FORCE™ Platform for Targeted Delivery of Oligonucleotide Therapeutics for Muscle Diseases

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Ravi, *living with DMD*

Forward-looking statements

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 expected timeline for dosing patients in trials, the anticipated design of the trials, 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 conduct of research activities and the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies; uncertainties as to the timing of and Dyne's ability to submit and obtain regulatory clearance for investigational new drug applications and other regulatory filings and initiate clinical trials, including with respect to its response to the DYNE-251 clinical hold letter and its ability to obtain regulatory clearance of the DYNE-251 IND; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; whether investigators and regulatory agencies will agree with the design of Dyne's planned clinical trials; whether Dyne's cash resources will be sufficient to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; uncertainties associated with the impact of the COVID-19 pandemic on Dyne's business and operations; 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.

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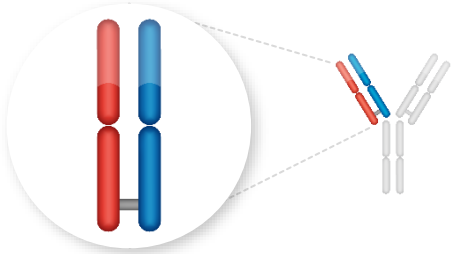
Dyne FORCE™ platform: Modern oligo therapeutics for muscle diseases

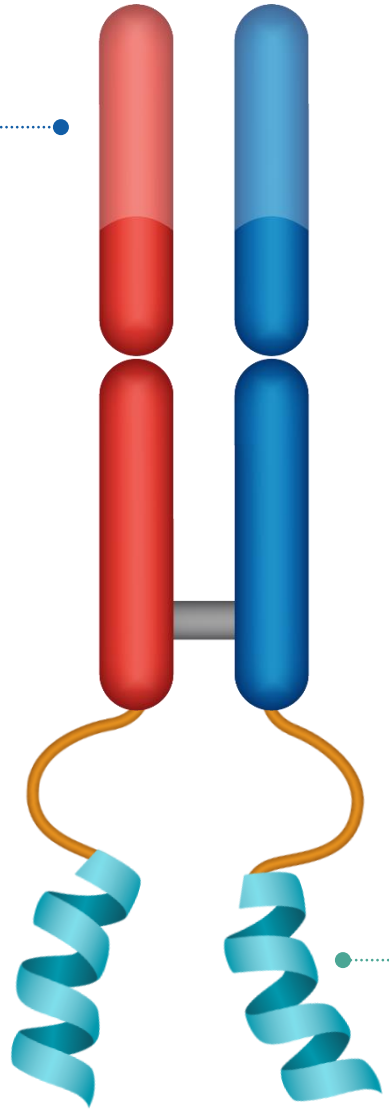
ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



LINKER

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

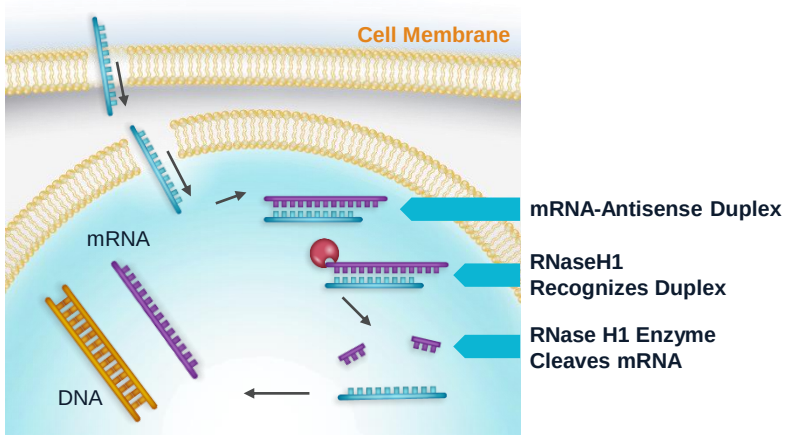


PAYLOAD

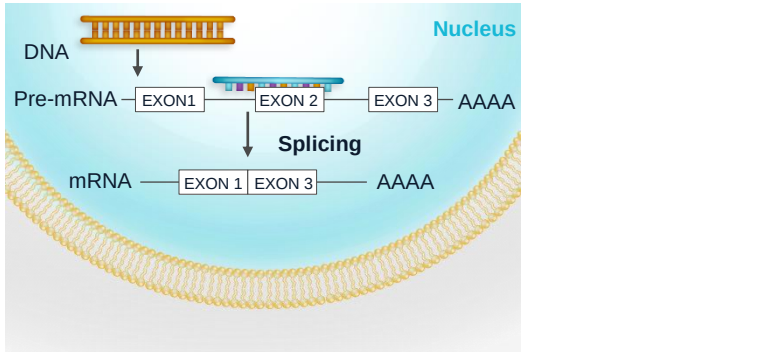
Modularity enables rational selection of payload to target the genetic basis of disease

Rationally select payload to target genetic basis of disease

ASO acts in the nucleus and cytoplasm

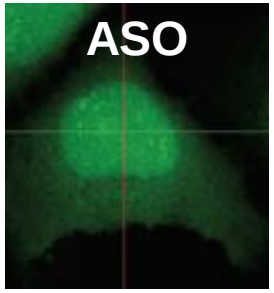


Splice-modulating ASO

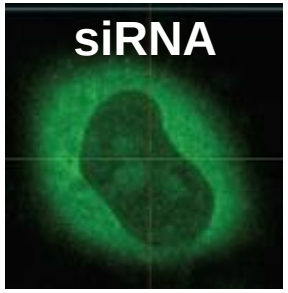


Single-Stranded Antisense

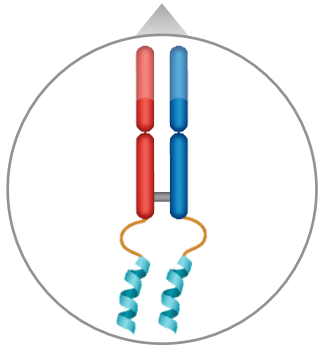
Subcellular distribution of ASO and siRNA



Nuclear localization

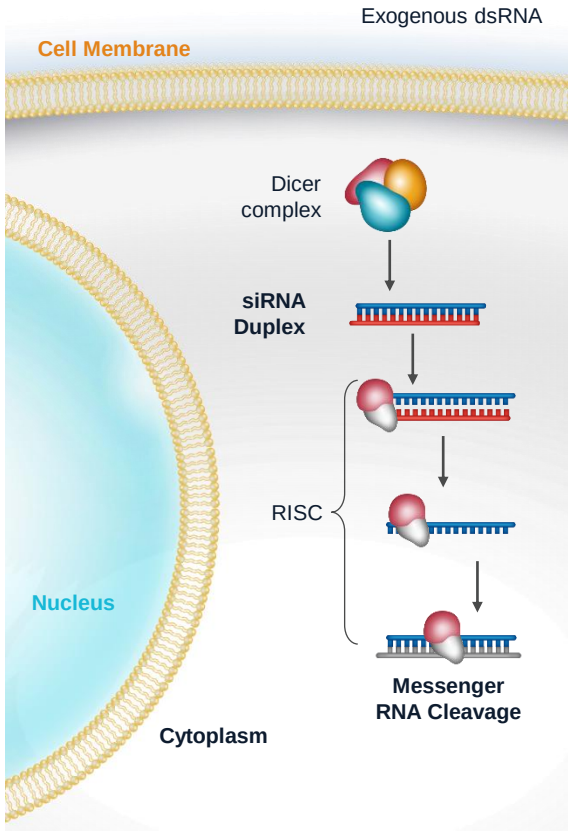


Cytoplasmic localization



FORCE delivers **ASO** payload for nuclear targets, **siRNA** payload for cytoplasmic targets

siRNA acts in the cytoplasm



Double-Stranded Antisense (siRNA)

Developing transformative therapies for people living with DM1

Overview

- Mutation in the *DMPK* gene
- Onset at any point, depending on DM1 phenotype
- Life expectancy of 45 - 60 years

Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

Population

- >40,000 (US)
- >74,000 (Europe)

