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

Thomas Natoli, Ph.D.

Senior Director

FSHD International Research Conference

June 13th, 2024

Laura & Chelsea, *living with FSHD*

Forward-Looking Statements & Disclaimer

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding Dyne's strategy, future operations, prospects and plans, objectives of management, the potential of the FORCE platform, the anticipated timelines for reporting additional data for DYNE-302, expectations regarding the initiation of additional preclinical studies or clinical trials of DYNE-302, and plans to provide future updates on pipeline programs, constitute forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. The words "anticipate," "believe," "continue," "could," "estimate," "expect," "intend," "may," "might," "objective," "ongoing," "plan," "predict," "project," "potential," "should," or "would," or the negative of these terms, or other comparable terminology are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Dyne may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various important factors, including: uncertainties inherent in the identification and development of product candidates, including the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies and clinical trials; the timing of and Dyne's ability to enroll patients in clinical trials; whether results from preclinical studies and initial data from early clinical trials will be predictive of the final results of the clinical trials or future trials; whether Dyne's cash resources will be sufficient to fund its foreseeable and unforeseeable operating expenses and capital expenditure requirements; as well as the risks and uncertainties identified in Dyne's filings with the Securities and Exchange Commission (SEC), including the Company's most recent Form 10-Q and in subsequent filings Dyne may make with the SEC. In addition, the forward-looking statements included in this presentation represent Dyne's views as of the date of this presentation. Dyne anticipates that subsequent events and developments will cause its views to change. However, while Dyne may elect to update these forward-looking statements at some point in the future, it specifically disclaims any obligation to do so.

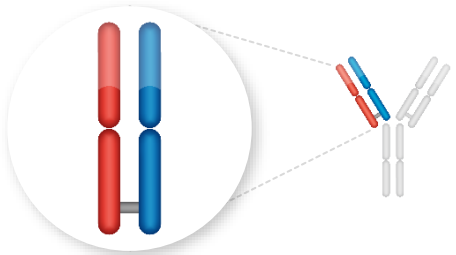
These forward-looking statements should not be relied upon as representing Dyne's views as of any date subsequent to the date of this presentation. This presentation also contains estimates, projections and other statistical data made by independent parties and by the Company relating to market size and growth and other data about the Company's industry and business. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. The Company has not independently verified the accuracy and completeness of the information obtained by third parties included in this presentation. In addition, projections, assumptions and estimates of the Company's future performance and the future performance of the markets in which the Company operates are necessarily subject to a high degree of uncertainty and risk.

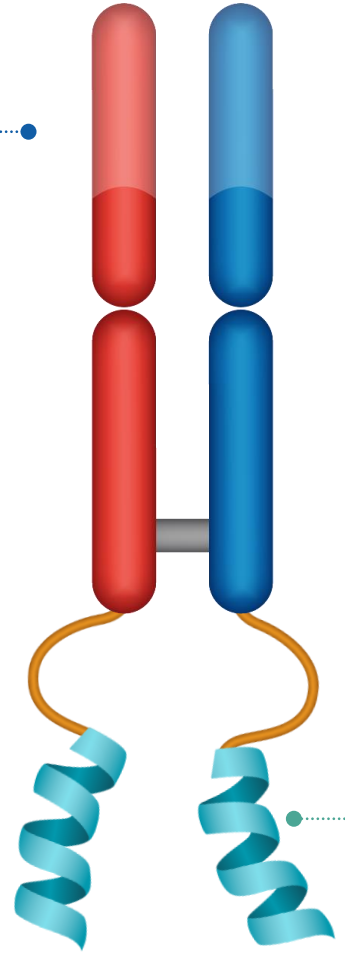
The FORCE platform and DYNE-302 are investigational or otherwise in development and have not been approved as safe or effective by the FDA or any other regulatory authority.

Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



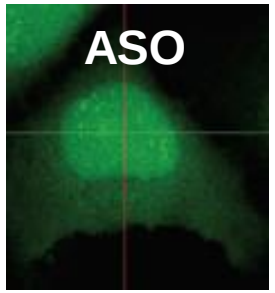


LINKER

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



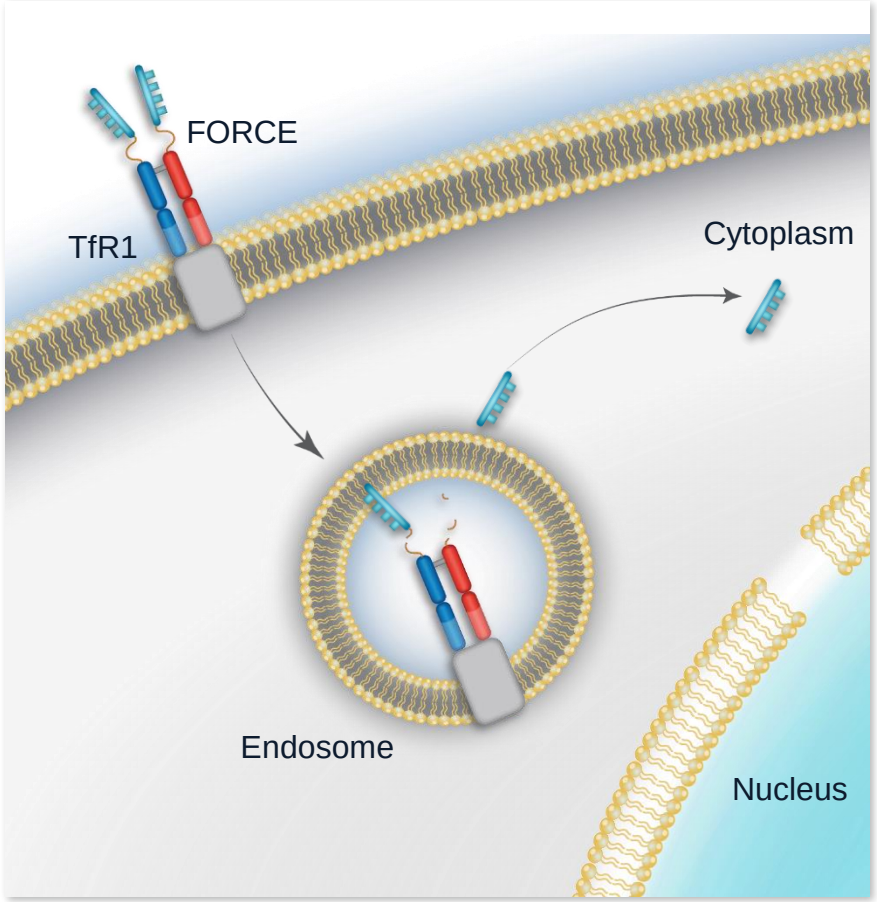
Nuclear localization

Cytoplasmic localization

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

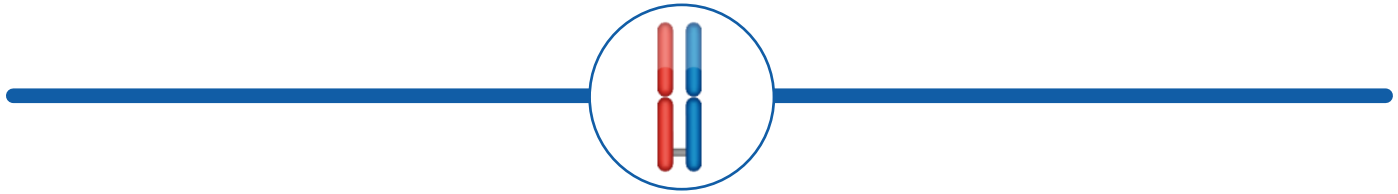
Adapted from Ohrt T., et al. *Nucleic Acids Res* 2006;34:1369.

FORCE Platform Harnesses Cell Biology to Modify Disease



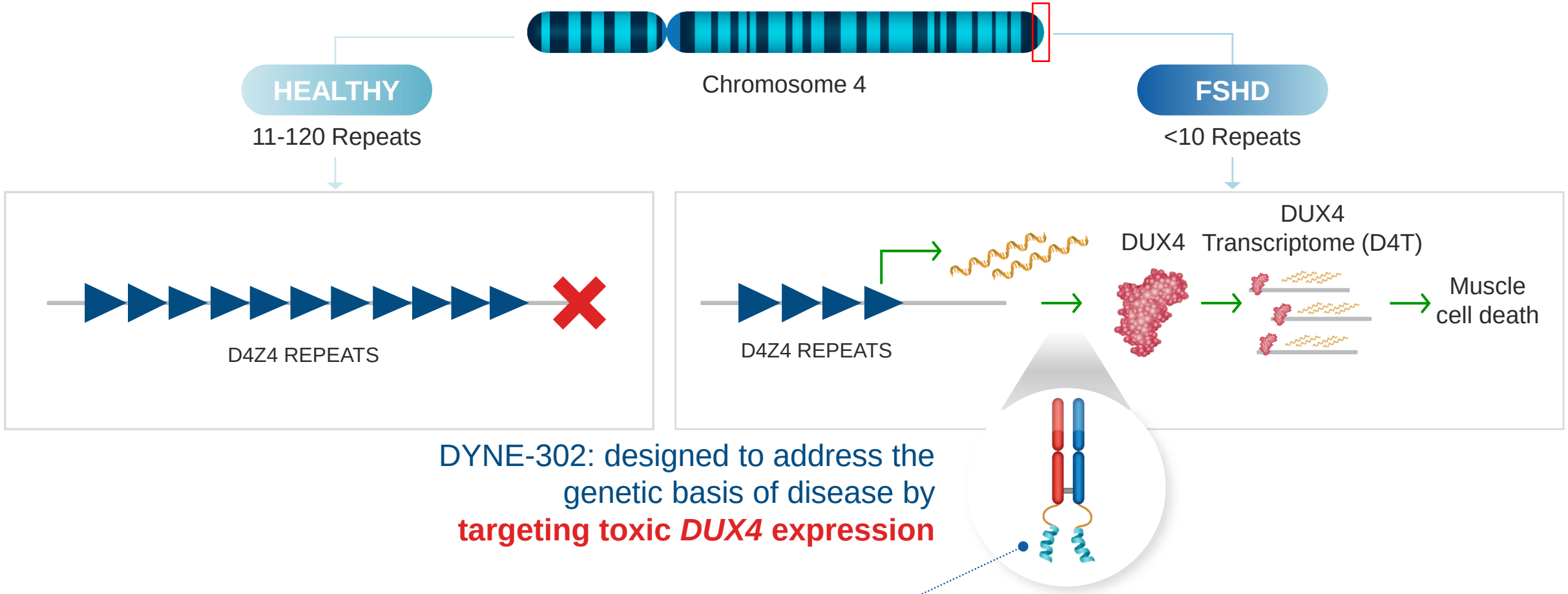
- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index

