DYNE-302 leads to functional improvement and resolves muscle transcriptomic changes in mouse models of FSHD

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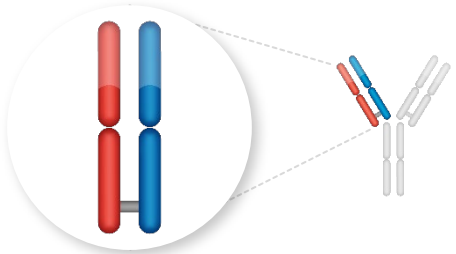
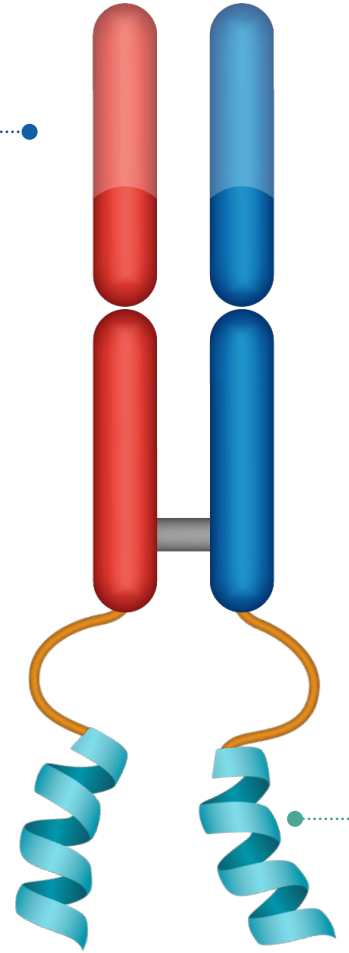
The FORCE™ platform and DYNE-302 are investigational or otherwise in development and have not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority.

Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



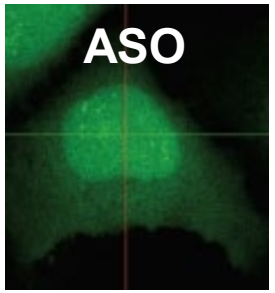


LINKER

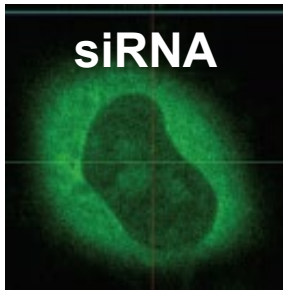
Val-cit cleavable linker, enables precise conjugation of multiple payloads to a single Fab

PAYLOAD

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



Nuclear localization



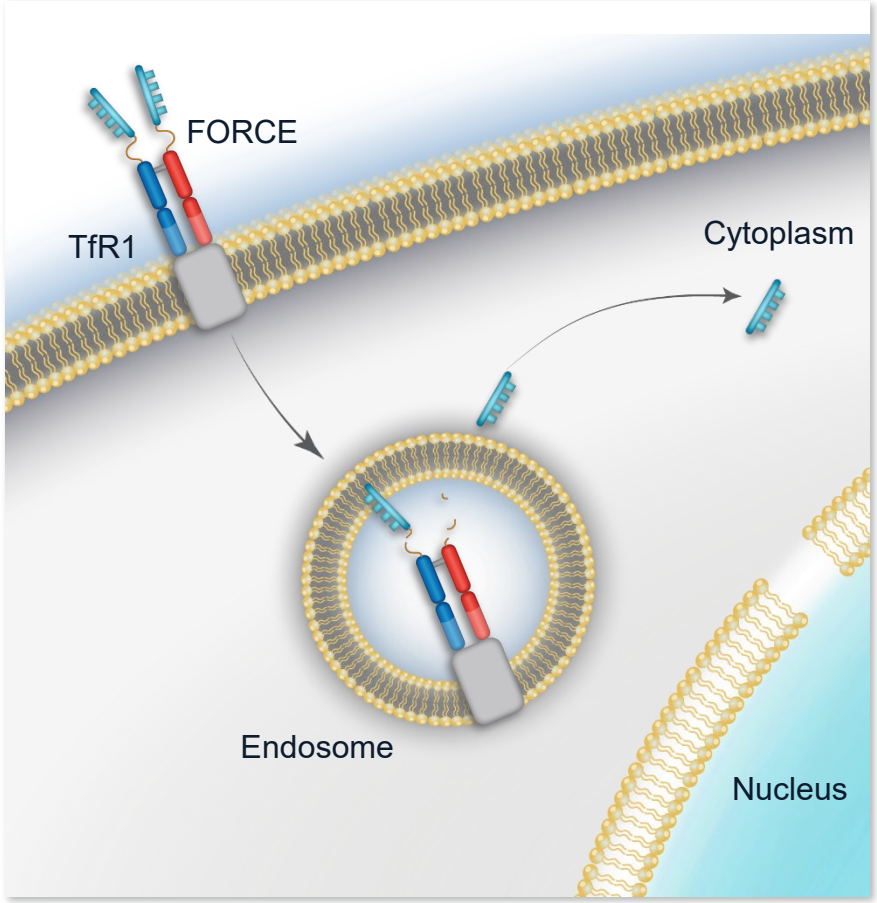
Cytoplasmic localization

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.