NO approved therapies

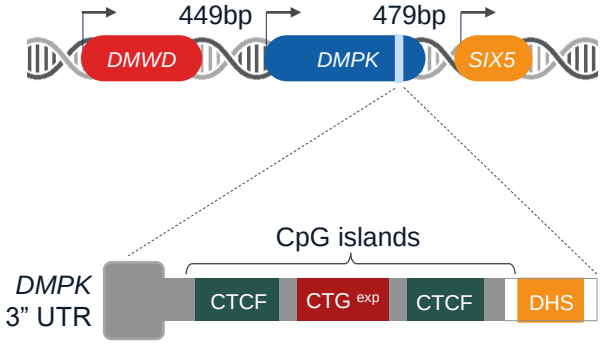
OUR APPROACH

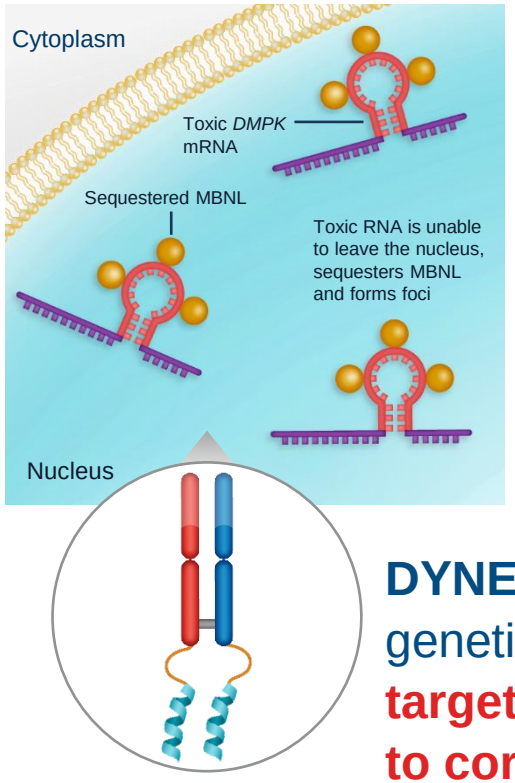
Disease-Modifying Nuclear *DMPK* Knockdown

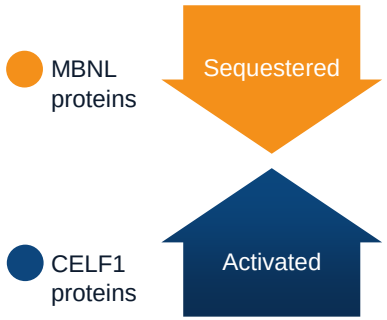
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE targets the genetic basis of DM1 to correct splicing

DNA Triplet Repeats → **Toxic RNA Forms Foci** → **RNA Binds Splicing Proteins** → **Clinical Presentation**



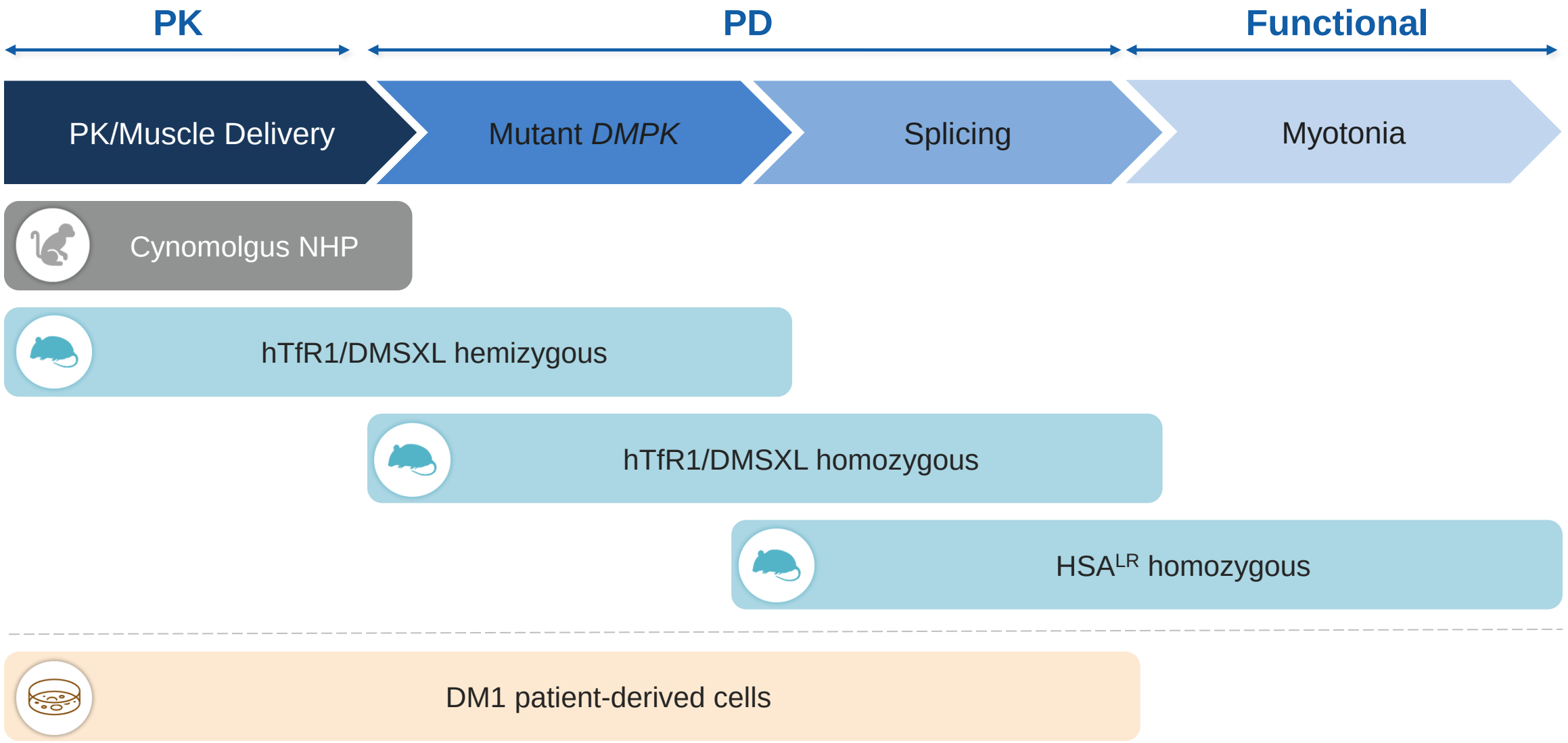




- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

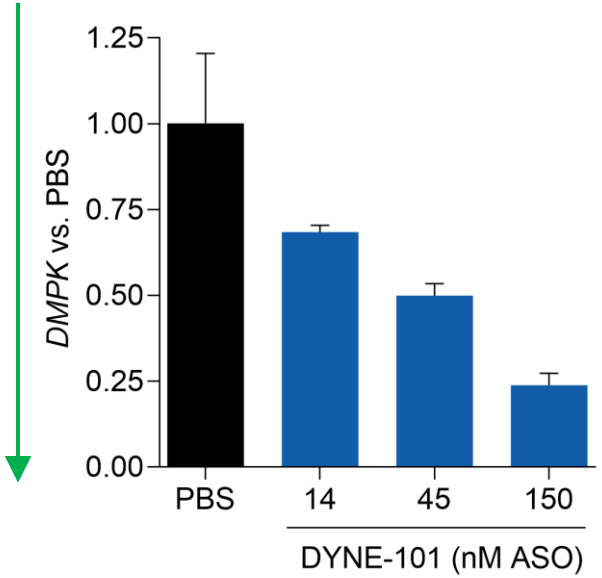
DYNE-101 designed to address the genetic basis of disease by **targeting toxic nuclear *DMPK* RNA to correct spliceopathy**

Data from multiple DM1 models demonstrate that FORCE delivers to muscle and drives disease modification

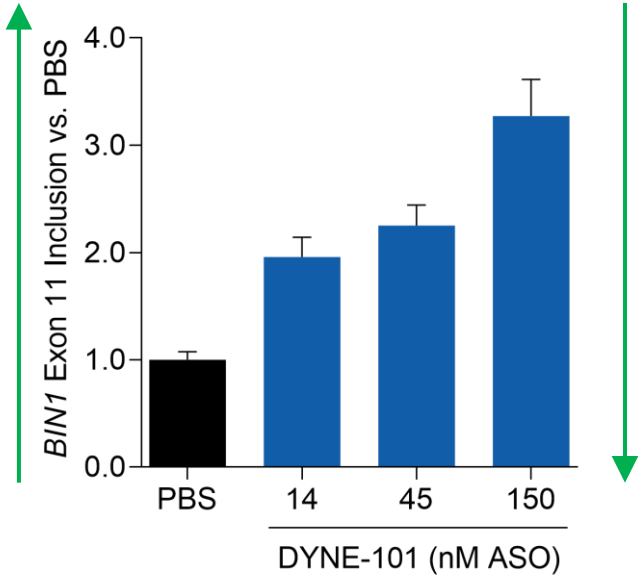


DYNE-101 demonstrated dose-dependent *DMPK* KD, splicing correction, and foci reduction in DM1 myotubes with 380 CTG repeats