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

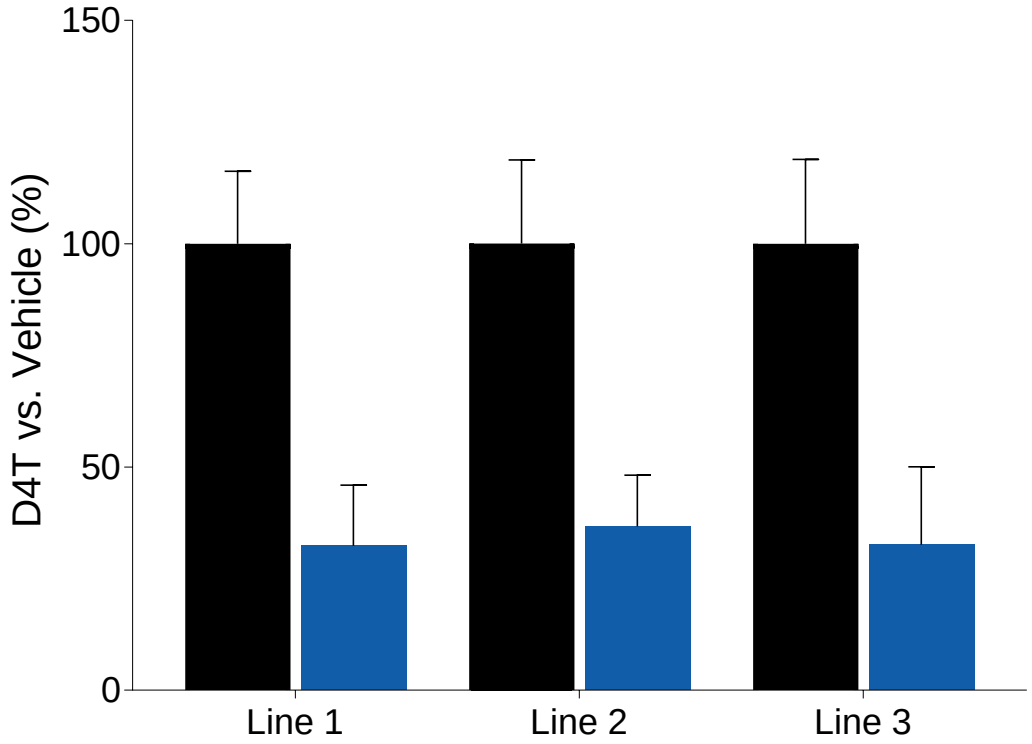


DYNE-302: designed to address the genetic basis of disease by **targeting toxic *DUX4* expression**

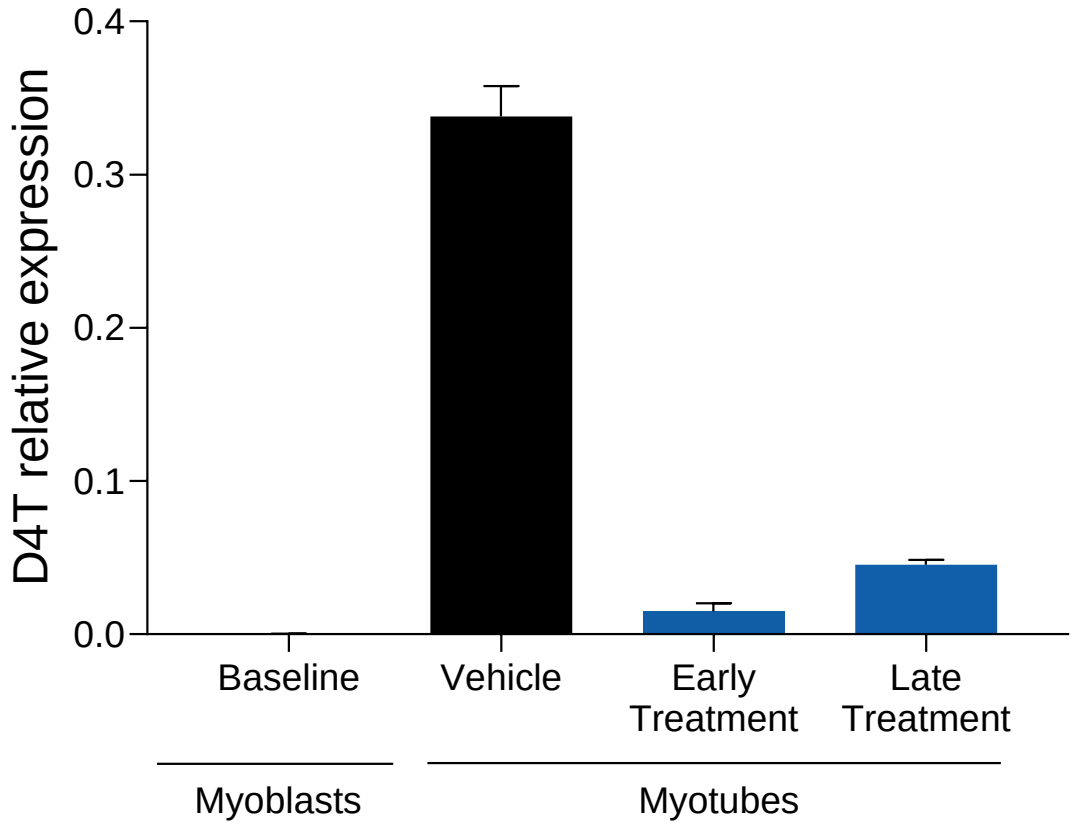
- Highly selective *DUX4* siRNA payload with favorable *in vitro* off-target and *in vitro* tolerability profile
- Extended duration of action intended to overcome sporadic DUX4 activation

