Redosable administration

Durable efficacy and treatment optionality



Enhanced Tolerability

Targeted delivery limits systemic drug exposure and use of Fab minimizes disruption to TfR1 receptor



Extended Durability

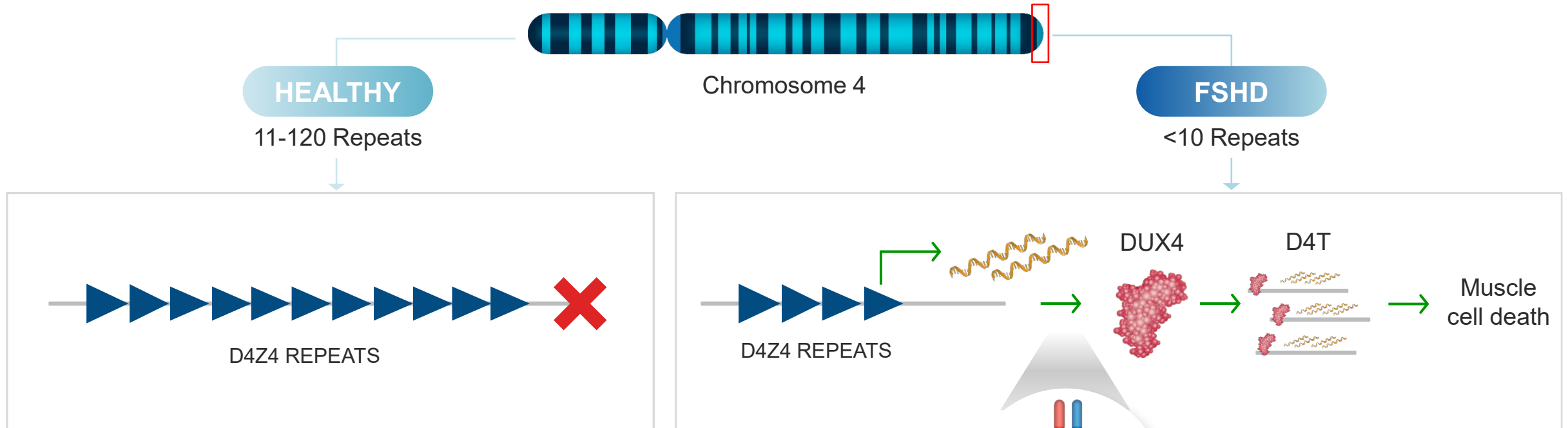
Potential for prolonged disease-modifying effects, enabling less frequent dosing



Reduced Development and Manufacturing Costs

A single Fab utilized across all programs

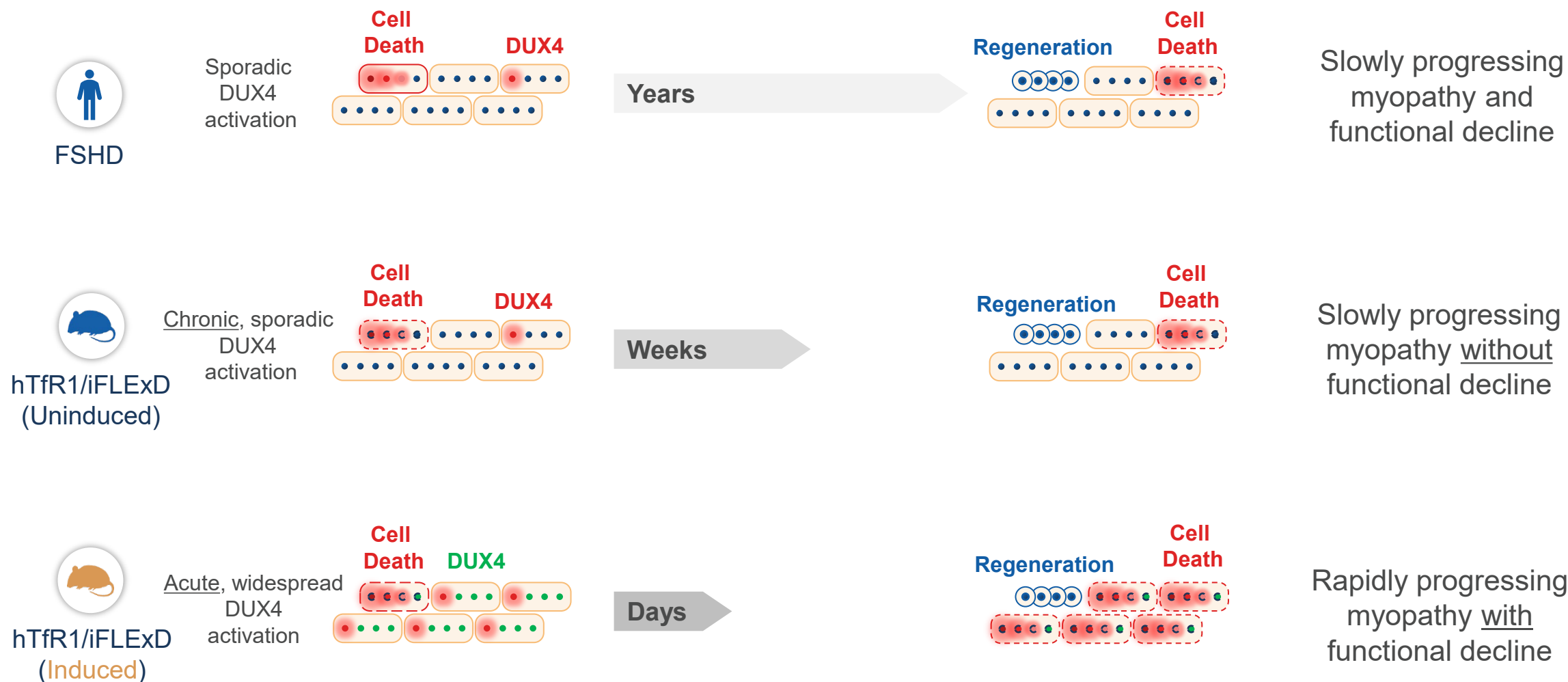
DYNE-302 Targets the Genetic Basis of FSHD