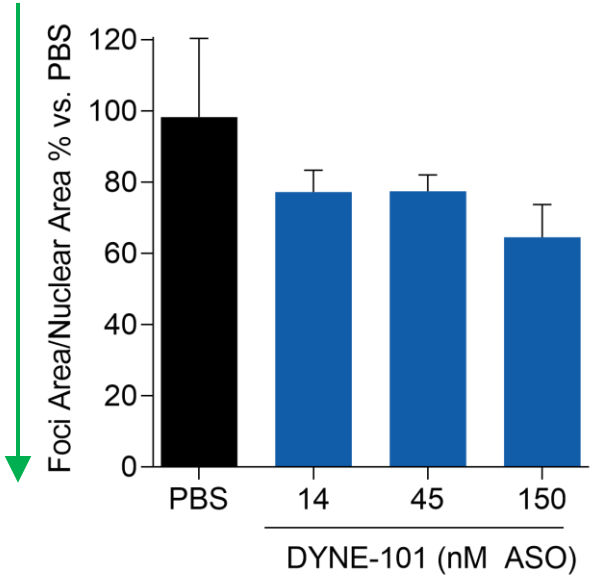
DMPK mRNA KD by qPCR



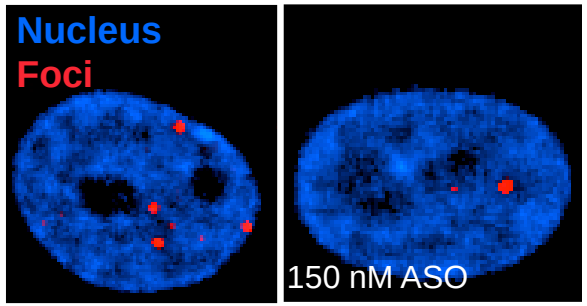
BIN1 splicing correction by qPCR



Toxic DMPK foci KD



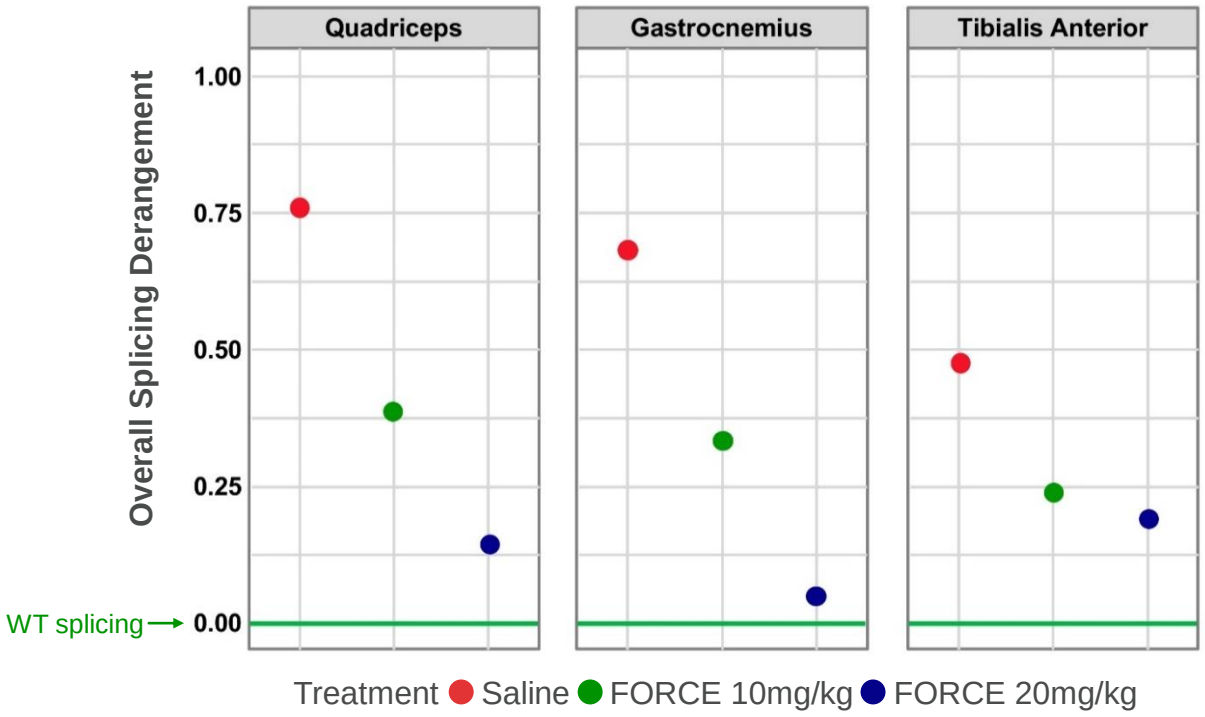
FISH with CAG PNA probe



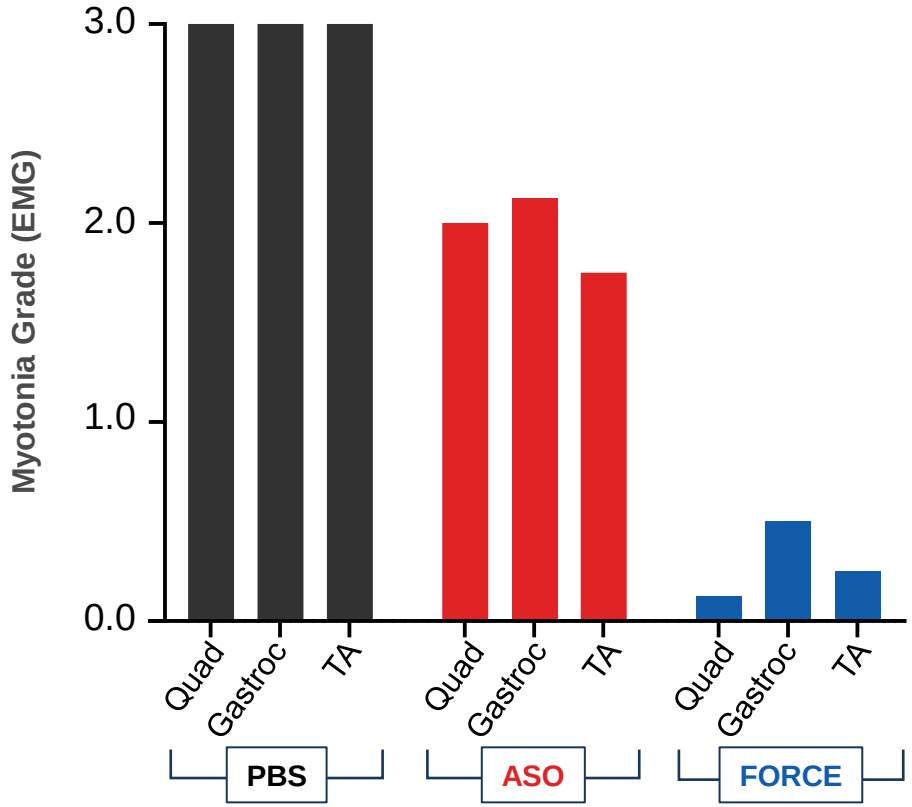
Note: Data are mean ±SD; n = 4

FORCE dose-dependently corrected splicing and reversed myotonia in the HSA^{LR} DM1 mouse model