The FORCE™ platform is investigational or otherwise in development and has not been approved as safe or effective by the US FDA, EMA, or any other regulatory authority.

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

Weeden et al., 2025

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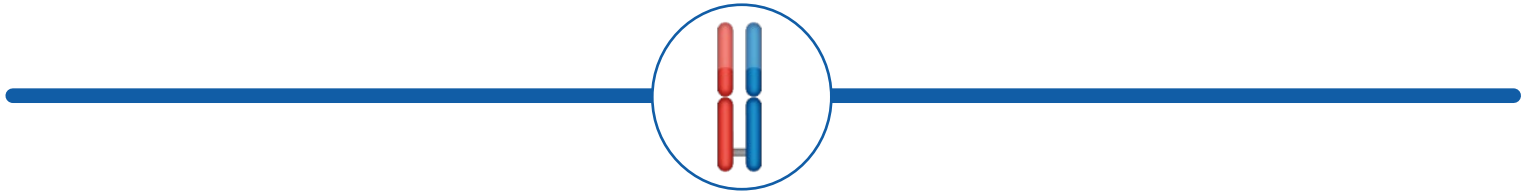
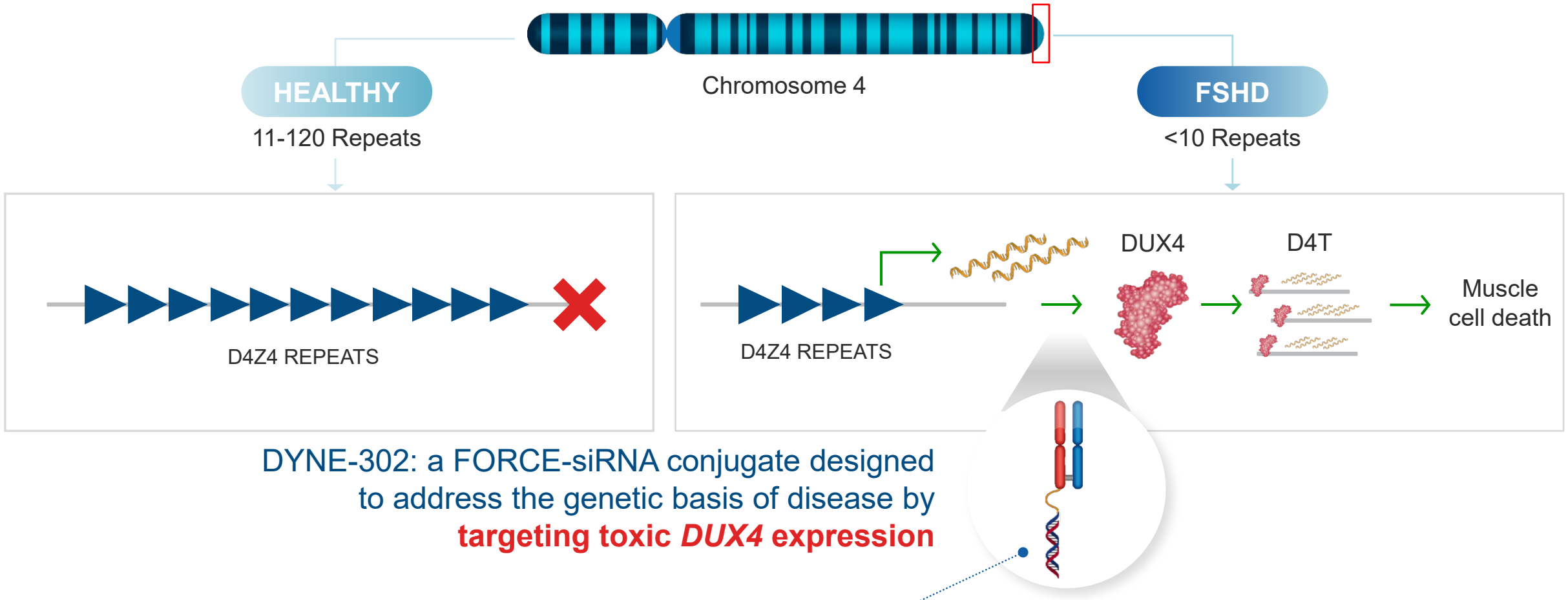
Fabs Offer Multiple Advantages for Targeted Delivery



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	✓

Notes: Fc, fragment crystallizable; Lesley J et al., 1989; Desjardins CA et al. 2022; El-Sayed A et al. 2018; Li Z et al. 2016; Yokota T, 1992; Jain RK, 1990; Kholodenko RV et al., 2019; St Clair JB et al. 2017.