DYNE-302: a FORCE-siRNA conjugate designed to address the genetic basis of disease by **targeting pathogenic *DUX4* expression**

- Highly selective *DUX4* siRNA payload with favorable *in vitro* off-target and *in vitro* tolerability profile
- Extended duration of action intended to overcome sporadic *DUX4* activation

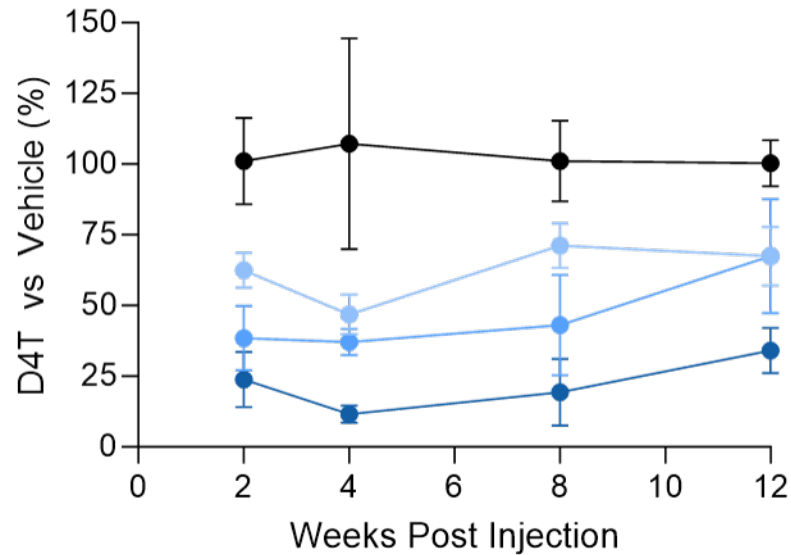
The hTfR1/iFLExD Mouse Model Recapitulates Multiple Aspects of Human FSHD



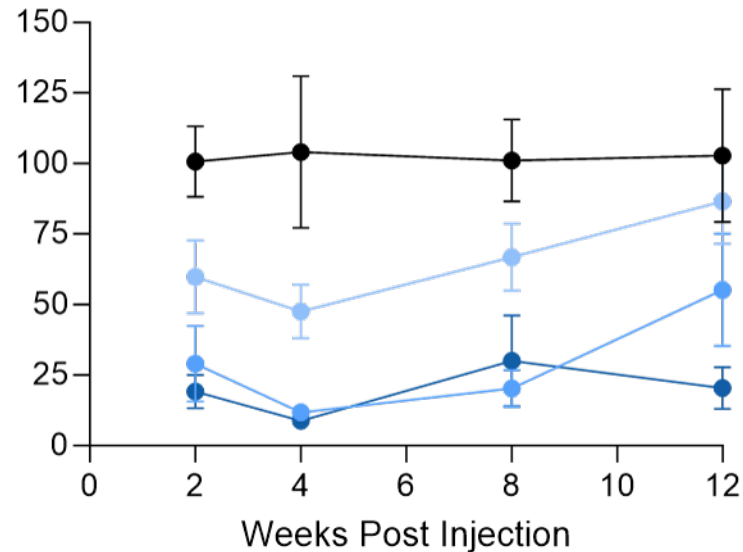
Single Dose of DYNE-302 Achieves Robust, Durable, and Dose-Dependent D4T KD in Skeletal Muscle of hTfR1/iFLExD FSHD Mice