Splicing Correction in Multiple Muscles

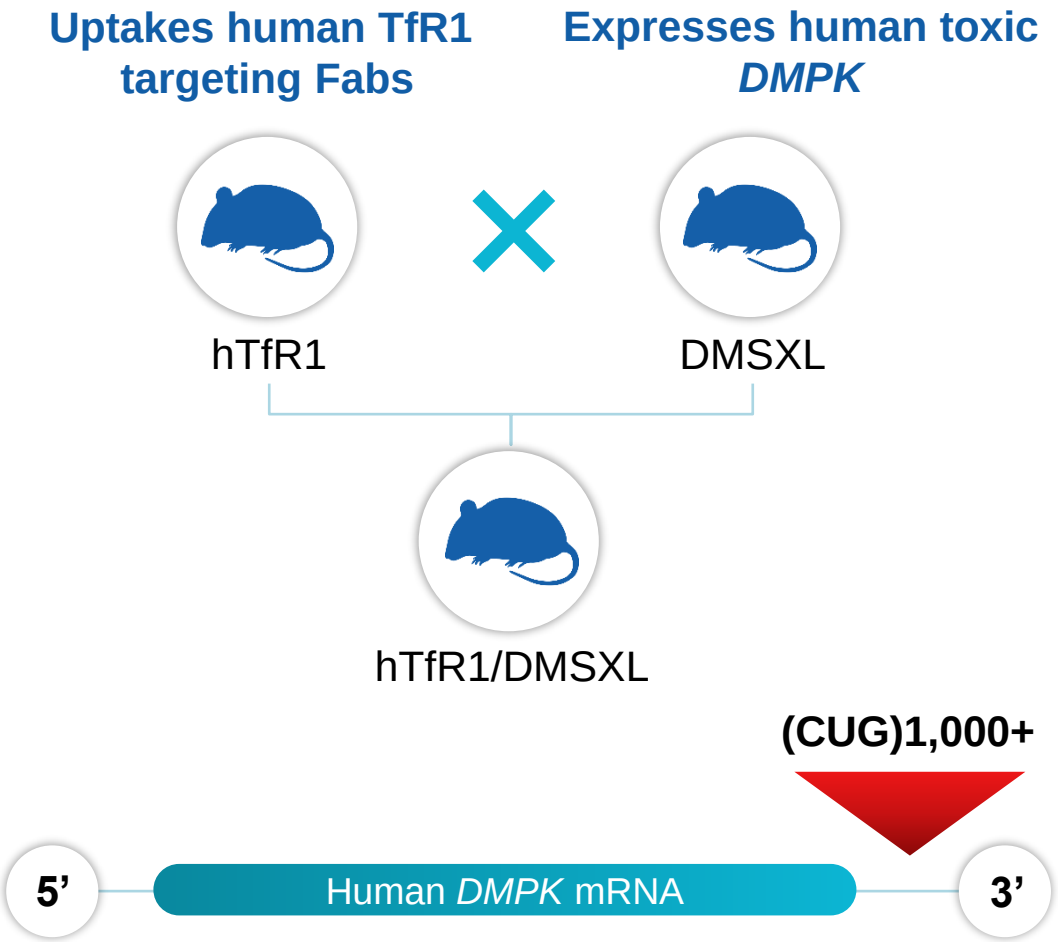


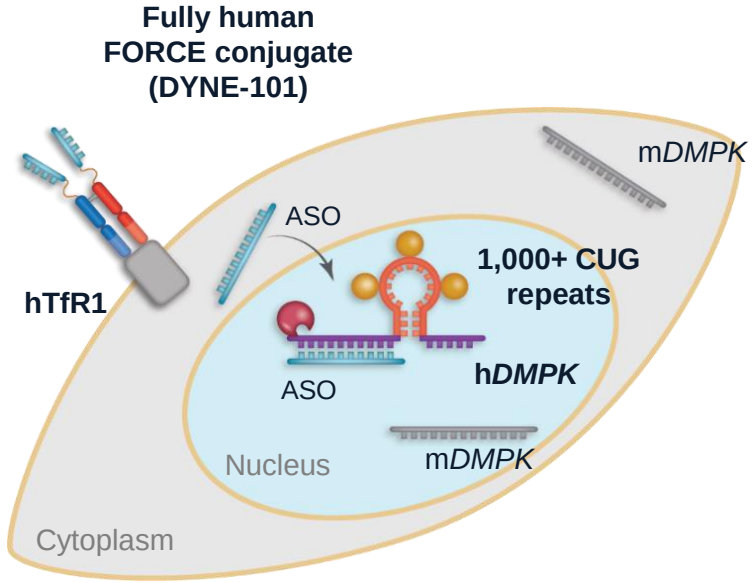
Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose



Note: HSA^{LR} mice, single dose 14-day study. Overall splicing derangement indexed to WT level of 0.00. EMG myotonic discharges were graded by a blinded examiner on a 4-point scale: 0, no myotonia; 1, occasional myotonic discharge in less than 50% of needle insertions; 2, myotonic discharge in greater than 50% of needle insertions; 3, myotonic discharge with nearly every insertion.

hTfR1/DMSXL: Innovative model developed by Dyne to evaluate PD by measuring toxic human nuclear *DMPK* KD



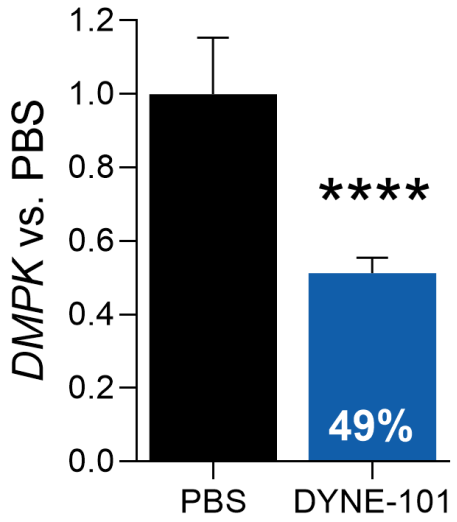


- Expresses human TfR1 receptor, enabling use of a human TfR1-targeting Fab
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

Note: DMSXL mice first described in PLOS Genetics 2012, 8(11):e1003043

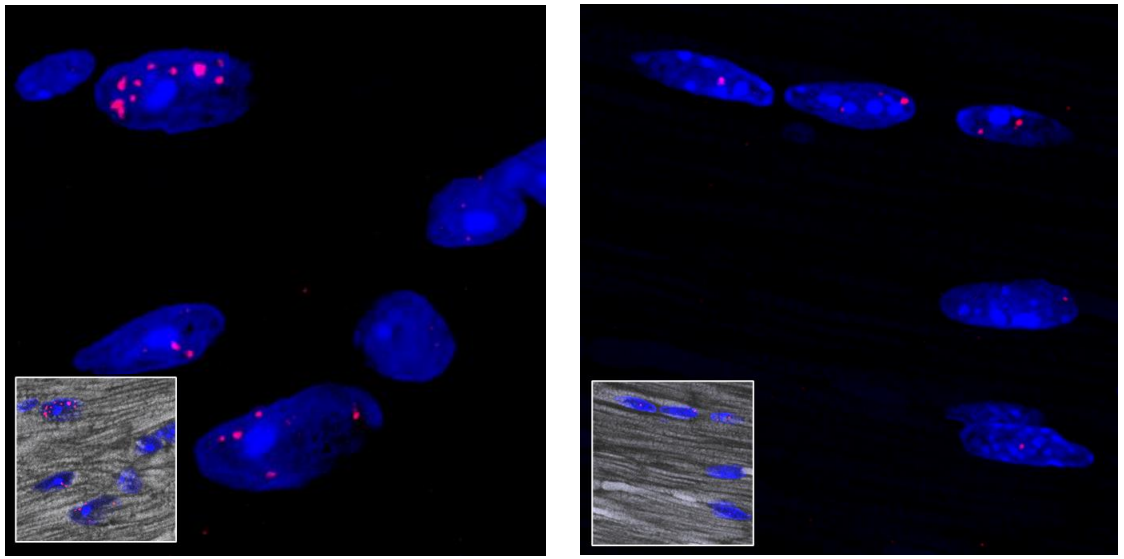
DYNE-101 demonstrated significant toxic human *DMPK* KD, foci reduction, and splicing correction in heart of hTfR1/DMSXL mice

Toxic human *DMPK* expression (%KD)



Toxic human *DMPK* foci reduction

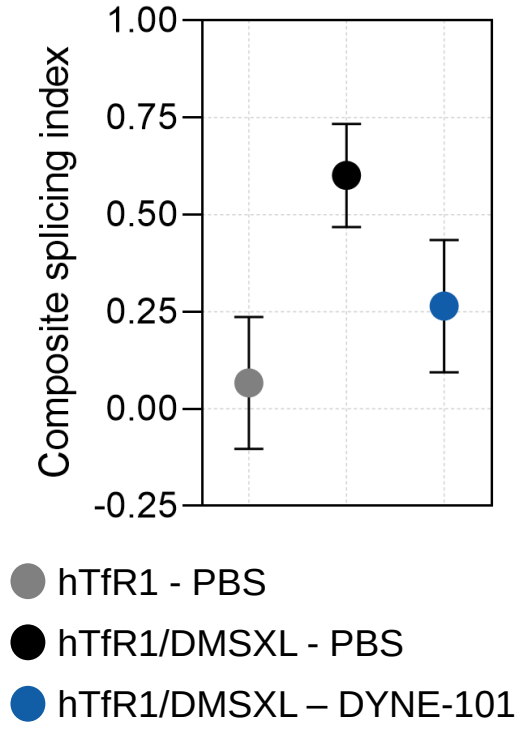
DMPK Foci Nuclei Myofibers



PBS DYNE-101

DYNE-101 reduces foci area by 49%*

Splicing correction

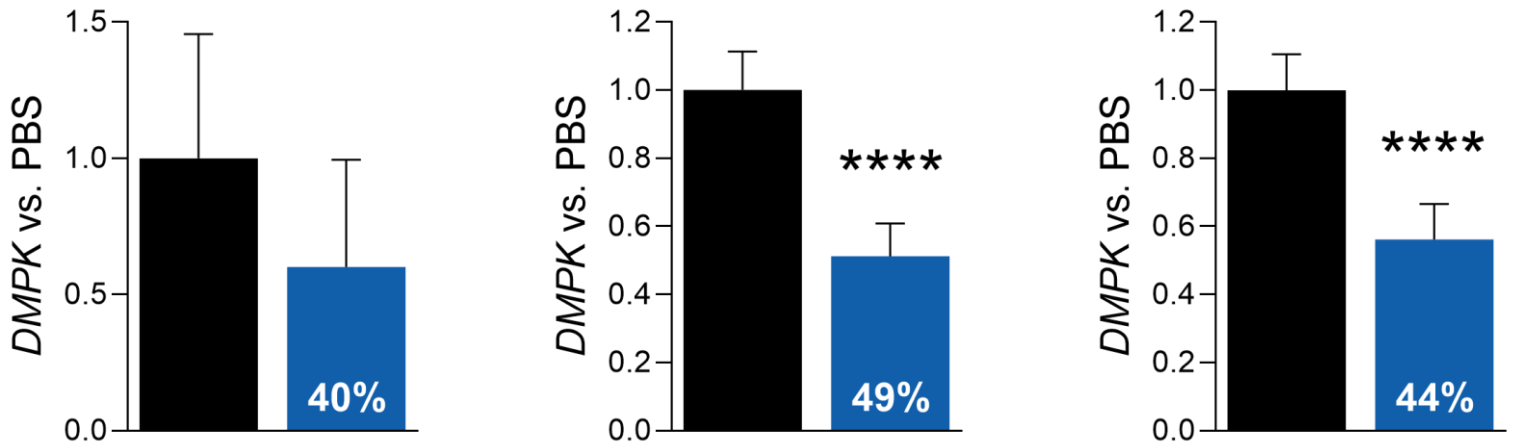


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are means ± SD, n = 6 – 7 per arm; * p <0.05, **** p < 0.0001 significant by t-test