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

Early treatment with DYNE-302 prevents D4T expression



DYNE-302 reverses established D4T expression



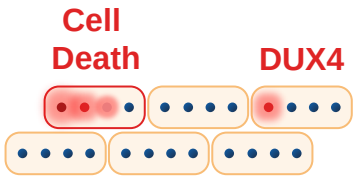
Vehicle DYNE-302

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

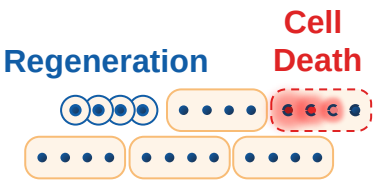
The hTfR1/iFLExD Mouse Model Recapitulates Multiple Aspects of Human FSHD

FSHD

Sporadic DUX4 activation



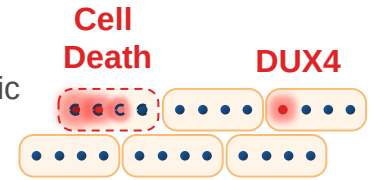
Years



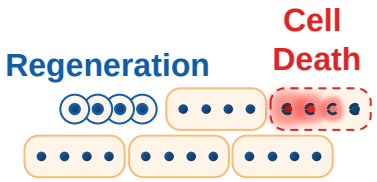
Slowly progressing myopathy and functional decline

hTfR1/iFLExD (Uninduced)

Chronic, sporadic DUX4 activation



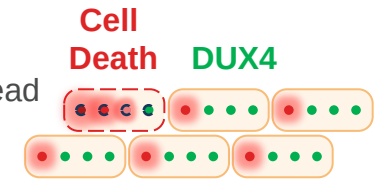
Weeks



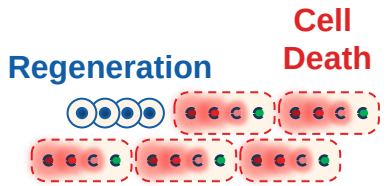
Slowly progressing myopathy without functional decline

hTfR1/iFLExD (Induced)