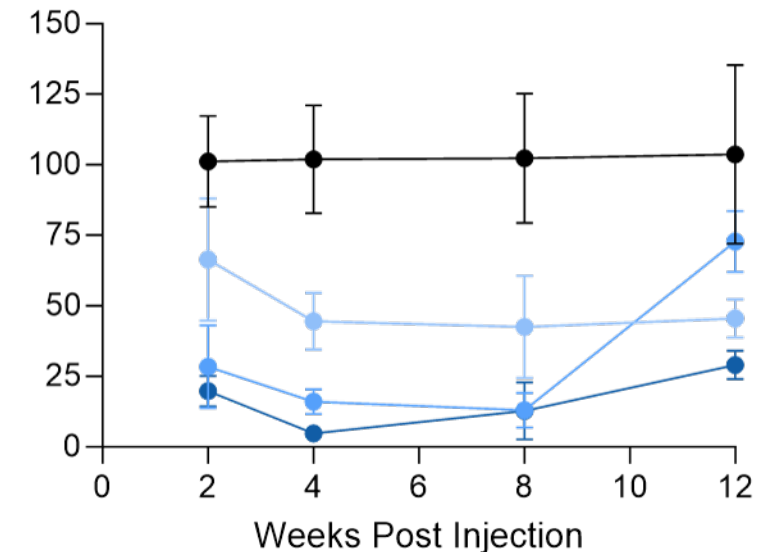
Quadriceps



Gastrocnemius



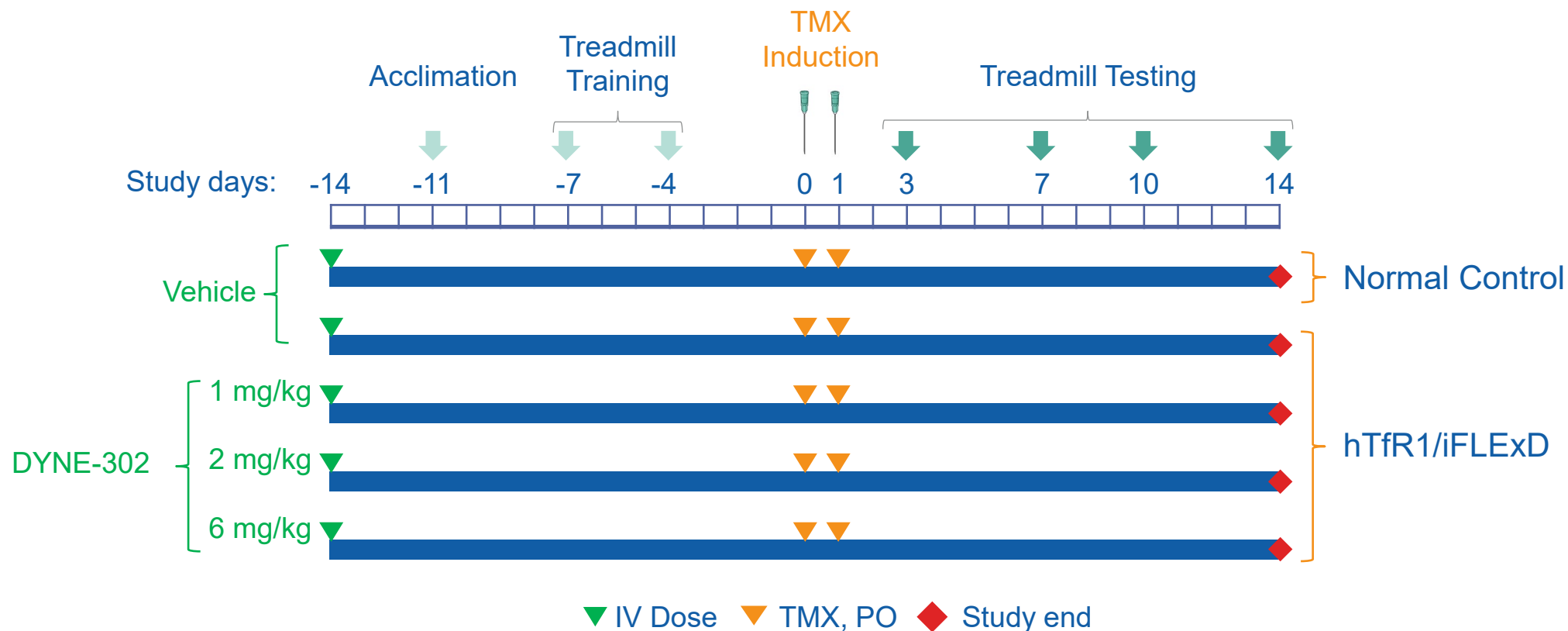
Tibialis anterior



● Vehicle ● DYNE-302 1 mg/kg ● DYNE-302 2 mg/kg ● DYNE-302 6 mg/kg

DYNE-302 demonstrates potential for infrequent dosing

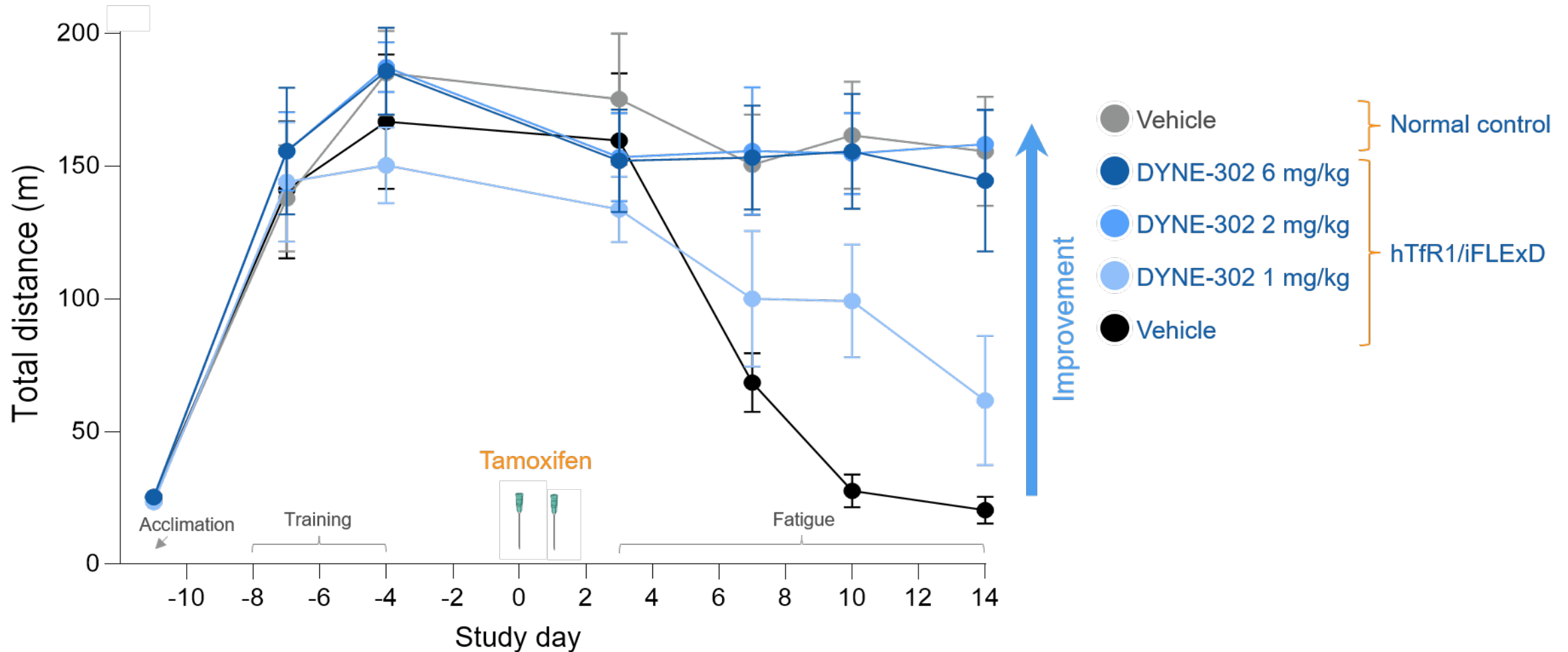
Study to Establish Impact of DYNE-302 Preventative Treatment in the Induced hTfR1/iFLExD Mice