DYNE-101 demonstrated toxic human *DMPK* KD and splicing correction in skeletal muscle of hTfR1/DMSXL mice

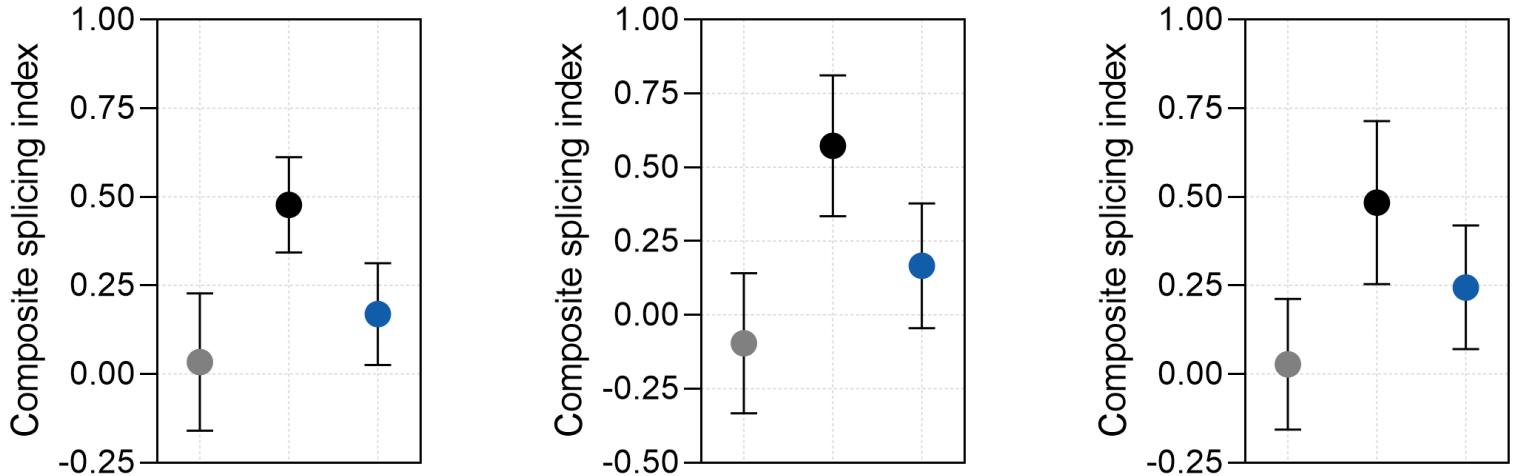
Toxic human *DMPK* expression (% KD)

- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101



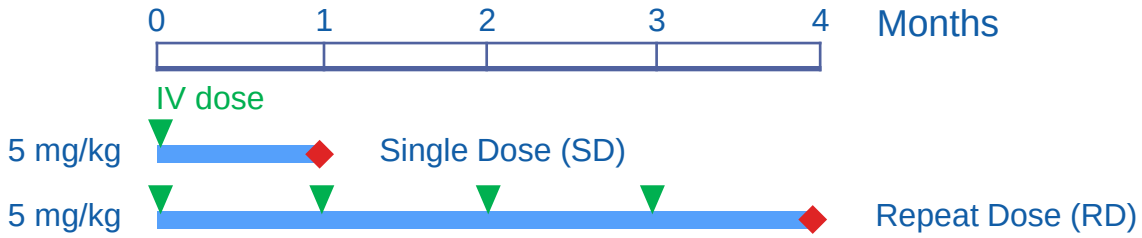
Splicing correction

- hTfR1 - PBS
- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101

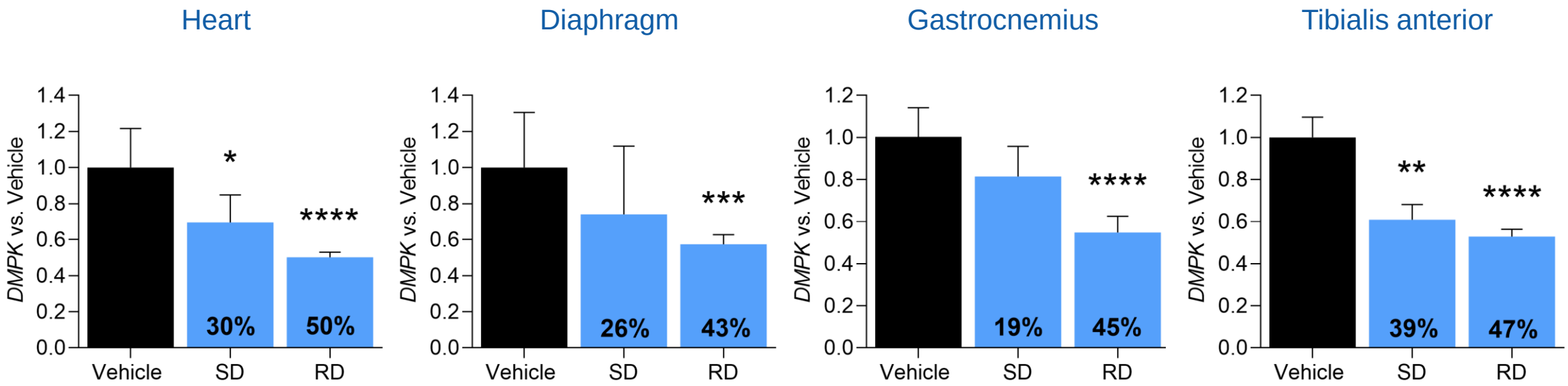


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing indices include *Bin1* E11, *Insr* E11, *Ldb3* E11, *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 mis-splicing measured by qRT-PCR. Data are means ± SD; n = 4 – 7; **** $p < 0.0001$ by *t*-test

Low monthly dosing of DYNE-101 in hTfR1/DMSXL mice enhanced toxic human *DMPK* KD in cardiac and skeletal muscle

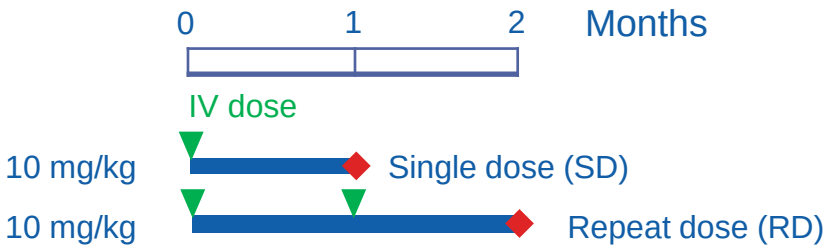


Toxic human *DMPK* expression (% KD)

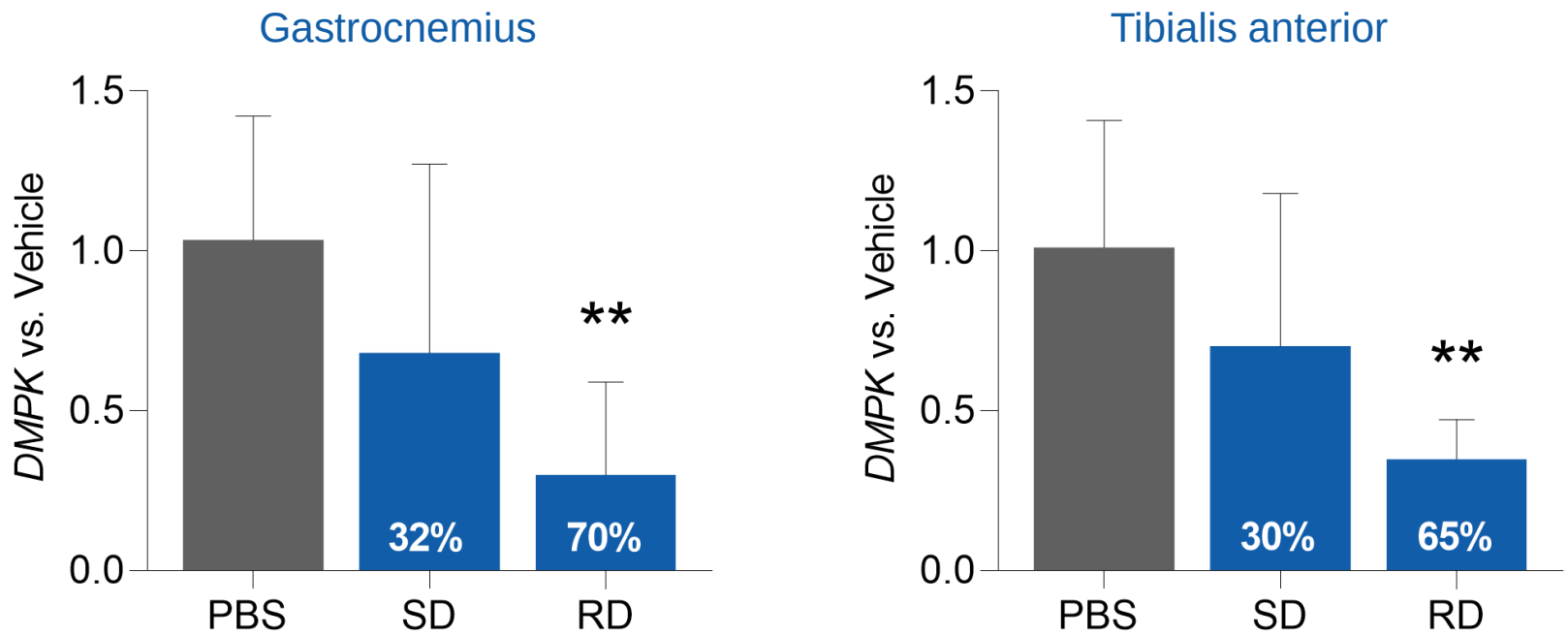


Note: hTfR1/DMSXL hemizygous mice. Data are means ± SD; n = 4 - 6 per arm; *p< 0.05, **p< 0.01, ***p< 0.001, ****p< 0.0001 significant by One-way ANOVA