DYNE-302 Targets the Genetic Basis of FSHD



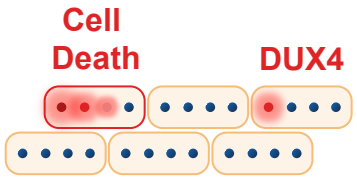
DYNE-302: a FORCE-siRNA conjugate designed to address the genetic basis of disease by **targeting toxic *DUX4* expression**

- 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

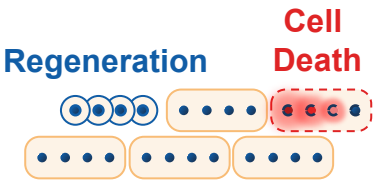
The hTfR1/iFLExD Mouse Model Recapitulates Multiple Aspects of Human FSHD

FSHD

Sporadic DUX4 activation



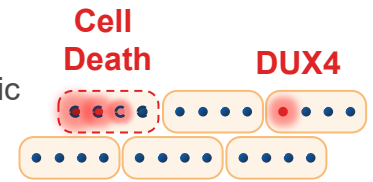
Years



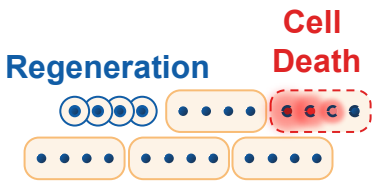
Slowly progressing myopathy and functional decline

hTfR1/iFLExD (Uninduced)

Chronic, sporadic DUX4 activation



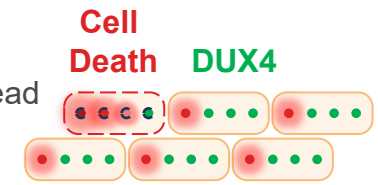
Weeks



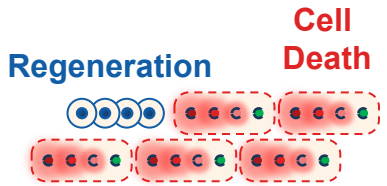
Slowly progressing myopathy without functional decline

hTfR1/iFLExD (Induced)

Acute, widespread DUX4 activation



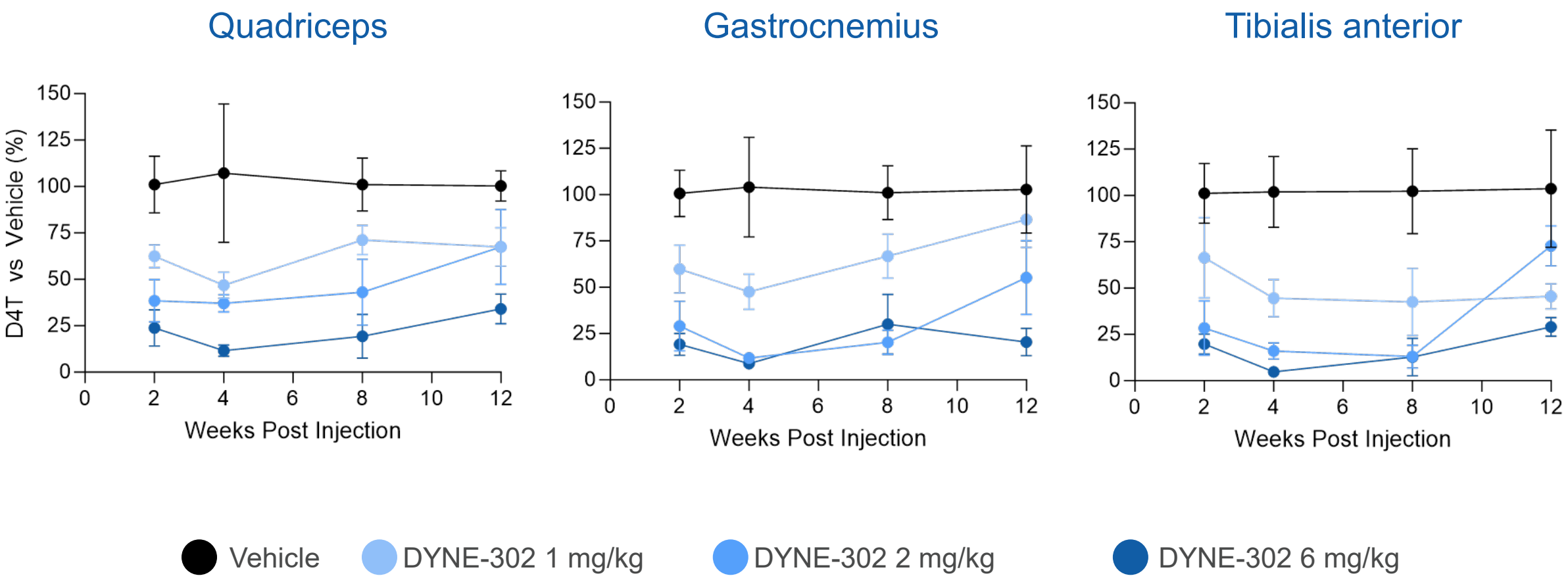
Days



Rapidly progressing myopathy with functional decline

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

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



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. KD = knockdown.

