The FORCE™ platform achieves robust and durable DUX4 suppression and functional benefit in FSHD mouse models

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Laura & Chelsea, *living with FSHD*

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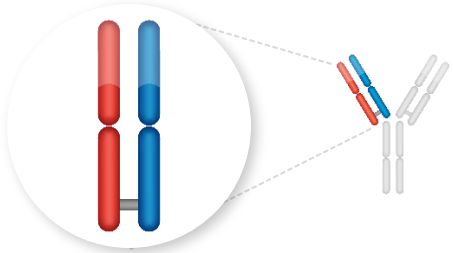
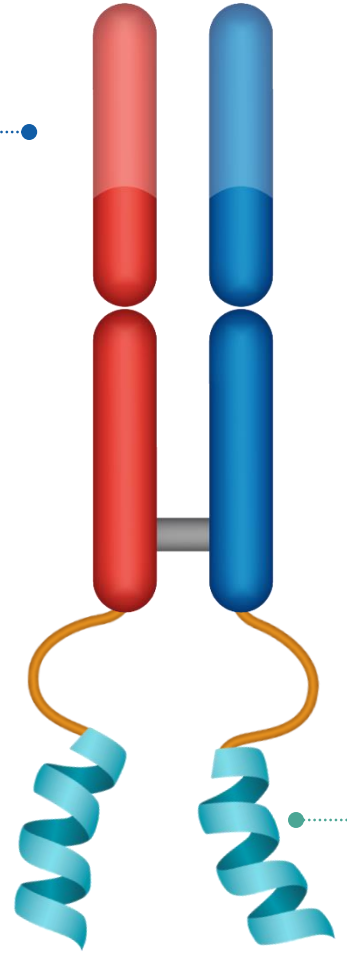
Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



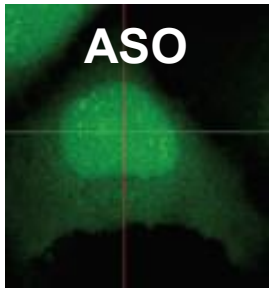


LINKER

Val-cit cleavable linker, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

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



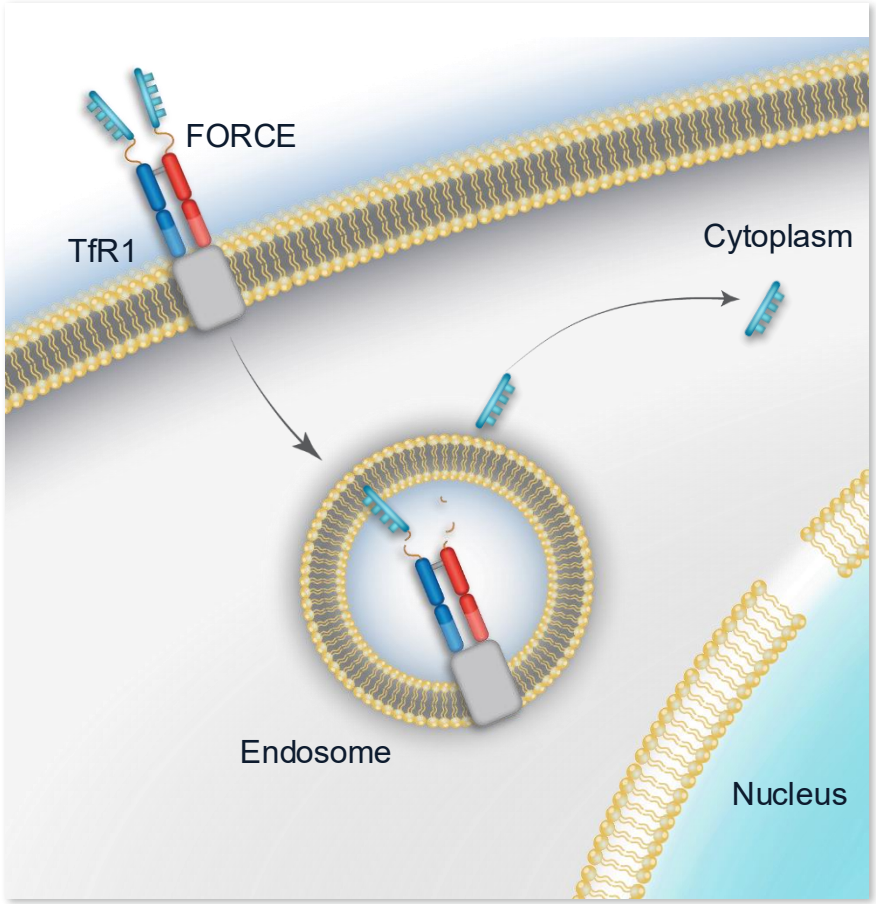
Nuclear localization

Cytoplasmic localization

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

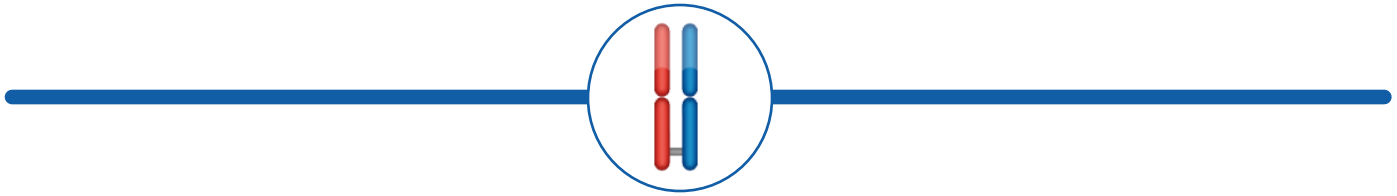
Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