Preventative Treatment with DYNE-302 Leads to Functional Improvement in hTfR1/iFLExD Mice



Functional improvement in forced treadmill run test



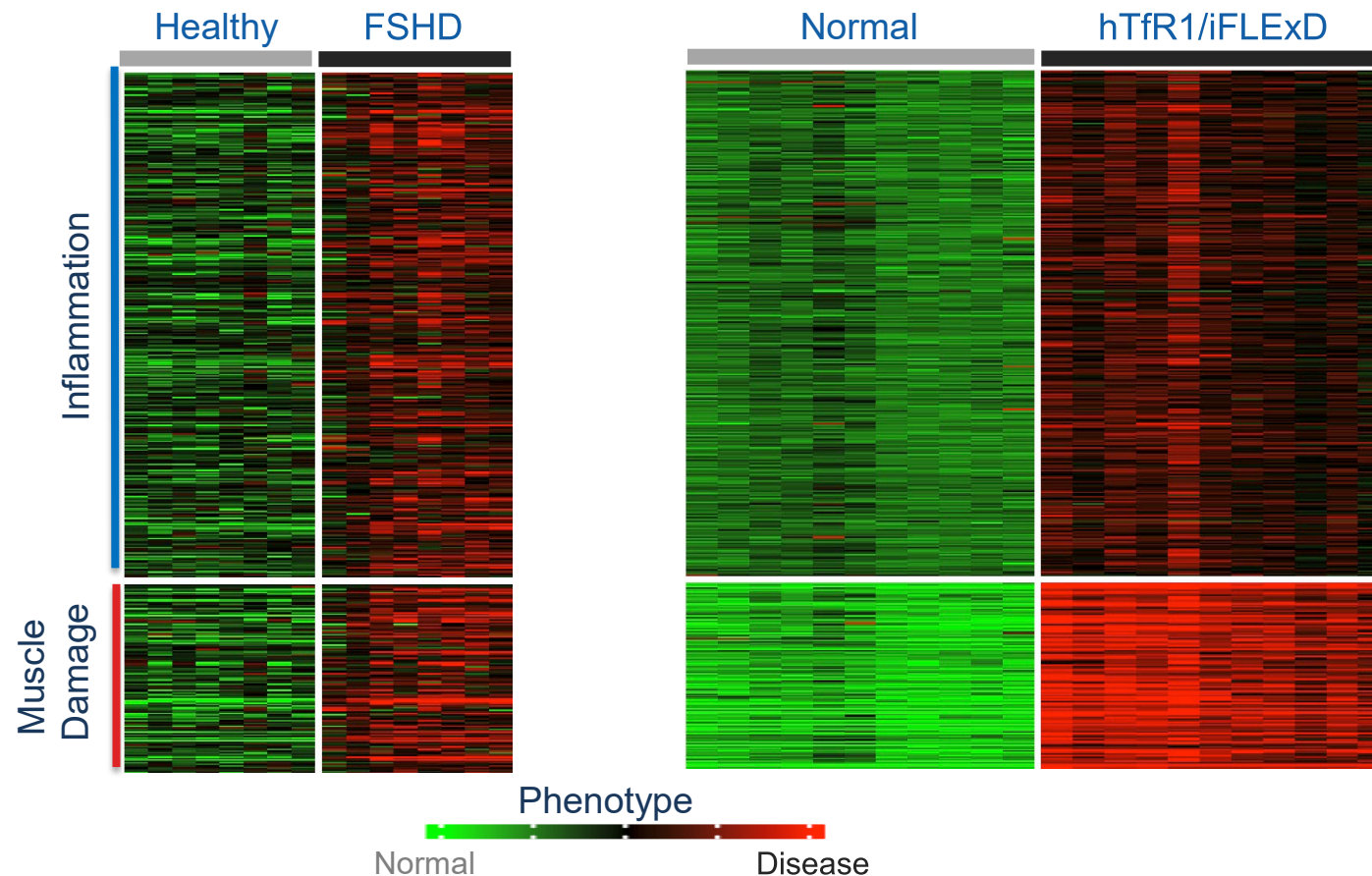
hTfR1/iFLExD Mice Recapitulate Transcriptional Profiles of Immune Response and Muscle Damage Seen in Human FSHD Muscle