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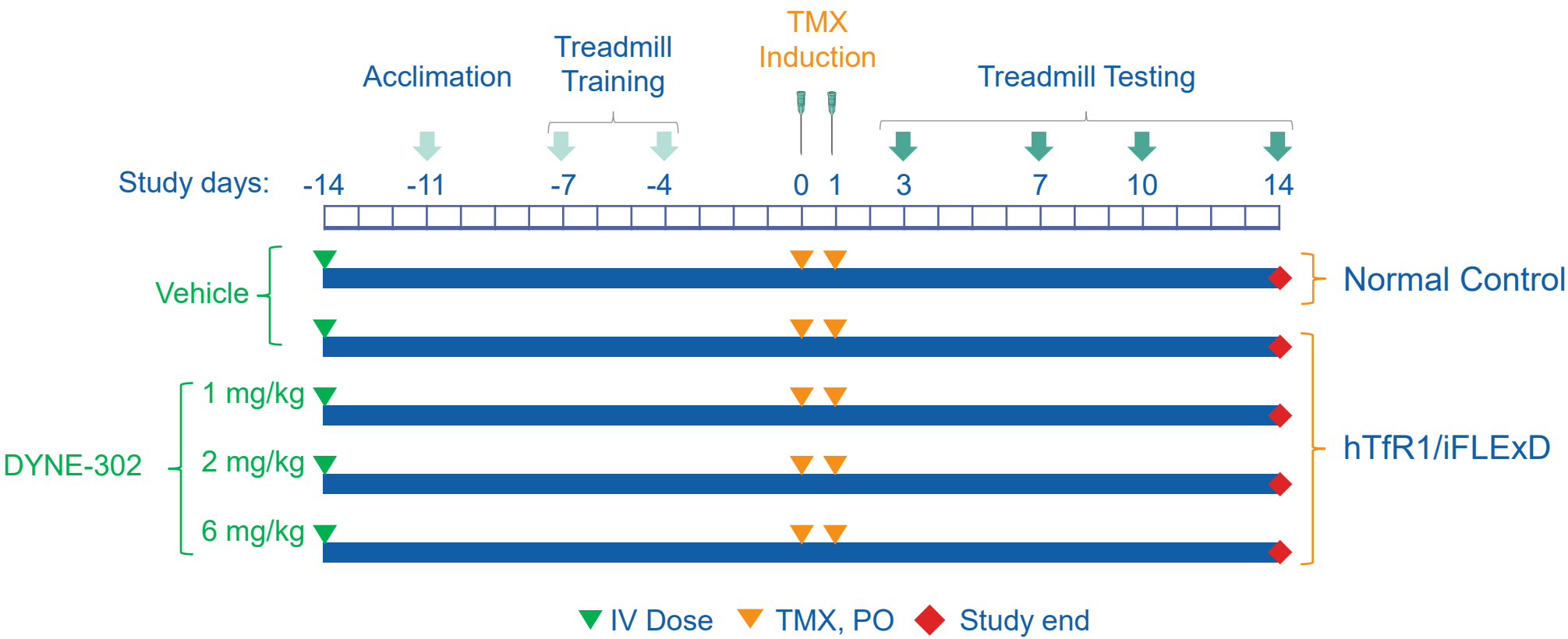
Study to Establish Impact of DYNE-302 Preventative Treatment in the Induced hTfR1/iFLExD Mice



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).

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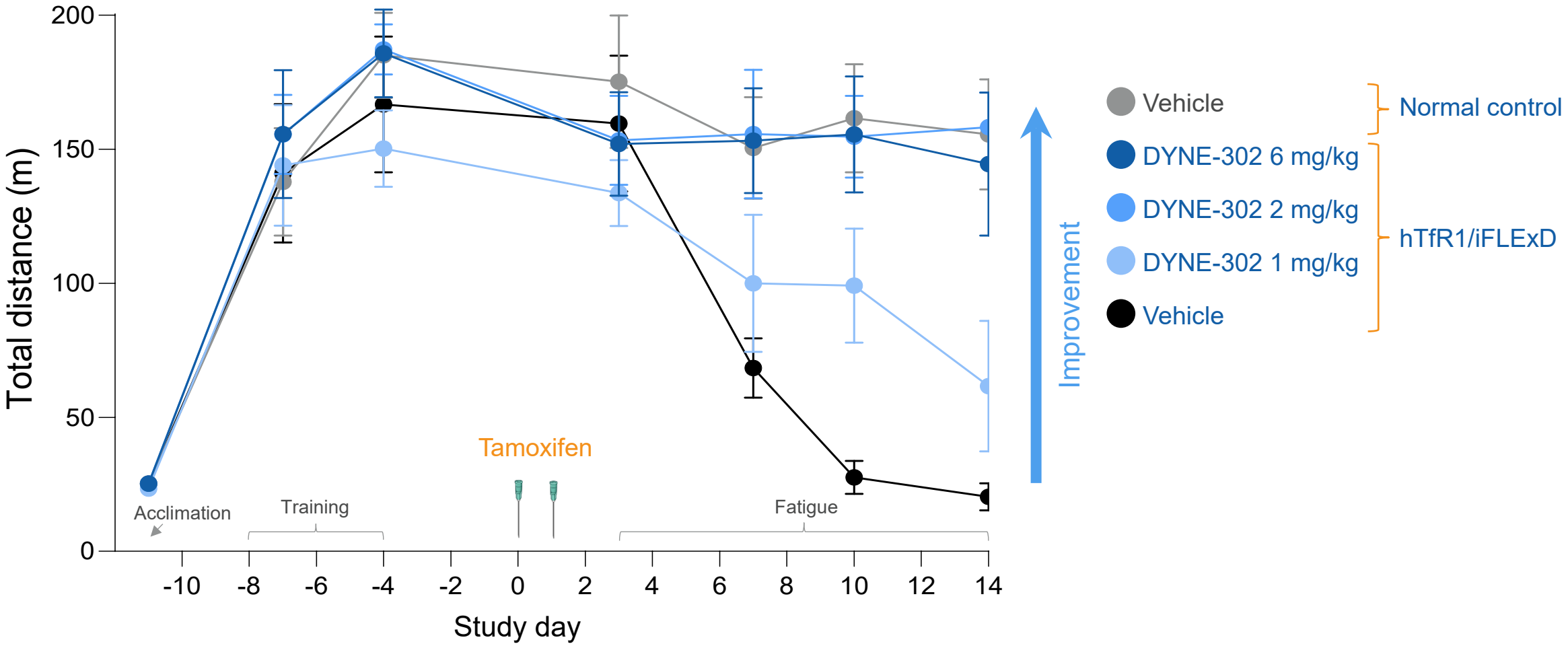
Preventative Treatment with DYNE-302 Leads to Functional Improvement in hTfR1/iFLExD Mice