FORCE Platform Harnesses Cell Biology to Modify Disease



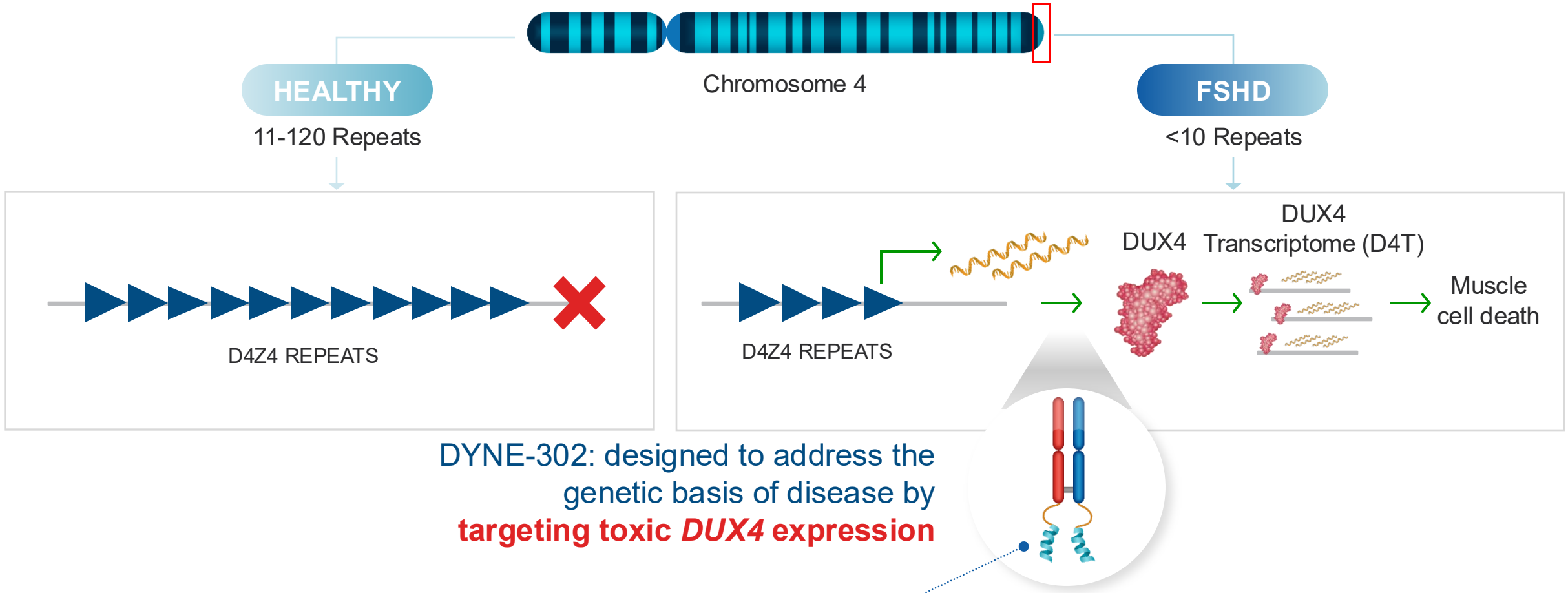
- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

Fabs Offer Multiple Advantages for Targeted Delivery



Feature	Fab	
Delivery to Muscle	Enhanced delivery of payloads	✓
Enhanced Tissue Penetration	1/3 size of mAb leads to increased tissue penetration	✓
Tolerability	Lower protein load leads to potentially increased tolerability	✓
Effector Cell Activation	Lower risk due to lack of Fc domain	✓
Complement Activation	Lower risk due to lack of Fc domain	✓
Large Scale Manufacturing	Yields enable large scale manufacturing	✓

DYNE-302 Targets the Genetic Basis of FSHD

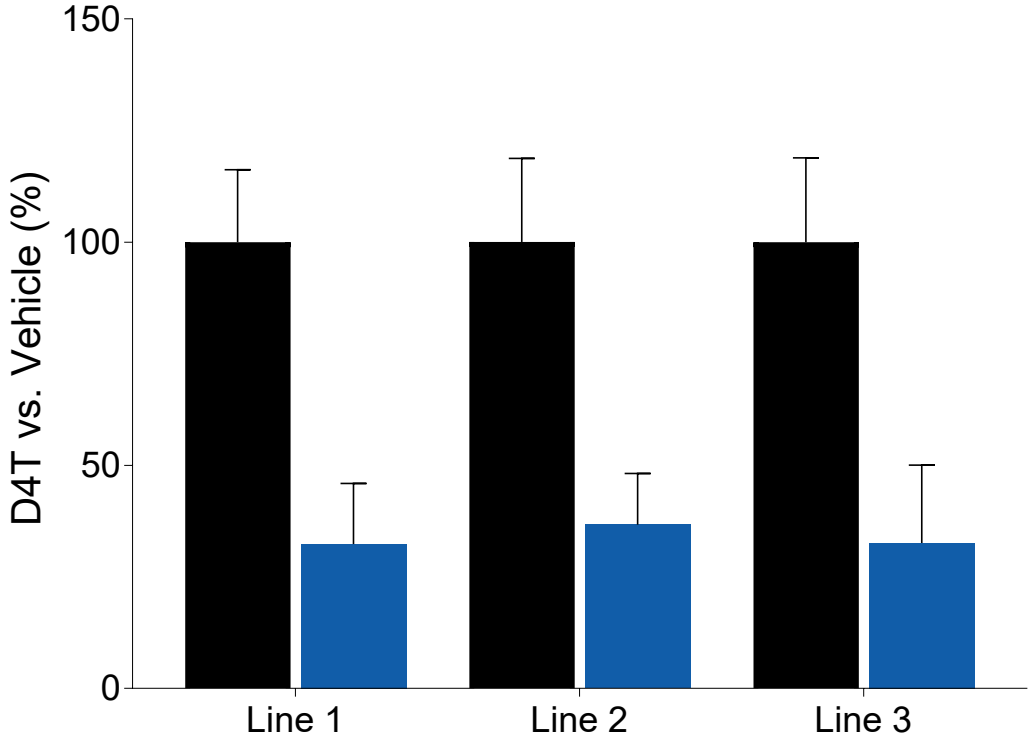


DYNE-302: designed to address the genetic basis of disease by **targeting toxic *DUX4* expression**