Acute, widespread DUX4 activation



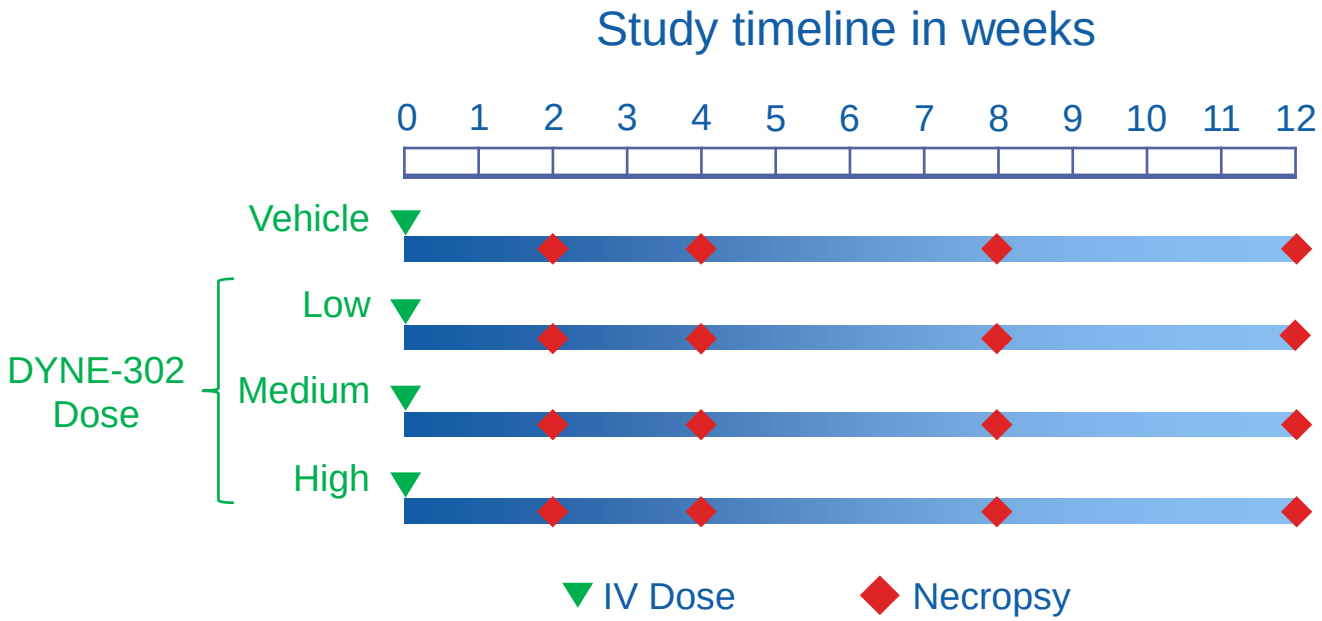
Days



Rapidly progressing myopathy with functional decline

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



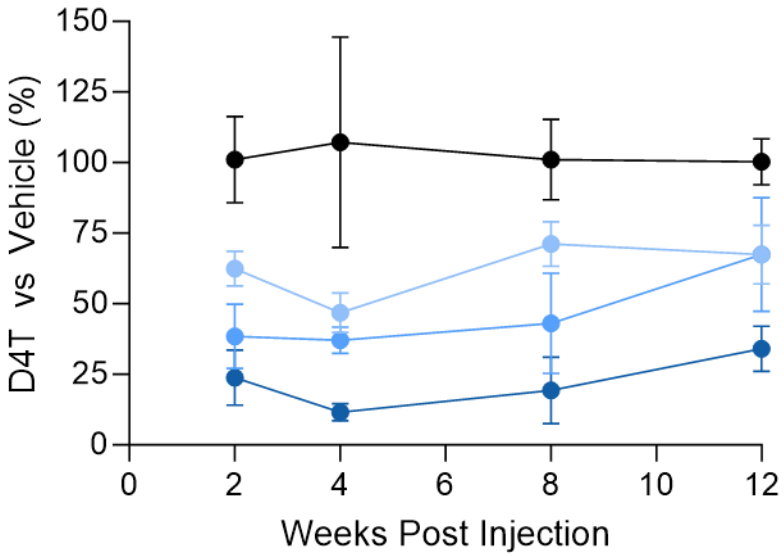
Readouts

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

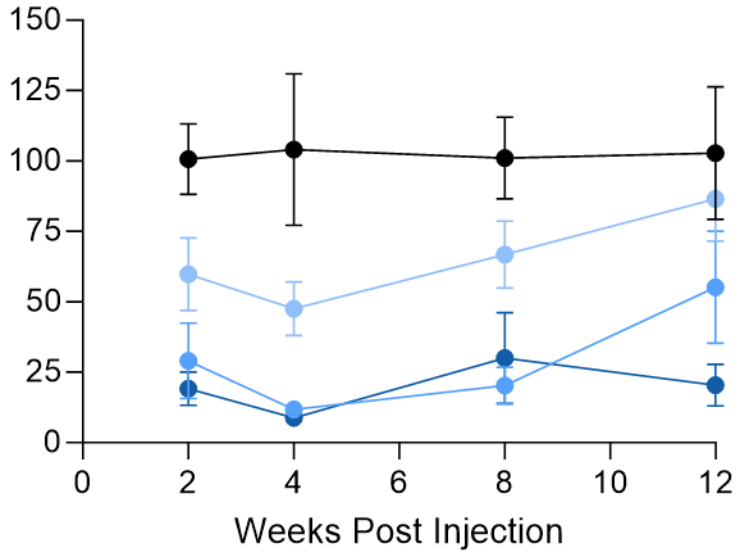
Notes: IV = intravenous

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

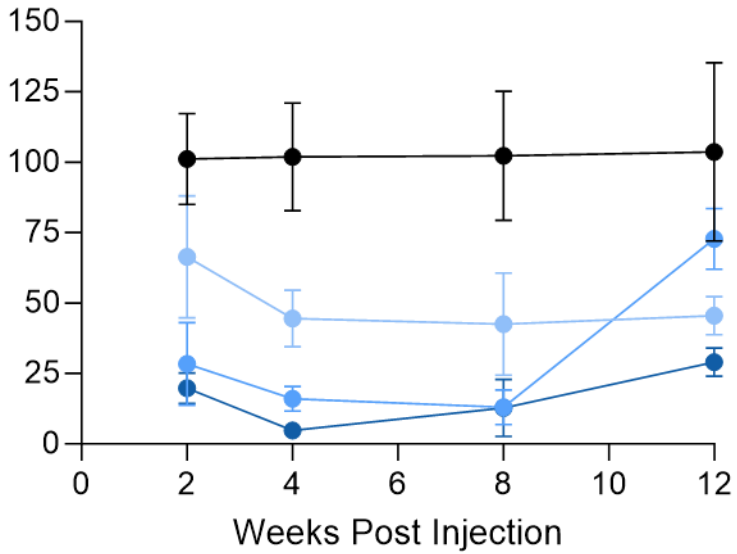
Quadriceps



Gastrocnemius



Tibialis Anterior



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

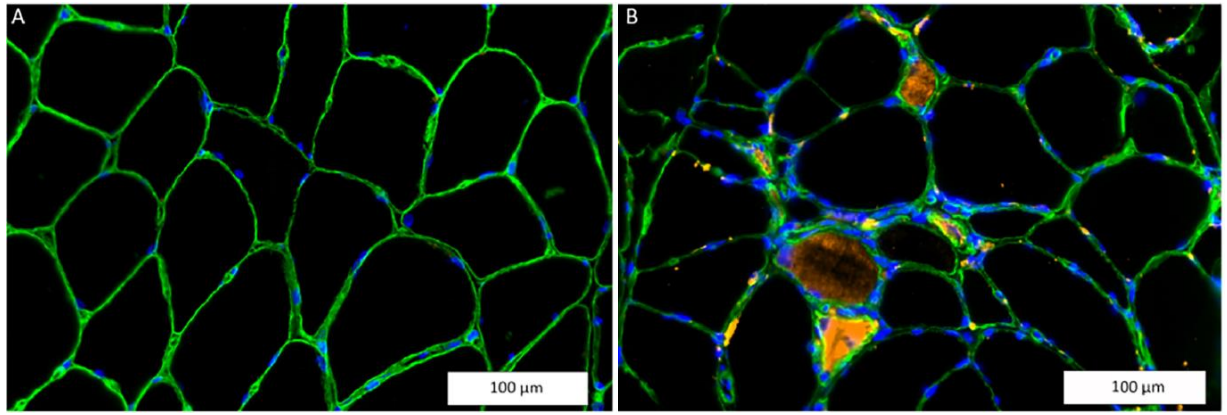
DYNE-302 demonstrates potential for infrequent dosing, out to Q12W