Functional improvement in forced treadmill run test



Notes: Mice dosed with vehicle or DYNE-302 on Day -14. Data are means ± SEM; n = 5 - 6. *$p < 0.05$; ***$p = 0.0001$, ****$p < 0.001$ compared to vehicle induced hTfR1/iFLExD mice, one-way ANOVA.
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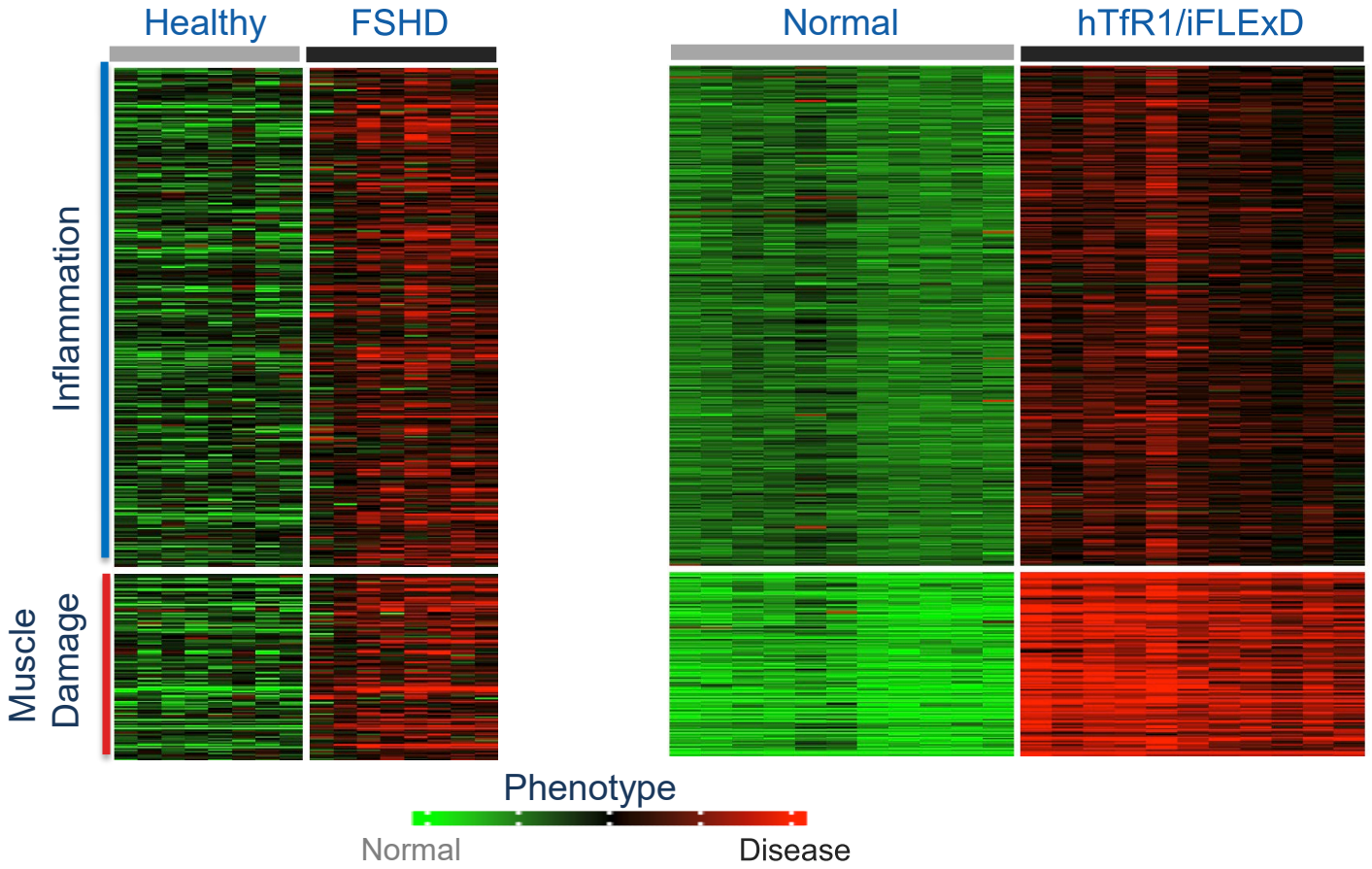
hTfR1/iFLExD Mice Recapitulate Transcriptional Profiles of Immune Response and Muscle Damage Seen in Human FSHD Muscle