Human transcriptome
in skeletal muscle biopsies



Mouse ortholog transcriptome
in quadriceps



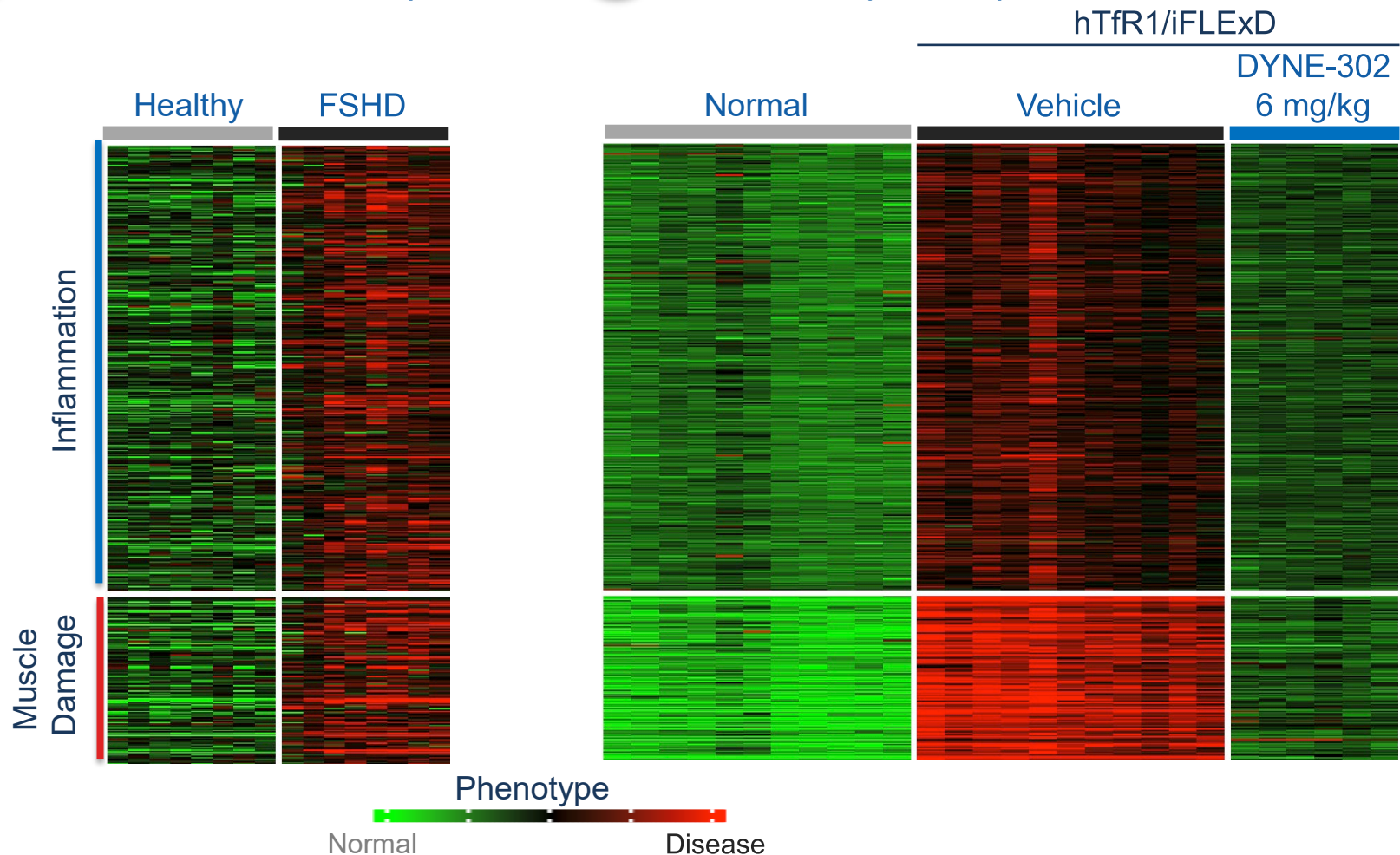
DYNE-302 Normalizes Transcriptional Profiles of Inflammation and Muscle Damage in hTfR1/iFLExD Mice