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

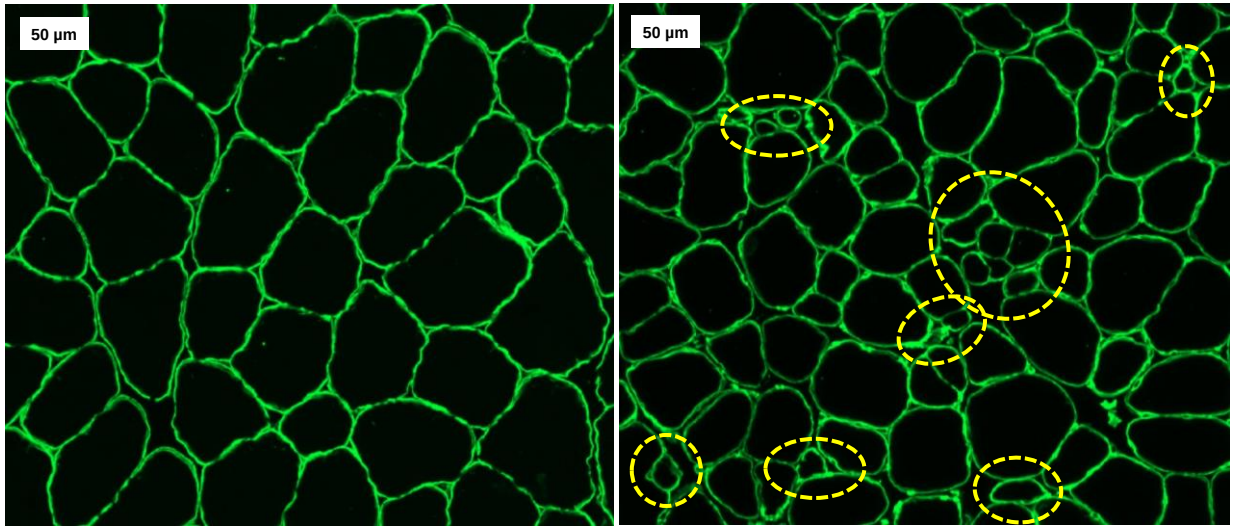


Laminin
Nuclei
Embryonic MHC

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

hTfR1/iFLExD mouse quadriceps

Normal | hTfR1/iFLExD

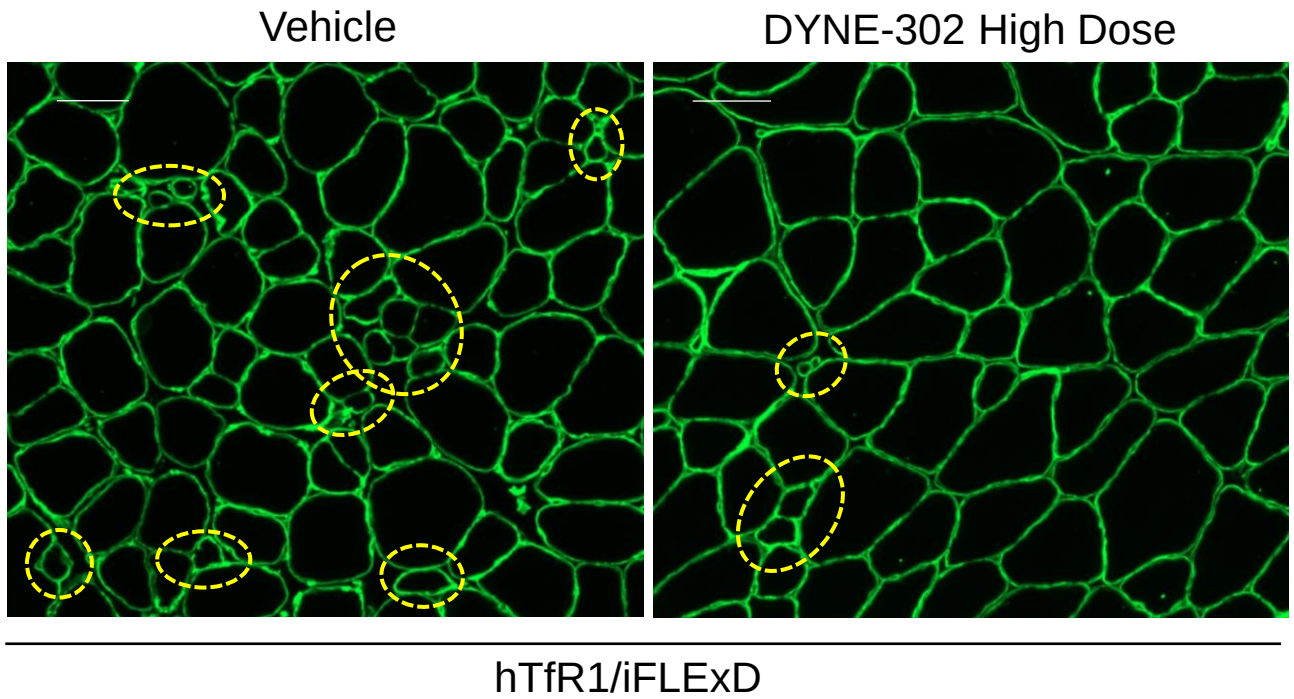


Laminin