DYNE-101 repeat monthly dosing in NHPs enhanced *DMPK* KD in skeletal muscle

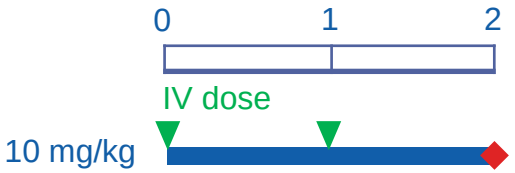


WT *DMPK* expression (% KD)

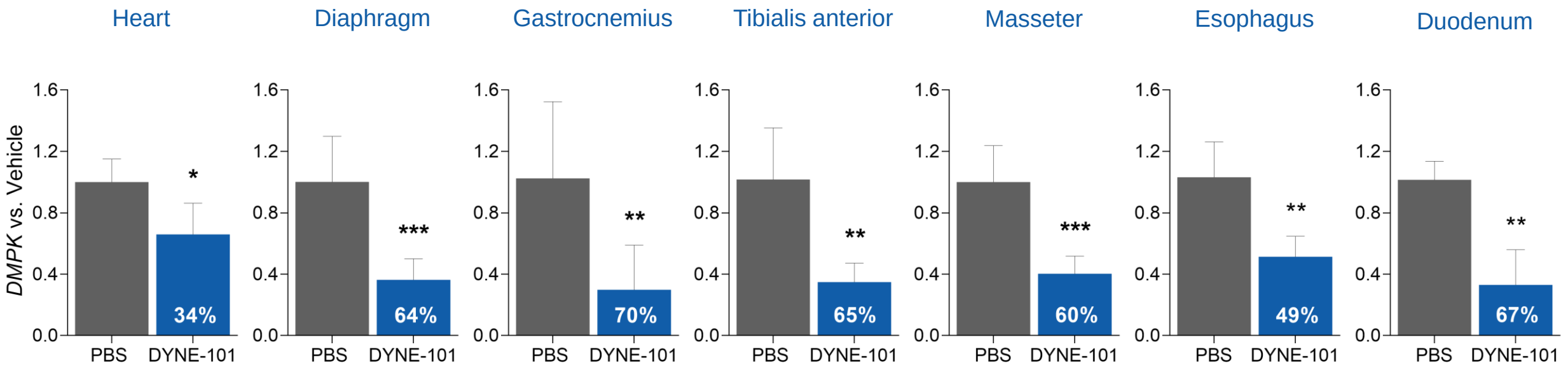


Note: Male cynomolgus monkeys. Data are means ± SD; n = 3 - 4 per arm; ***p*< 0.01 significant by One-way ANOVA

Repeat monthly dosing of DYNE-101 in NHPs achieved significant WT *DMPK* KD demonstrating translatability to higher species



WT *DMPK* expression (% KD)



Note: Male cynomolgus monkeys. Data are means ± SD; n = 3 - 4 per arm; * $p<0.05$, ** $p< 0.01$, *** $p< 0.001$ significant by One-way ANOVA

DYNE-101 was well-tolerated in an NHP 13-week GLP toxicology study[1]

- No dose limiting toxicity observed up to a maximally feasible dose[2]
- No changes in cardiac, respiratory, neurologic, or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested

Notes: 1. Based on conclusions of report from third-party CRO. 2. Dosed once every three weeks.
NOAEL: No-observed-adverse-effect level

DM1 program summary

- **Targeted** toxic *DMPK* in the nucleus in patient cells
- **Robust and durable toxic human *DMPK* KD** in novel hTfR1/DMSXL model
- **Reduced nuclear foci** *in vitro & in vivo*
- **Corrected splicing** changes *in vitro & in vivo*
- **Reversed myotonia** in HSA^{LR} model
- **Achieved WT *DMPK* KD** in NHP muscle tissues with low monthly dosing
- **Favorable safety profile in NHP GLP tox study**

Building a global DMD franchise of transformative therapies

Overview

- Mutation in the *DMD* gene that encodes for dystrophin
- Onset in first few years of life
- Life expectancy ~30 years

Clinical Presentation

- Muscle weakness
- Progressive loss of function
- Loss of ambulation
- Respiratory/cardiac failure

Population

- ~12,000 - 15,000 (US)
- ~ 25,000 (Europe)

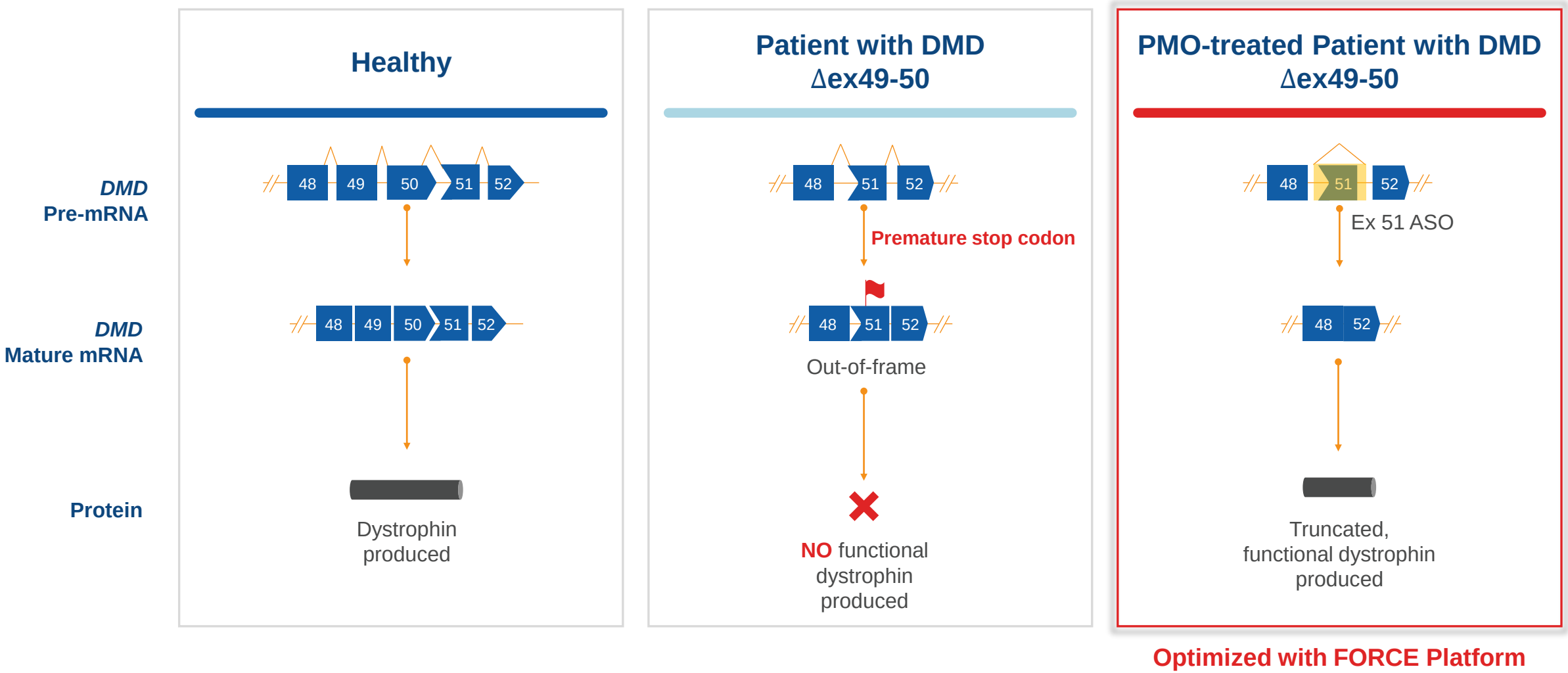
Current Approved Exon 51 Therapies Only Increased Dystrophin Production <1%