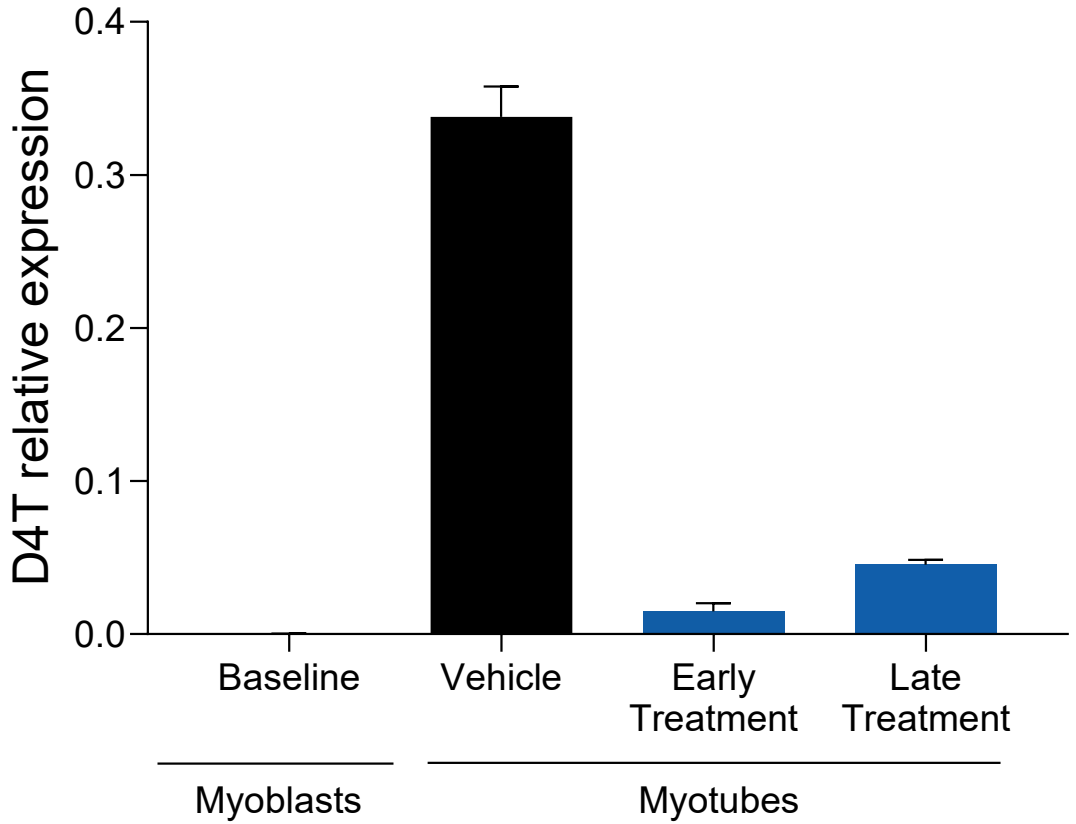
- Highly selective *DUX4* siRNA payload with favorable *in vitro* off-target and *in vitro* tolerability profile
- Extended duration of action intended to overcome sporadic DUX4 activation