Human transcriptome
in skeletal muscle biopsies

Mouse ortholog transcriptome
in quadriceps

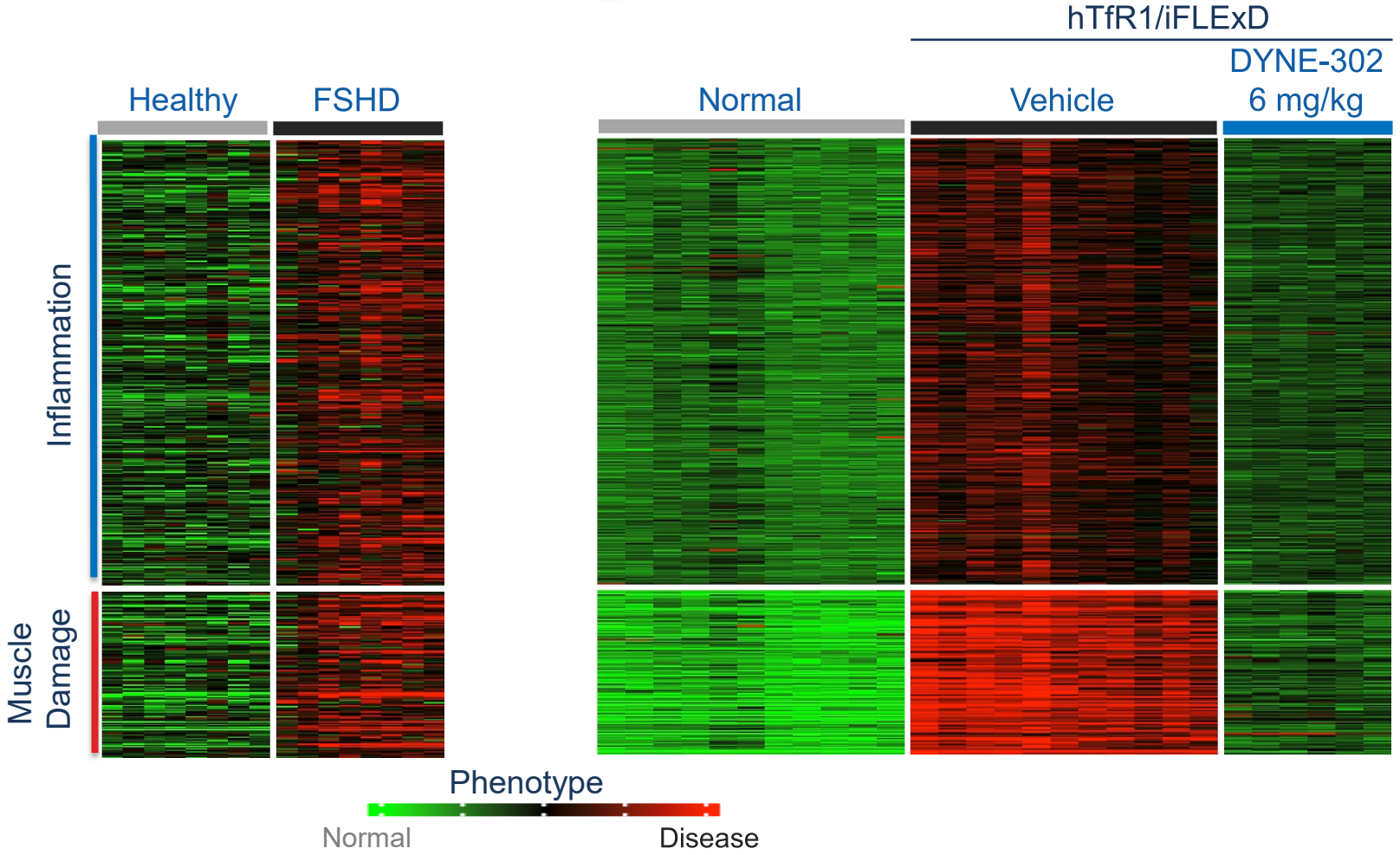


Notes: each column represents one individual, each row represents an individual gene; human data from Wang et al., 2019.