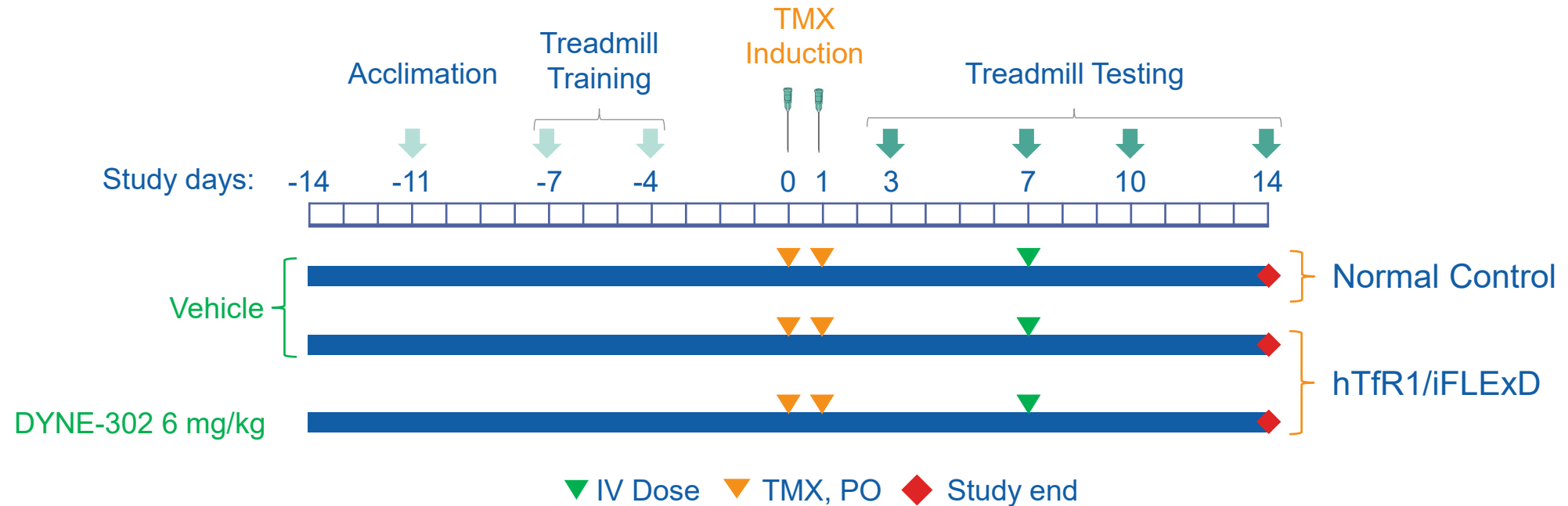
Human transcriptome
in skeletal muscle biopsies



Mouse ortholog transcriptome
in quadriceps



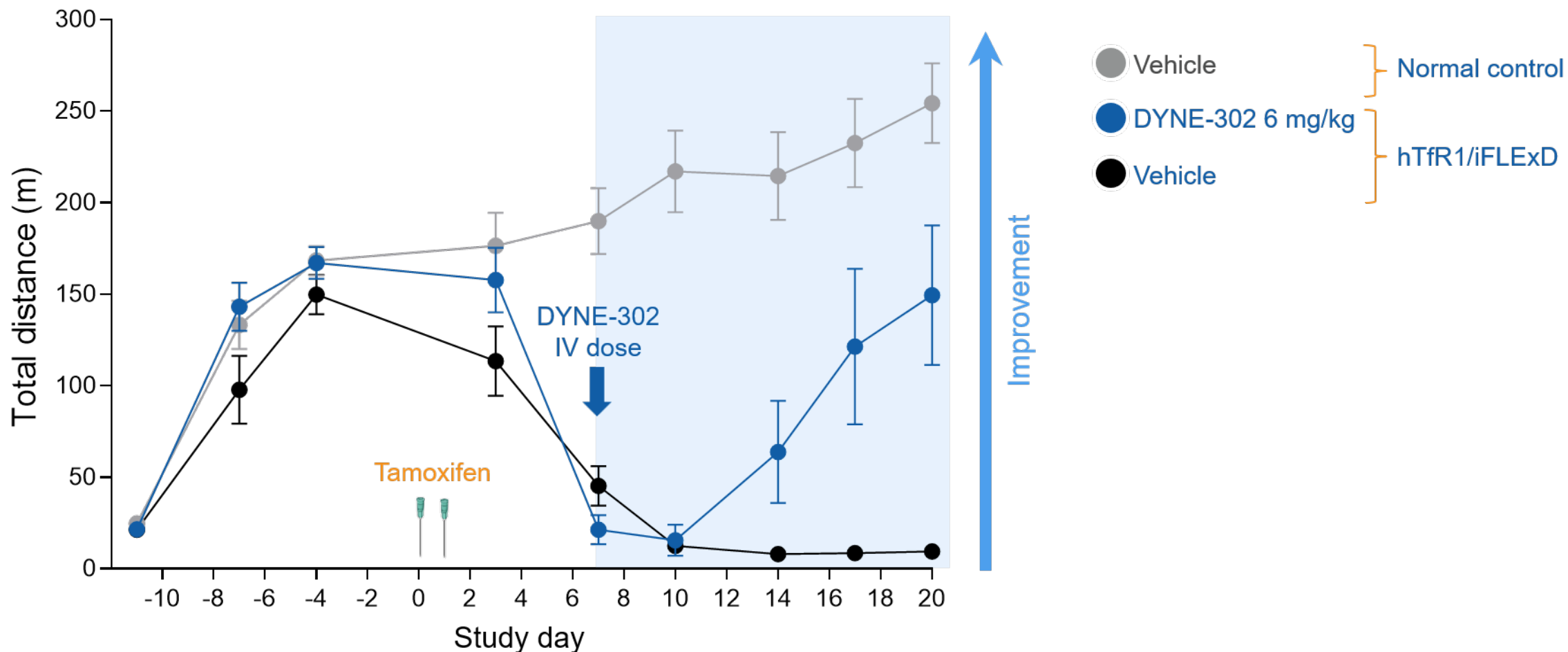
Study to Establish Impact of DYNE-302 Interventional Treatment in the Induced hTfR1/iFLExD Mice