DYNE-302 Suppresses D4T Expression *in vitro* in FSHD Myotubes

Early treatment with DYNE-302 prevents D4T expression



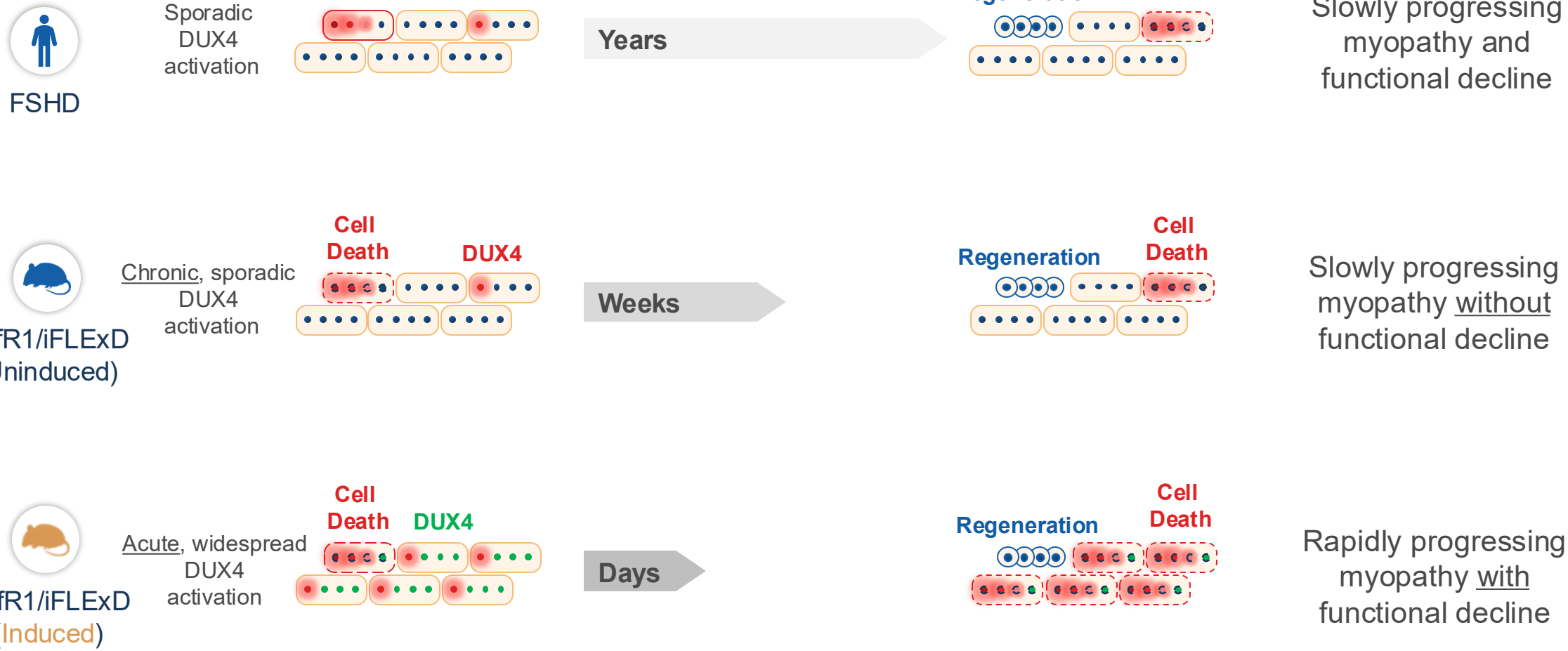
DYNE-302 reverses established D4T expression



Vehicle DYNE-302

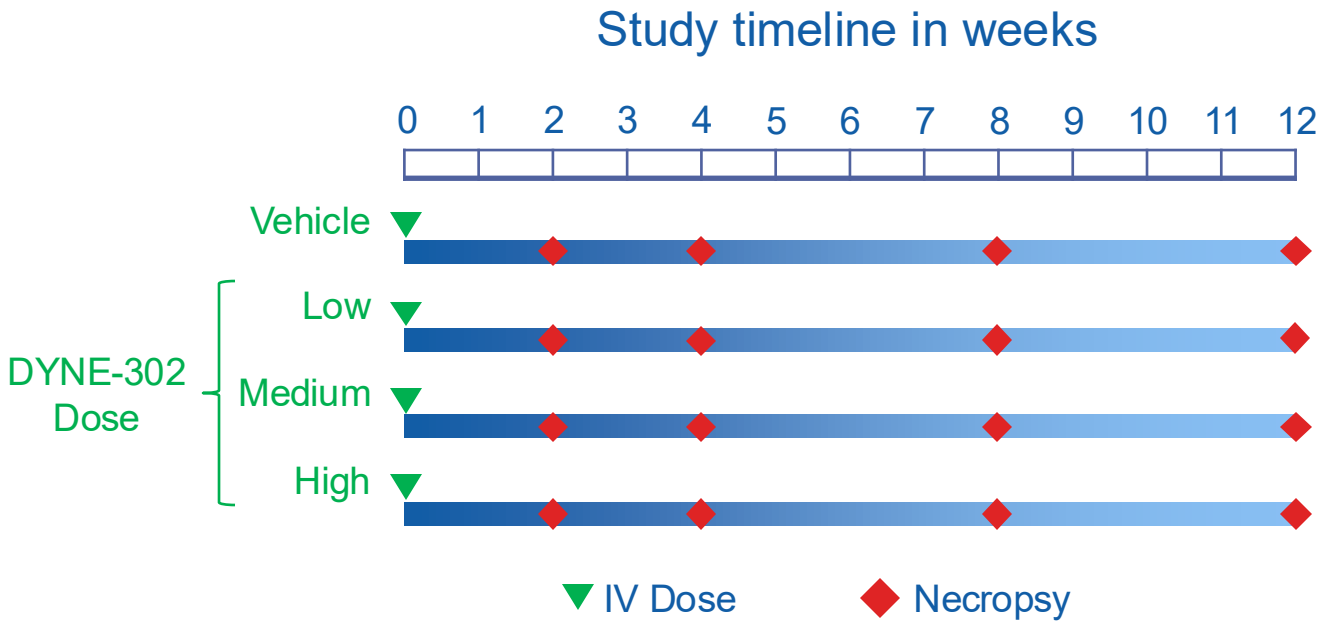
Notes: DYNE-302 added at day 0 (early treatment) or day 5 (late treatment) post-differentiation. Left: Geometric mean +/- SD 7 days post-differentiation, DYNE-302 added at Day 0
Data are mean + SD; n = 3; D4T (DUX4 transcriptome) is the mean of *MBD3L2, TRIM43, ZSCAN4* mRNA expression. *RPL13A* was used as housekeeping gene for D4T expression

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



Notes: Jones et al. (2020) DOI: 1186/s13395-020-00227-4

Study to Establish DYNE-302 Extent and Duration of Action *in vivo* in the Uninduced hTfR1/iFLExD FSHD Mouse Model