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



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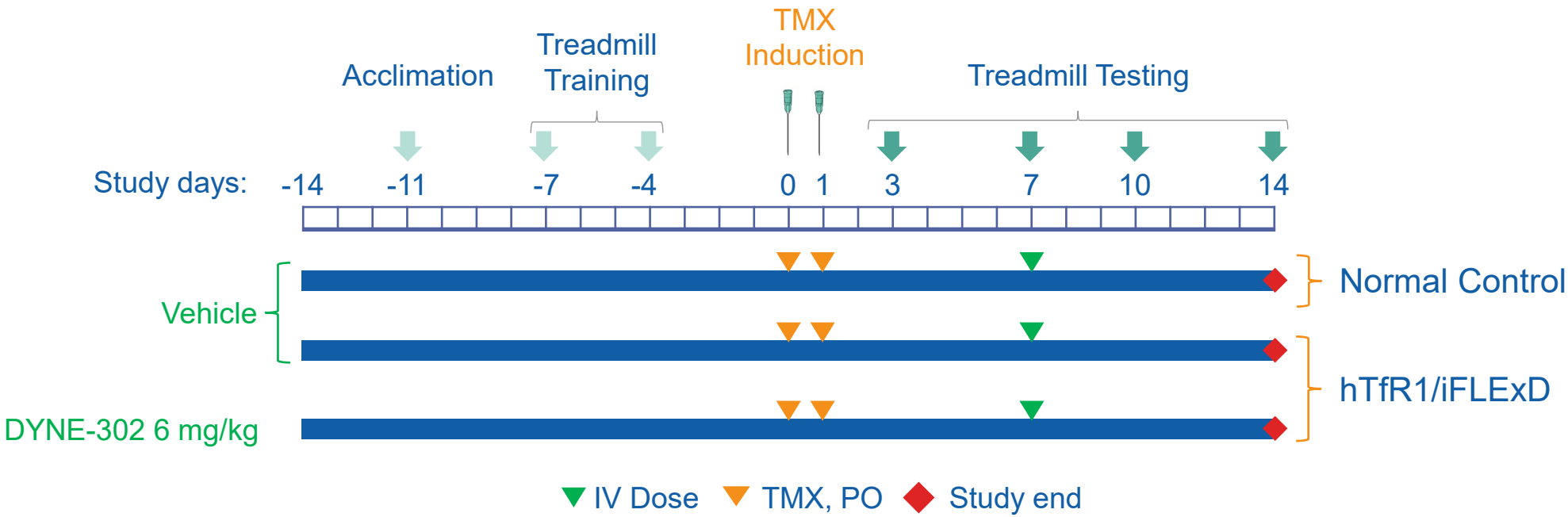
Study to Establish Impact of DYNE-302 Interventional Treatment in the Induced hTfR1/iFLExD Mice



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).

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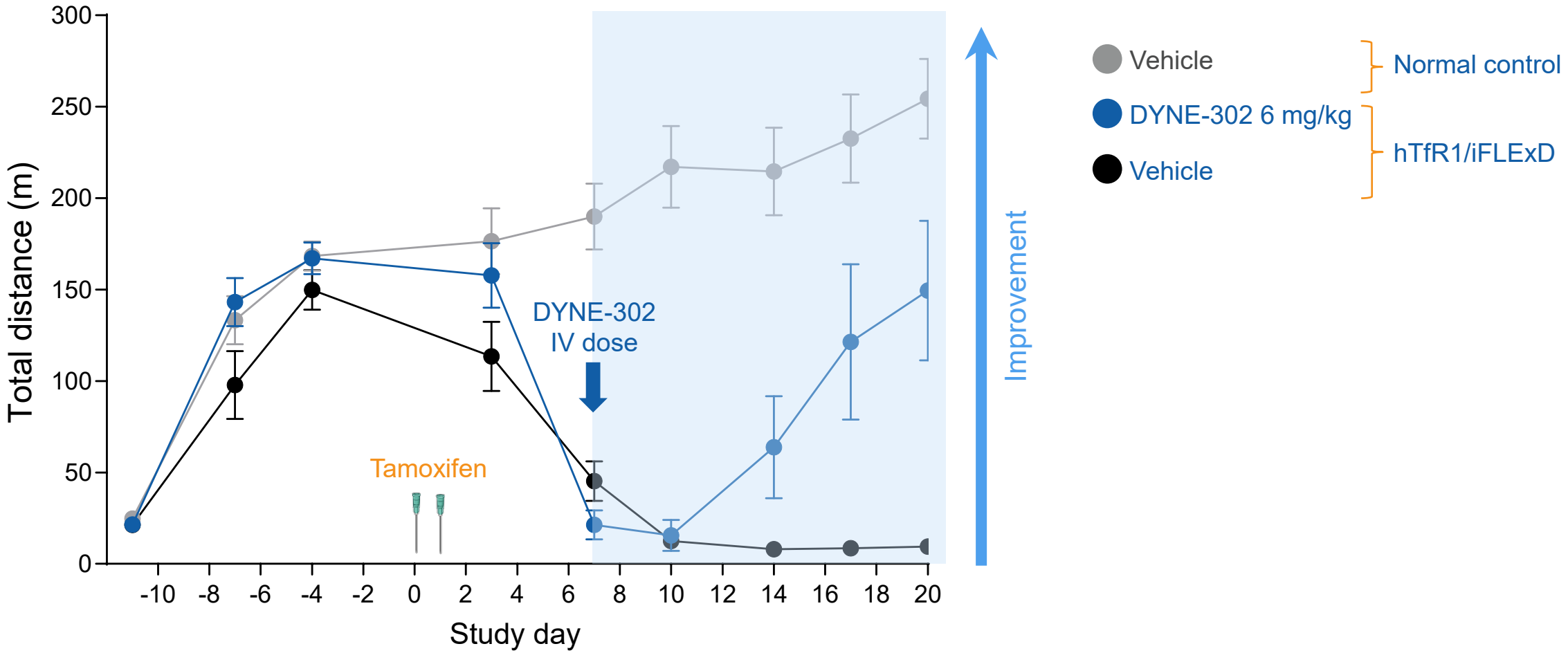
DYNE-302 Interventional Treatment Leads to Functional Improvement in hTfR1/iFLExD Mice

Functional improvement in forced treadmill run test



Notes: Mice tested for function on treadmill run test. Treatment with single DYNE-302 dose 6 mg/kg. Data shown are means ± SEM, n = 6 - 7 animals/group. ****$p < 0.001$ compared to vehicle induced hTfR1/iFLExD mice, one-way ANOVA.