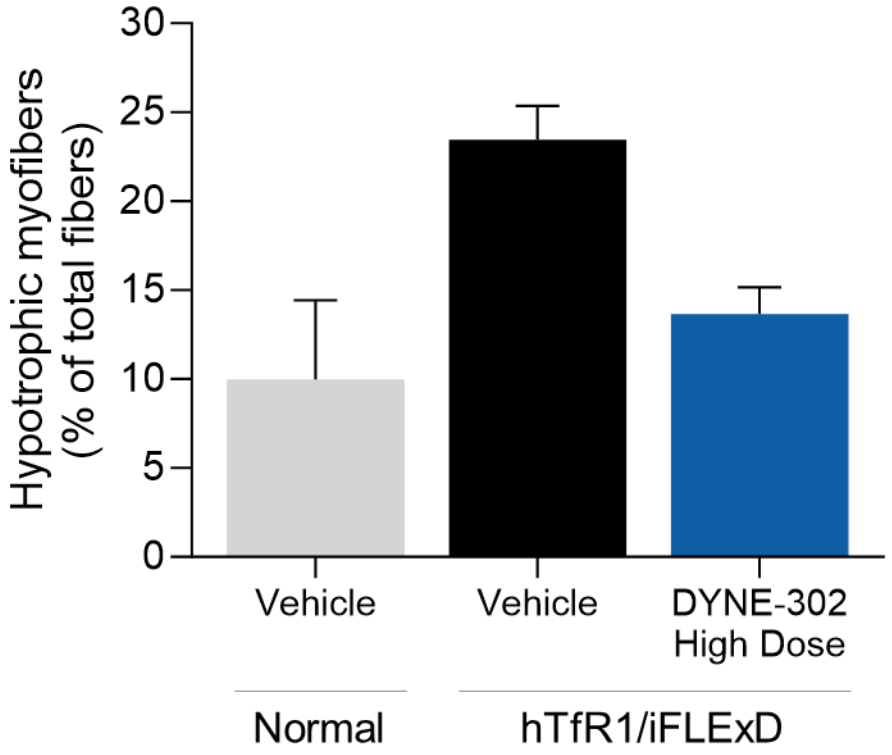
Fiber splitting

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

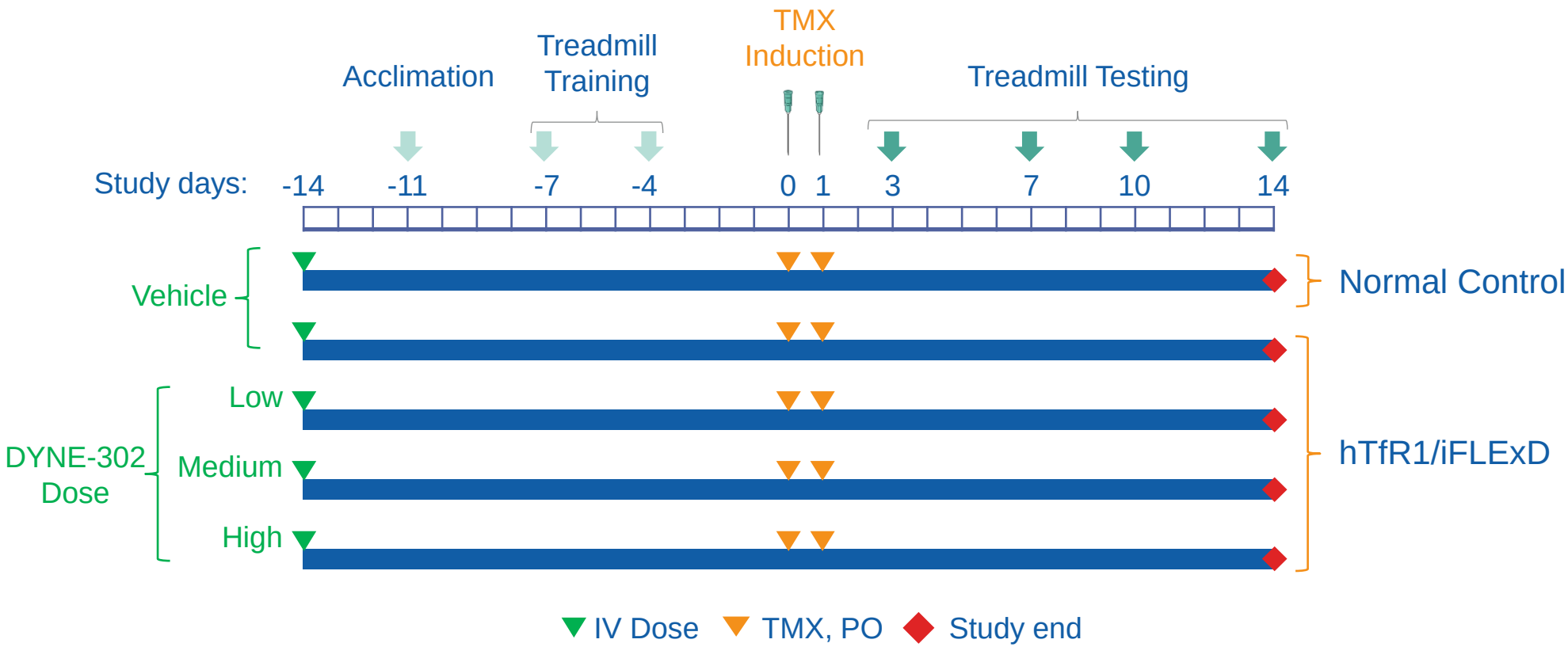


Quantification of hypotrophic myofiber reduction



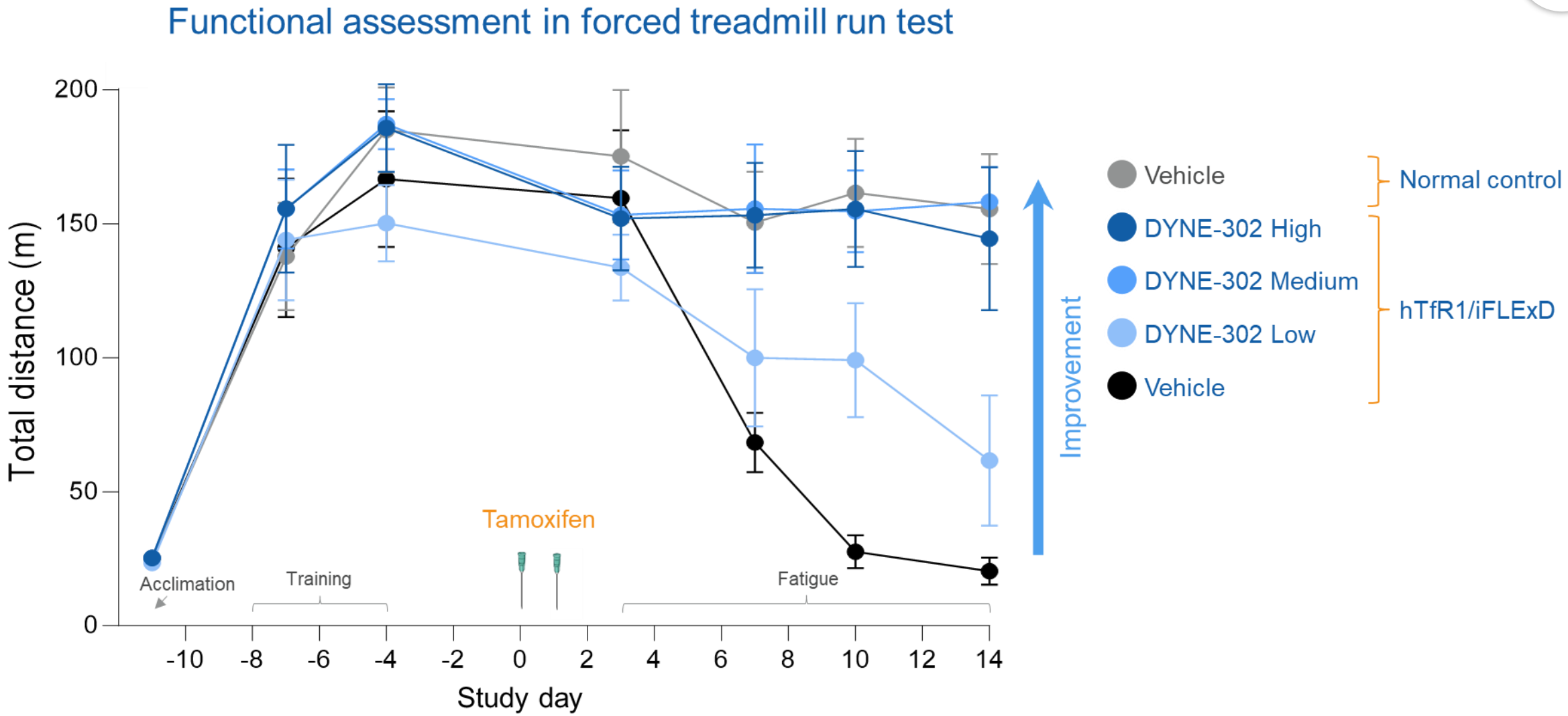
Notes: Uninduced hTfR1/iFLExD mice dosed with vehicle or DYNE-302 on day 0, analyzed on week 12. Data are means + SD; n = 4 – 9.

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

Special thanks

- Dr. Rabi Tawil, *University of Rochester, Rochester, NY*
- Dr. Peter Jones, *University of Nevada, Reno, NV*
- Dr. Vincent Mouly, *Institut de Myologie, Paris, France*

Dyne R&D