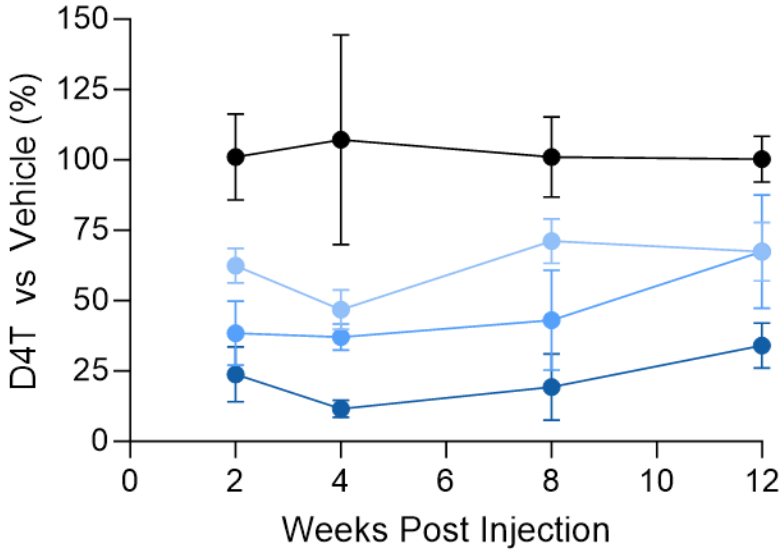
Readouts

- D4T KD dose-response and duration in skeletal muscle
- Myofiber pathology in skeletal muscle

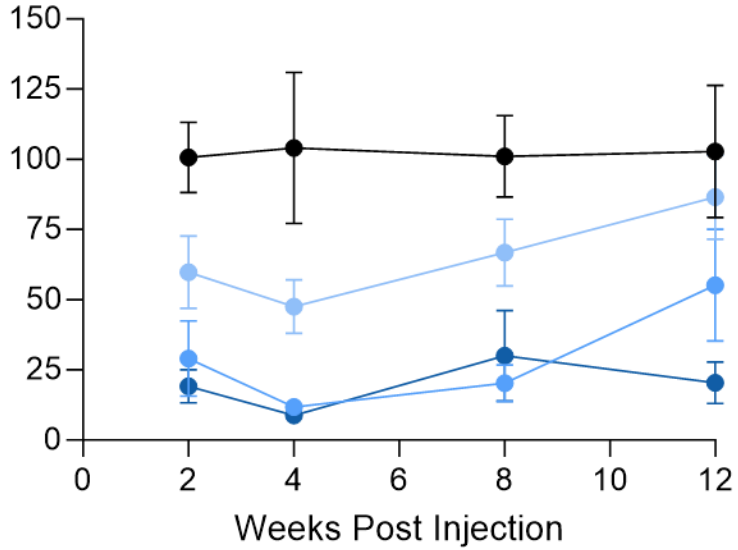
Notes: IV = intravenous

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

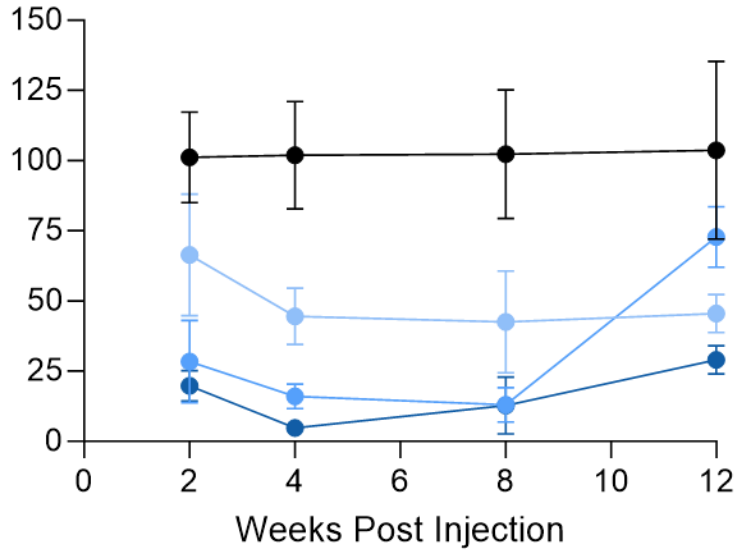
Quadriceps



Gastrocnemius



Tibialis Anterior



Vehicle | DYNE-302 Low Dose | DYNE-302 Medium Dose | DYNE-302 High Dose

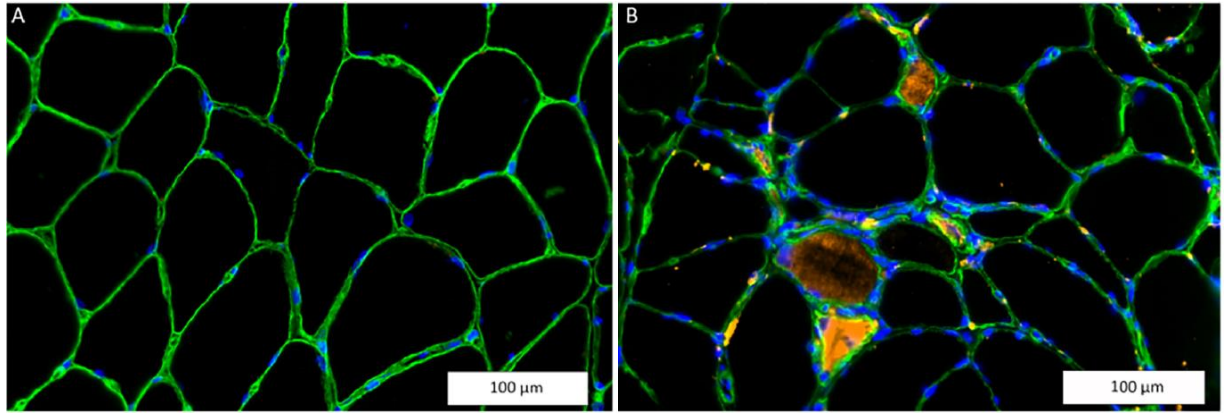
DYNE-302 demonstrates potential for infrequent dosing, out to Q12W