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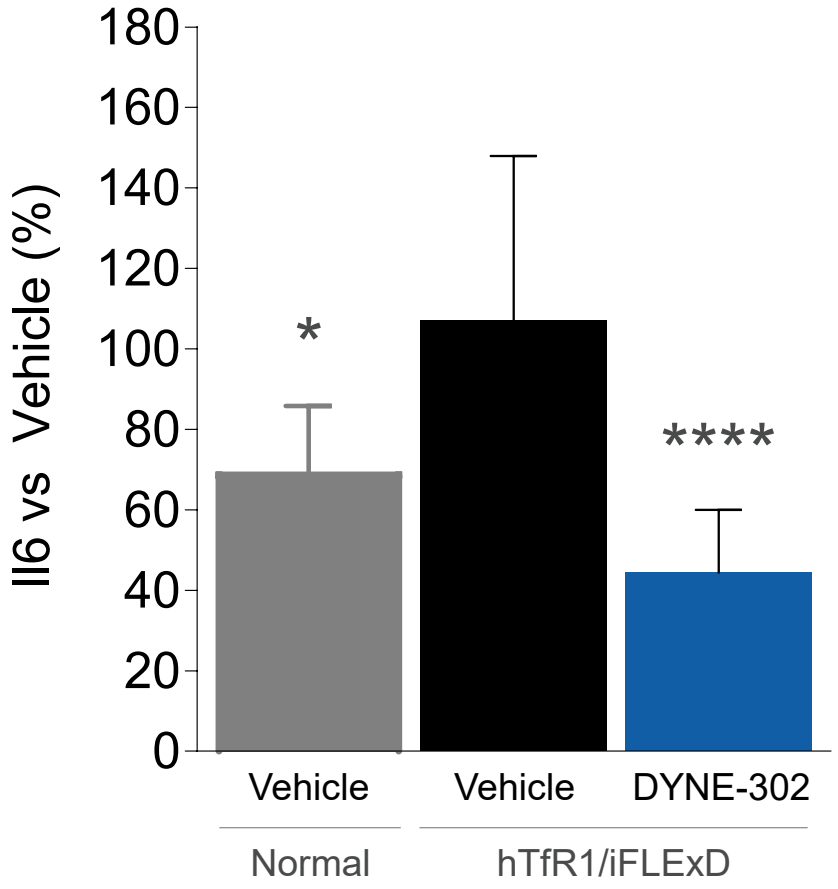
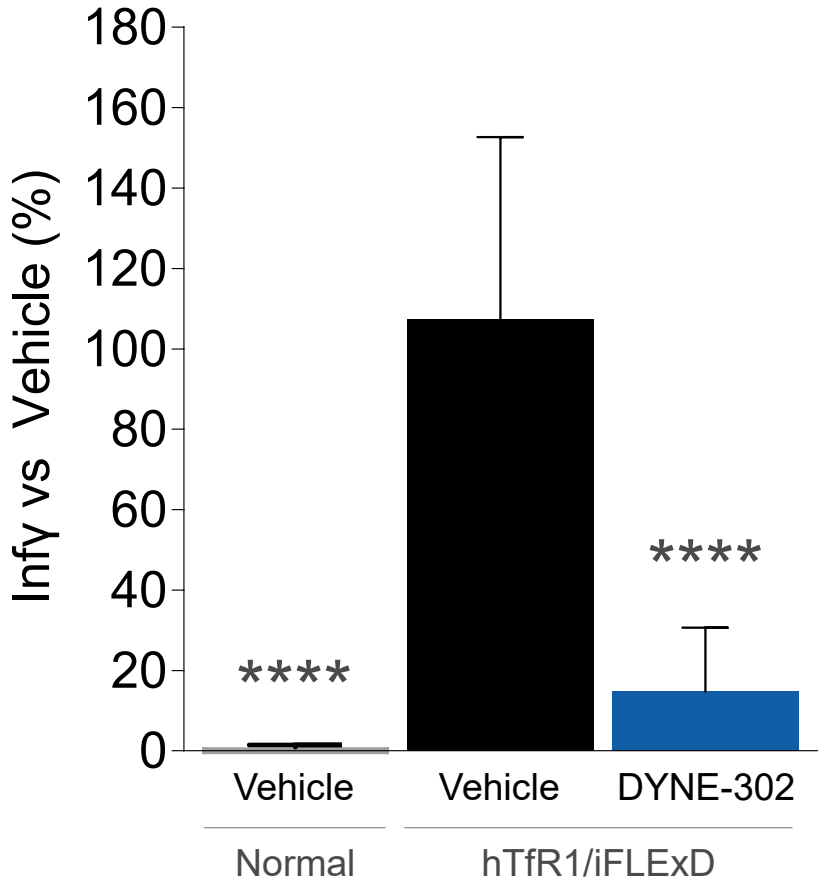
DYNE-302 Interventional Treatment Suppresses *Il6* and *Ifnγ* Expression in hTfR1/iFLExD Mice

Il6 suppression



Ifnγ suppression



Notes: Data are means + SD; n= 6-7 ; *$p < 0.05$; ****$p < 0.001$ compared to hTfR1/iFLExD mice administered with vehicle, one-way ANOVA.
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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

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

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Dyne R&D