OUR APPROACH

Best-in-class Targeted Exon Skipping

Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

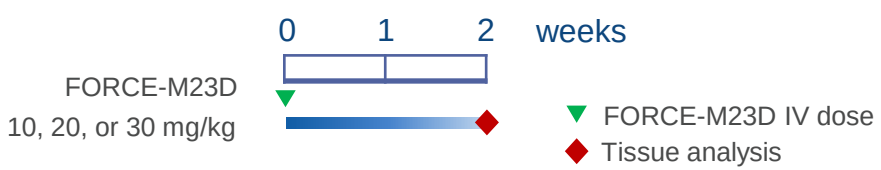
Targeting the genetic basis of DMD with a proven mechanism



Optimized with FORCE Platform

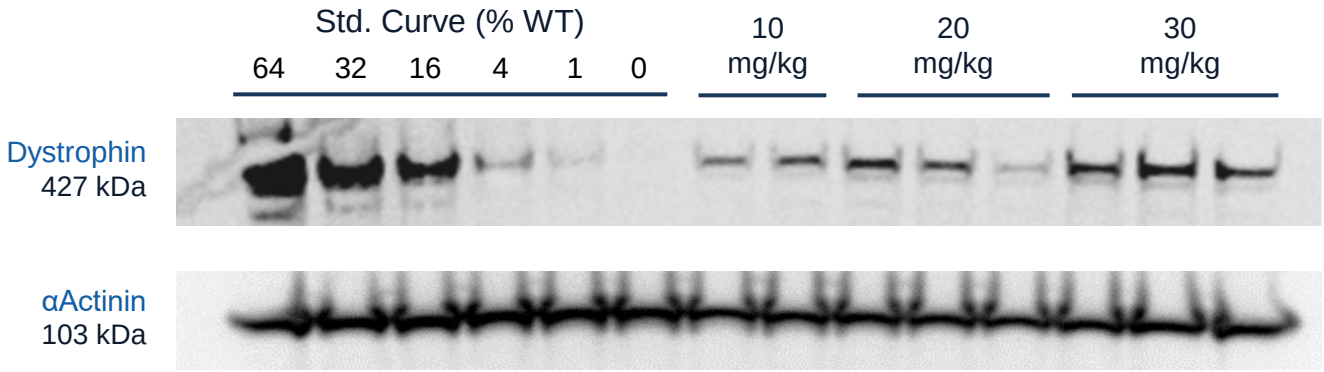
Adapted from Lim KRQ., et al. *Drug Des Devel Ther* 2017;11:533.

FORCE-M23D dose-dependently increased dystrophin expression



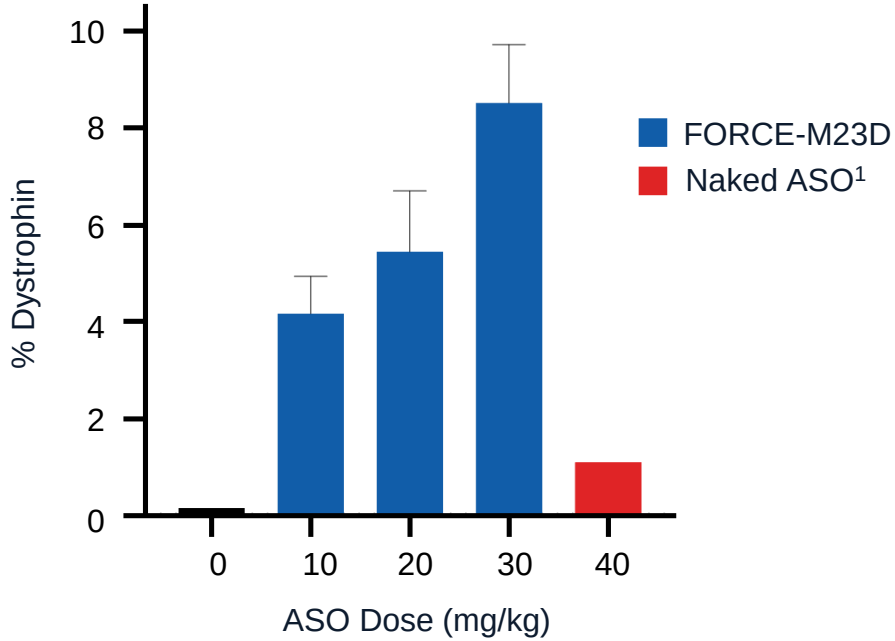
Quadriceps

Dose-Dependent Increase in Dystrophin Expression



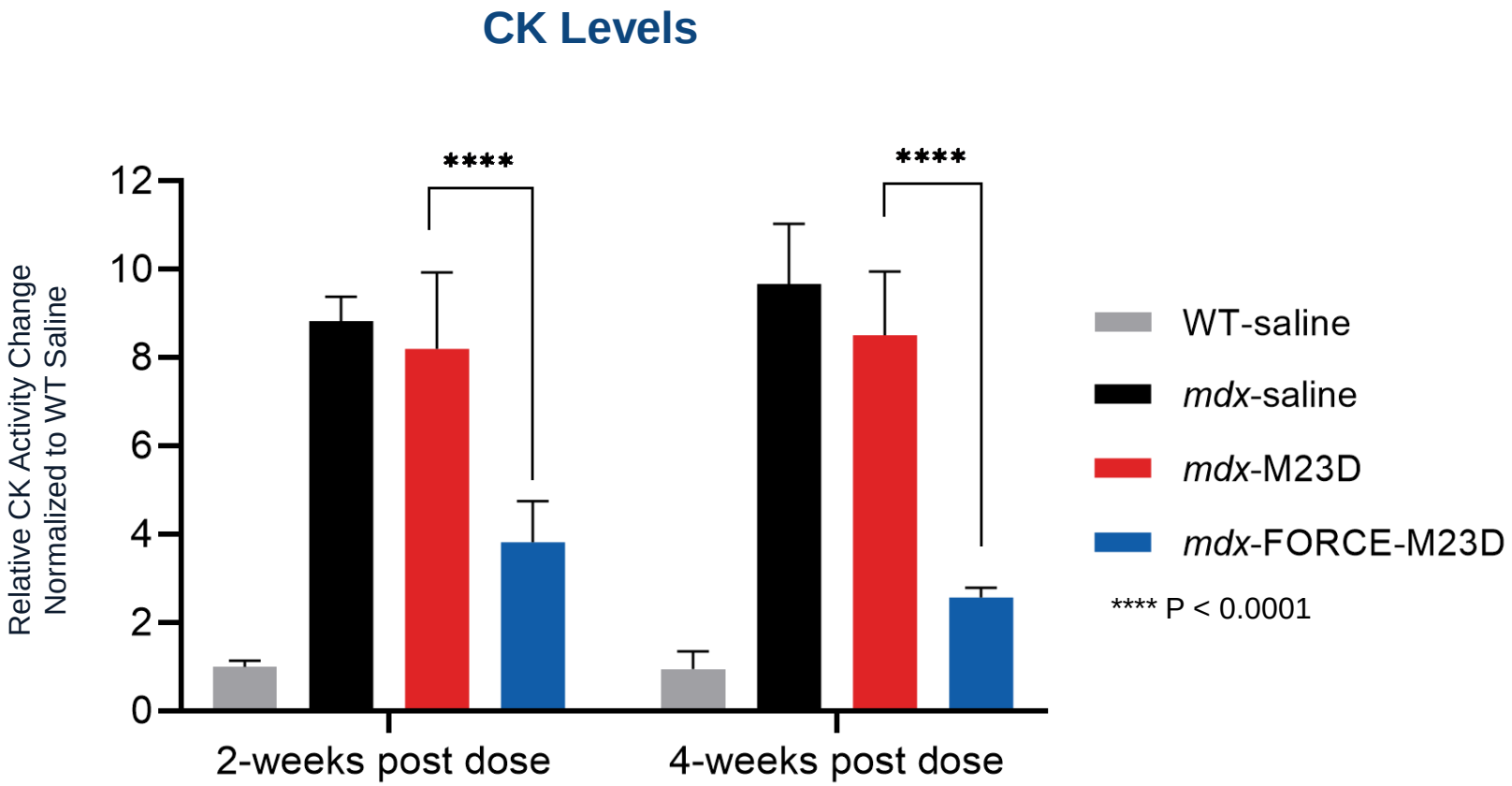
Standard curve - Used pooled WT protein and pooled mdx protein,
% indicates amt. of WT spiked into sample

Restored Dystrophin Expression



Note: Single IV dose of FORCE-M23D in *mdx* mouse model on day 0; assessment on day 14.
[1]Naked ASO data consist of Sarepta Therapeutics data disclosed in a patent application filed Dec. 13, 2017 after single IV dose.
Subramanian R, et al. *American Society for Cell and Gene Therapy 2020 Annual Meeting.* Abstract 1074.