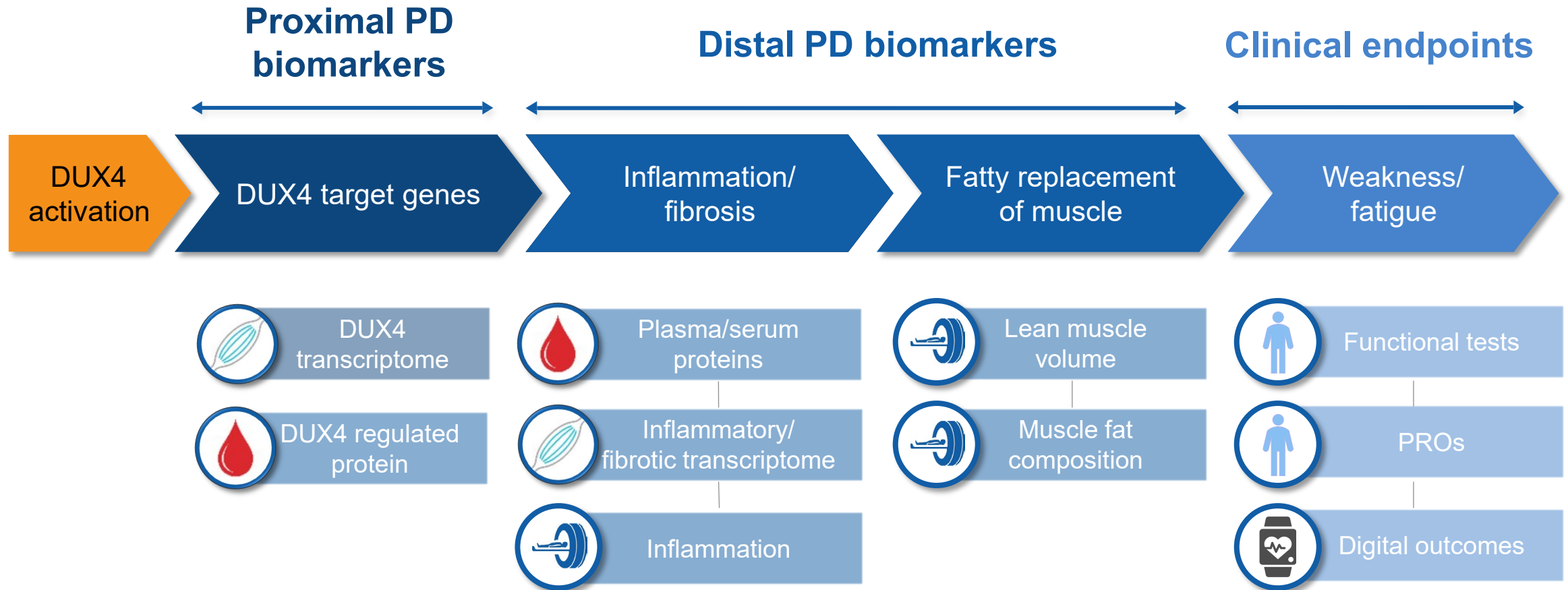
DYNE-302 Interventional Treatment Leads to Functional Improvement in hTfR1/iFLExD Mice



Functional improvement in forced treadmill run test



FSHD Disease Pathogenesis Is the Foundation of DYNE-302 Biomarker Selection Strategy



Unbiased Proteomics Identified DUX4-Regulated KHDC1L as a Circulating Biomarker Candidate in FSHD Plasma



Study Subjects

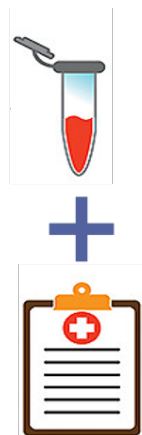


FSHD patients from
Patient Registry
(N=10)



Healthy control
subjects
(N=10)

Sample Collection



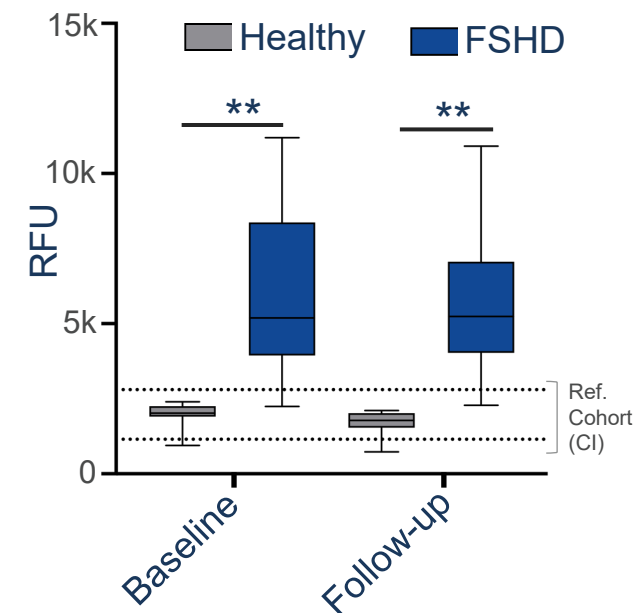
Plasma and metadata
(Baseline, 180 days)