Notes: Uninduced hTfR1/iFLExD mice dosed with vehicle or DYNE-302 on day 0, analyzed at indicated weeks. Data are means ± SD; n = 4 - 12. D4T is an average of mouse *Wfdc3*, *Sord*, and *Serpinb6c* mRNA markers.

hTfR1/iFLExD Mouse Model Recapitulates Fiber Splitting Characteristic of FSHD Muscle

Human FSHD muscle

Normal | FSHD

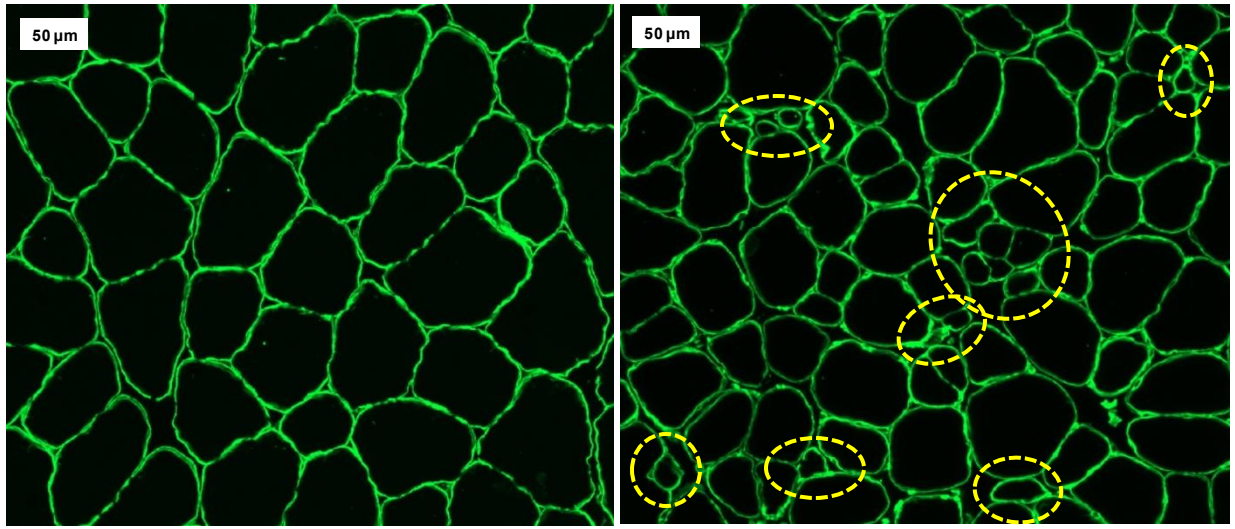


Laminin
Nuclei
Embryonic MHC

Source: Hubregtse et al., *Neuromuscular Disorders* 36:6-15, 2024

hTfR1/iFLExD mouse quadriceps

Normal | hTfR1/iFLExD

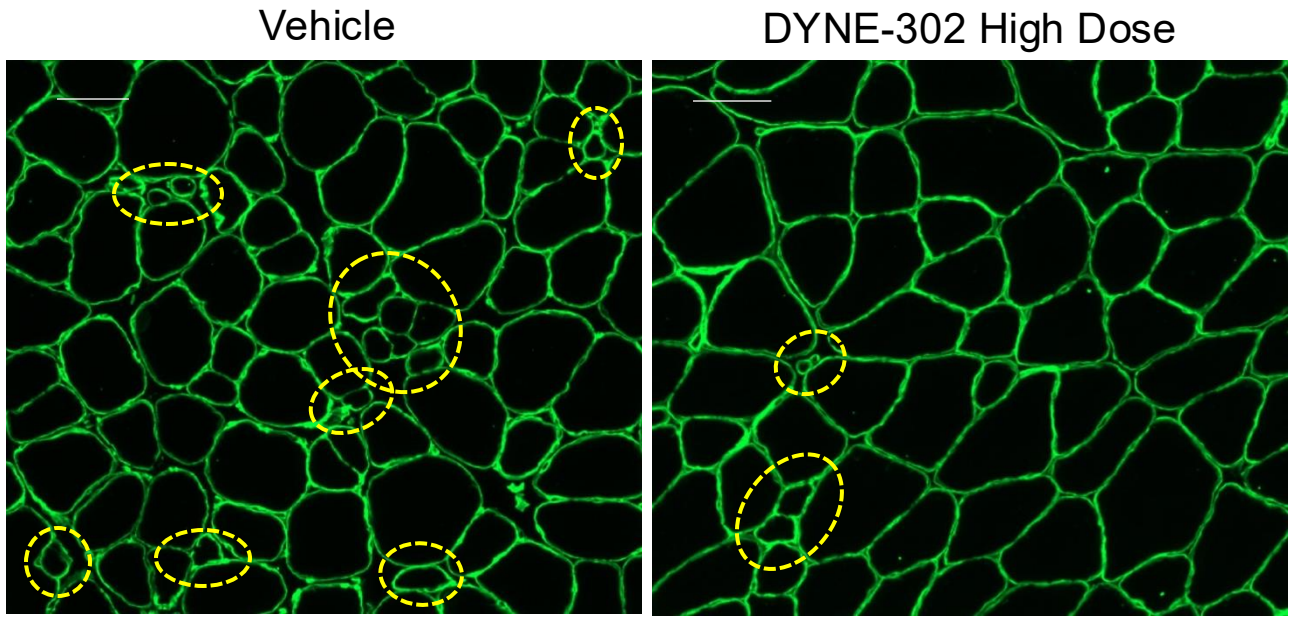


Laminin

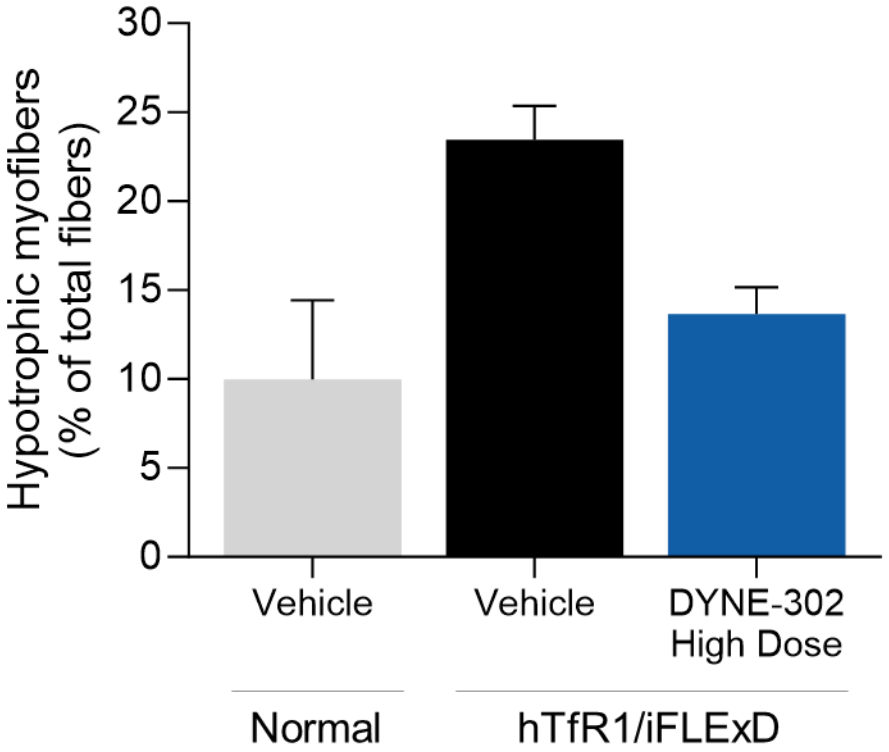
Fiber splitting

Single Dose of DYNE-302 Corrects Muscle Pathology in Quadriceps of the Uninduced hTfR1/iFLExD FSHD Model at 12 Weeks

DYNE-302 reduces hypotrophic myofibers

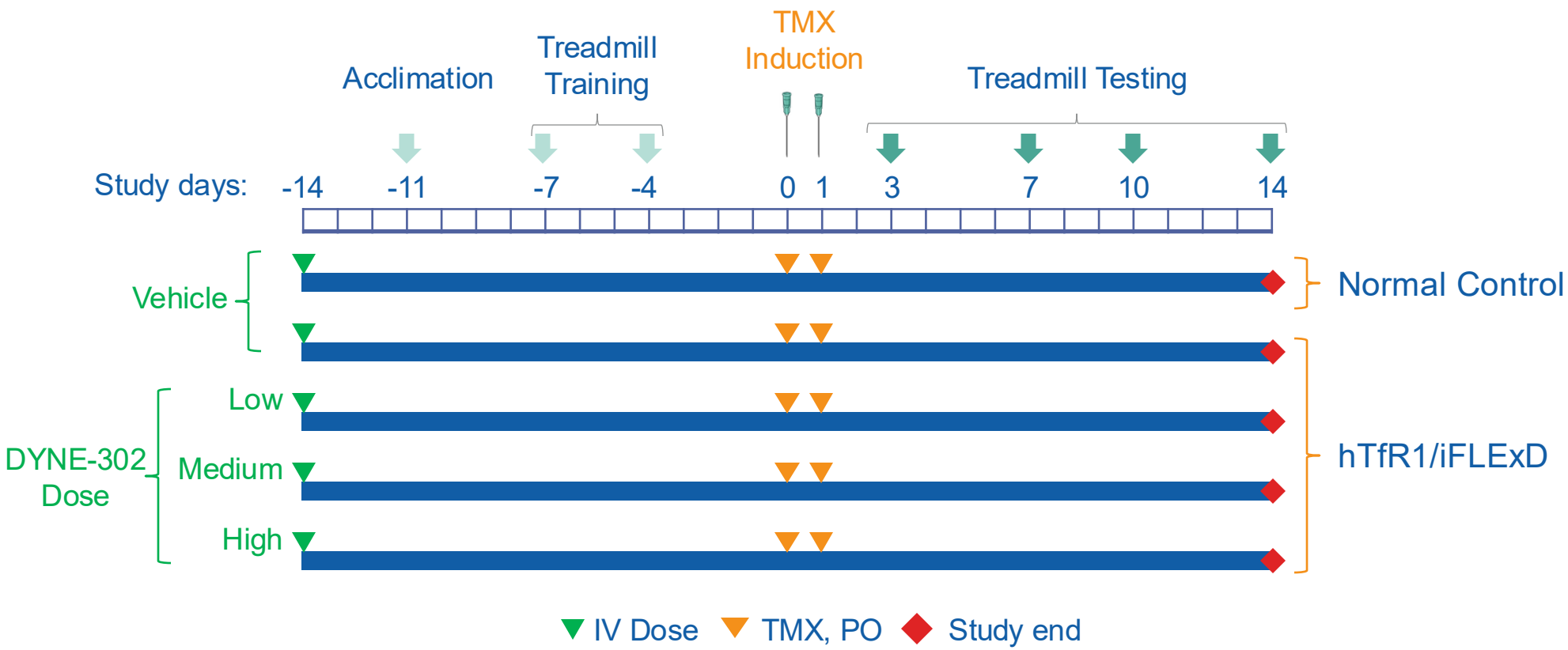


Quantification of hypotrophic myofiber reduction



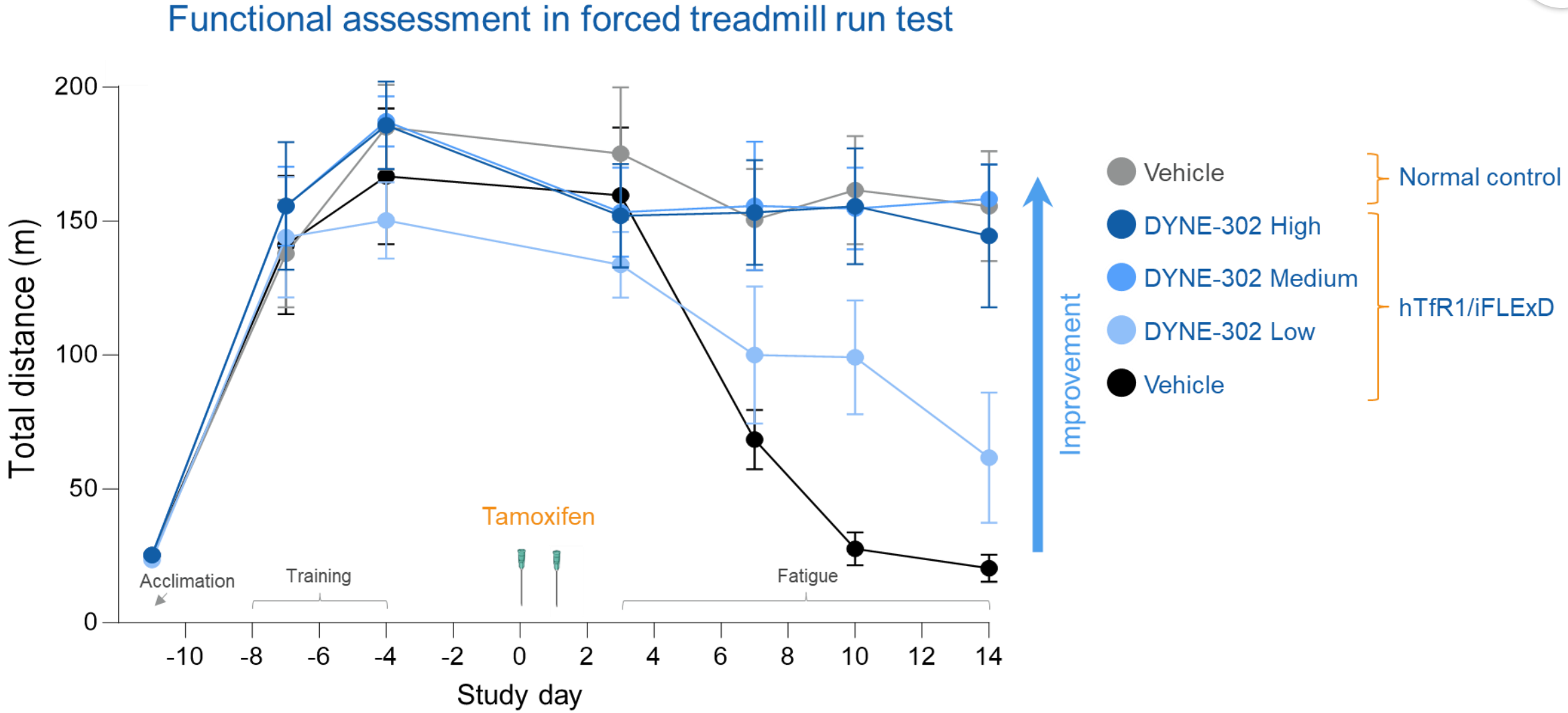
Notes: Uninduced hTfR1/iFLExD mice dosed with vehicle or DYNE-302 on day 0, analyzed on week 12. Data are means + SD; n = 4 – 9.

Study to Establish DYNE-302 Functional Benefit in the Induced hTfR1/iFLExD FSHD Mouse Model



Notes: IV = intravenous; PO = oral gavage; TMX = tamoxifen; hTfR1/iFLExD mice lacking ACTA-CRE-ER transgene were used as controls for TMX effect on function (normal control). hTfR1/iFLExD mice that were not induced with tamoxifen were also included as uninduced control (not shown).

Single Dose of DYNE-302 Demonstrates Functional Benefit in the Induced hTfR1/iFLExD FSHD Mouse Model



Notes: Mice dosed with vehicle or DYNE-302 on Day -14. Data are means ± SEM; n = 5 - 6.

Conclusions

- DYNE-302 suppresses expression of D4T in myotubes from individuals with FSHD
- DYNE-302 demonstrates dose-dependent, durable D4T KD and normalizes muscle pathology in a chronic mouse model of FSHD
- DYNE-302 effectively preserves muscle function in an acute mouse model of FSHD
- Durability of pharmacodynamics in muscle suggests potential for quarterly dosing
- Effective delivery of siRNA to muscle confirms modularity of the FORCE platform

Data support the potential of DYNE-302 for the treatment of FSHD

Acknowledgements

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Dyne R&D