Proteomic Profiling



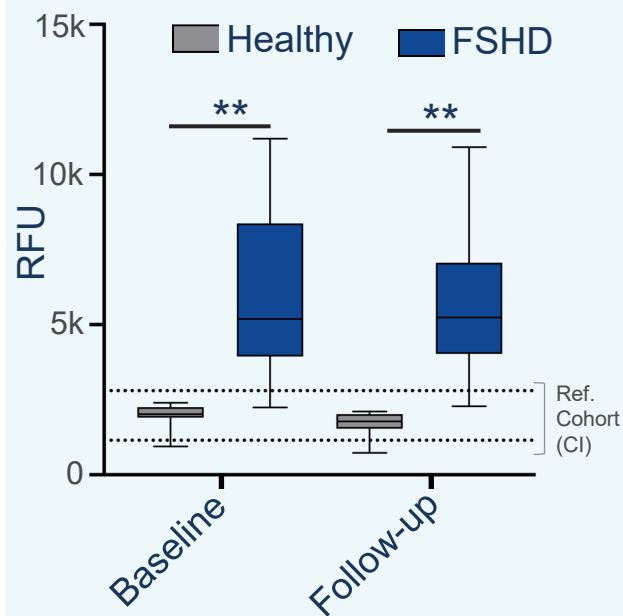
- 11K Proteins (~50% of Human Proteome)
- Reference cohort : ~3K healthy individuals

Plasma KHDC1L Discovered in-house

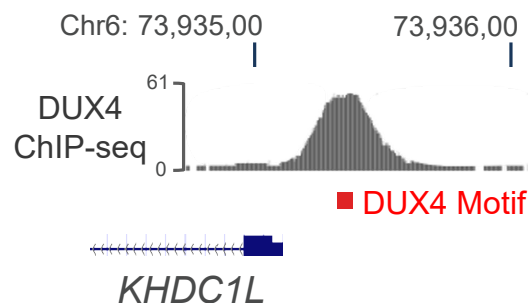


KHDC1L Upregulation in FSHD Tissue and Plasma: Consistent Evidence from Gene to Transcript to Protein

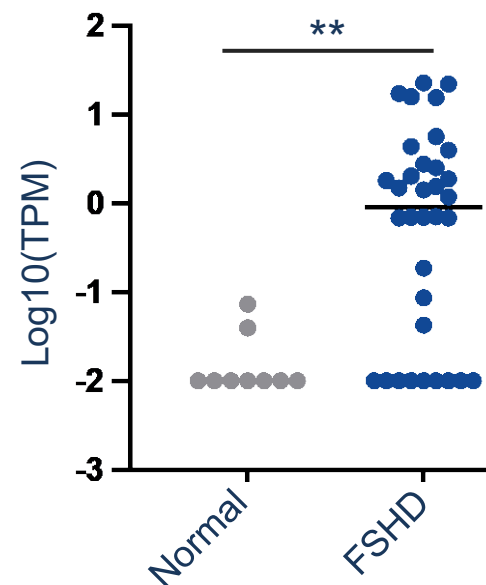
KHDC1L plasma protein levels increased in FSHD



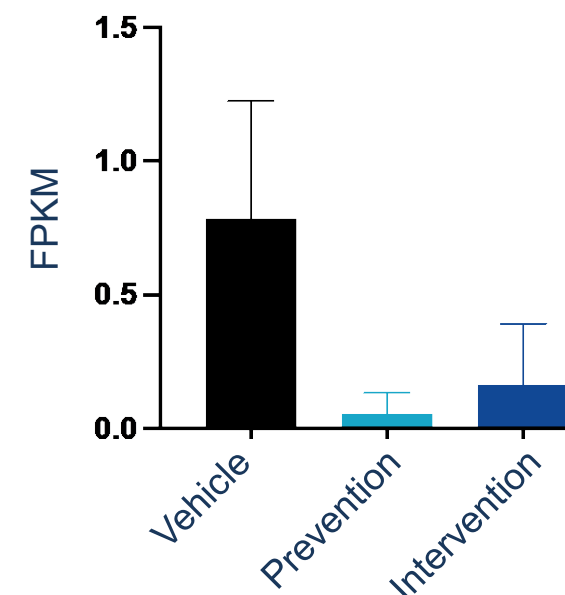
DUX4 binding site in *KHDC1L* promoter¹



KHDC1L mRNA is increased in FSHD muscle biopsies²



DUX4 KD inhibits *KHDC1L* mRNA expression in vitro



Conclusions

- DYNE-302 achieves dose-dependent and durable D4T KD in a chronic mouse model of FSHD
- DYNE-302 normalizes inflammatory and muscle damage transcriptome in an FSHD mouse model
- DYNE-302 leads to functional improvement in an FSHD mouse model with pre-existing and severe disease
- Circulating KHDC1L levels may provide a non-invasive PD biomarker of DUX4 KD

DYNE-302 has received FDA clearance for a Ph1 trial in FSHD

Acknowledgements

Special thanks

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Dyne R&D