Single dose of FORCE-M23D significantly reduced serum creatine kinase (CK)



- CK is found inside normal muscle and does not leak into serum
- Serum CK is a clinical biomarker of muscle damage
- FORCE-M23D significantly reduced serum CK after a single dose

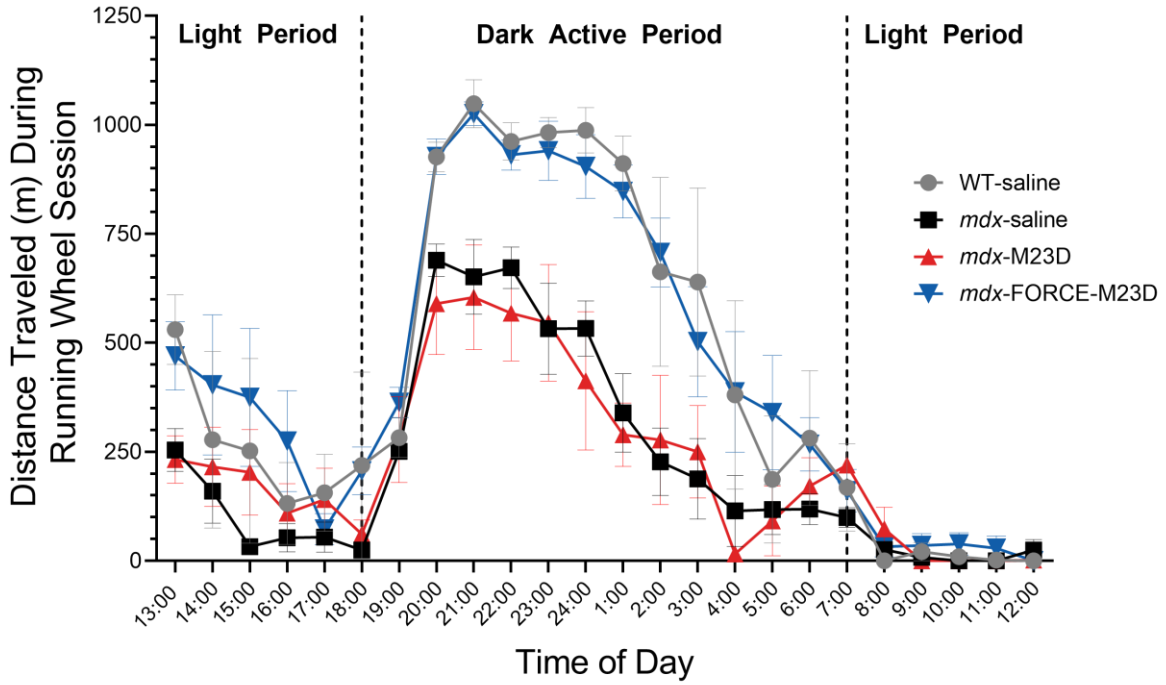
Note: single 30 mg/kg dose of FORCE-M23D in *mdx* model. Statistical analysis comparison to naked mdx-M23D group one-way using ANOVA followed by post-hoc Dunnett's test.

Subramanian R, et al. *American Society for Cell and Gene Therapy 2020 Annual Meeting.* Abstract 1074.

FORCE-M23D demonstrated functional benefit with a single dose

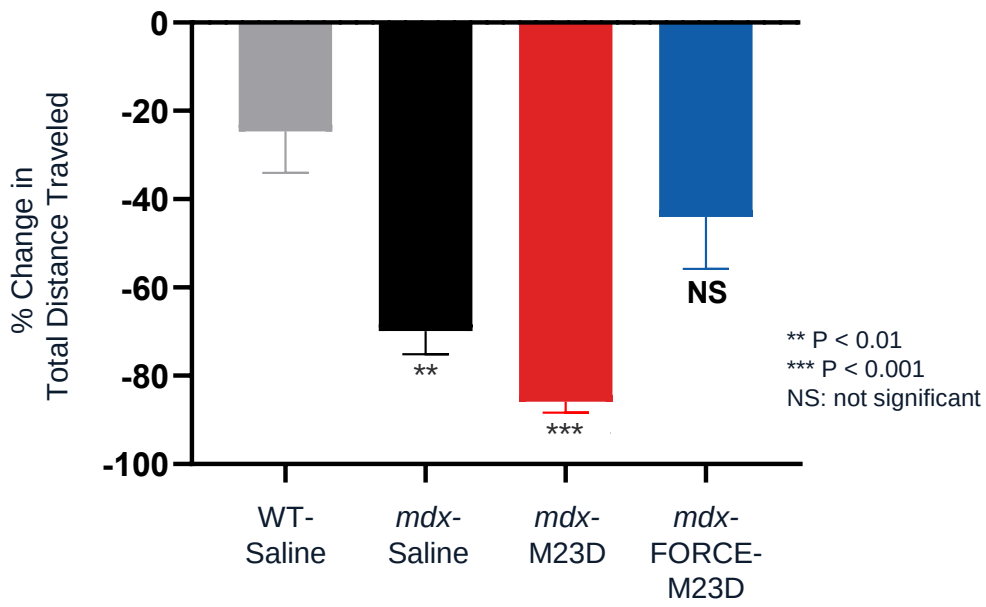
Distance Traveled in Home Cage Running Wheel

(Assessed 4 weeks after treatment)



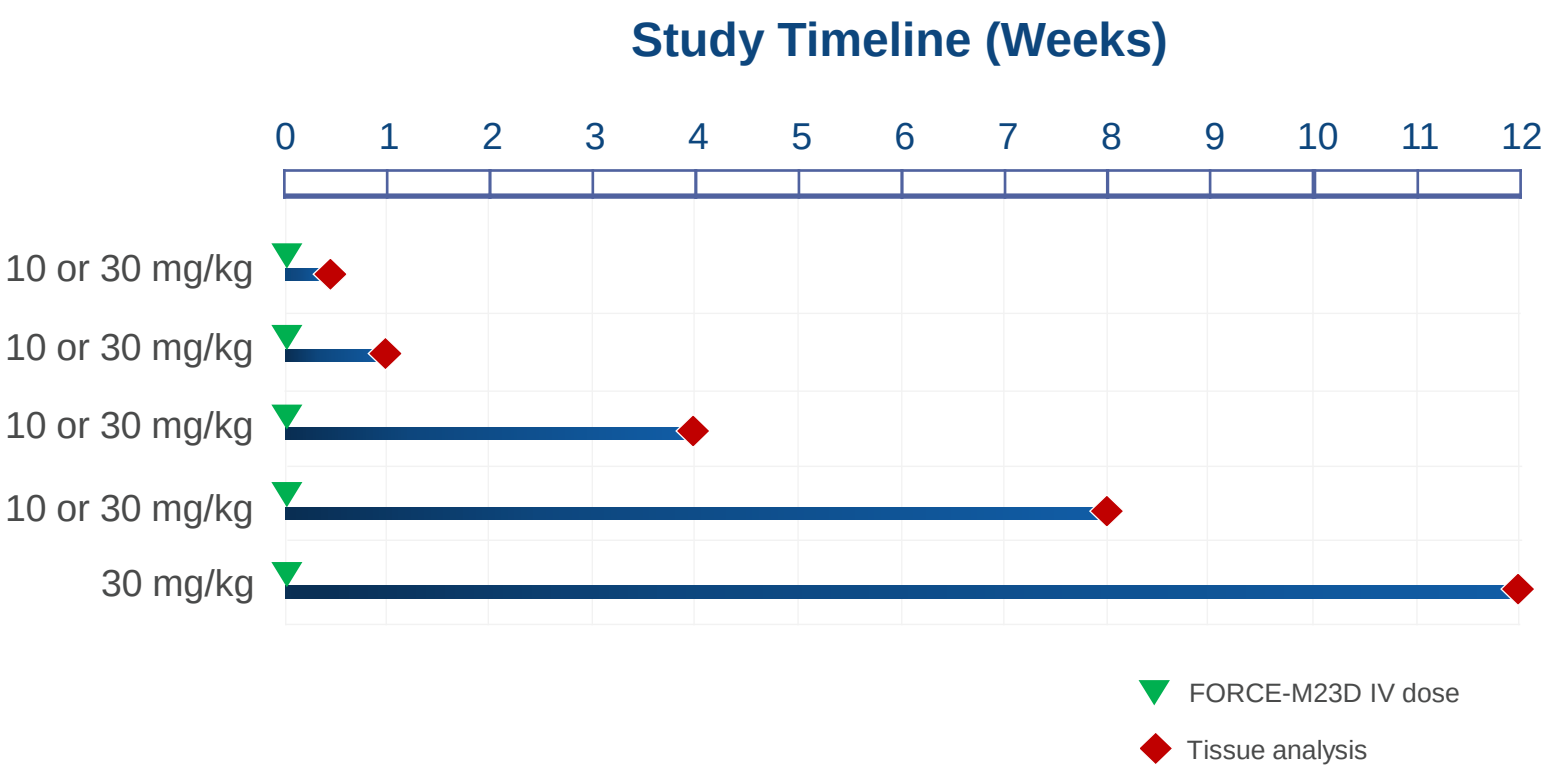
Distance Traveled in Open Field Following Hind Limb Fatigue Challenge

(Assessed 2 weeks after treatment)



Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model. Hind limb fatigue challenge test statistical analysis comparison to wild type (WT) group using one-way ANOVA followed by post-hoc Dunnett's test.

Study evaluated dynamic of FORCE-M23D on dystrophin expression up to 12 weeks after a single dose



Endpoints

- ASO muscle concentration
- Exon skipping by PCR
- Dystrophin protein by WB
- Dystrophin localization by IF

Tissues analyzed

- Quadriceps
- Diaphragm
- Heart

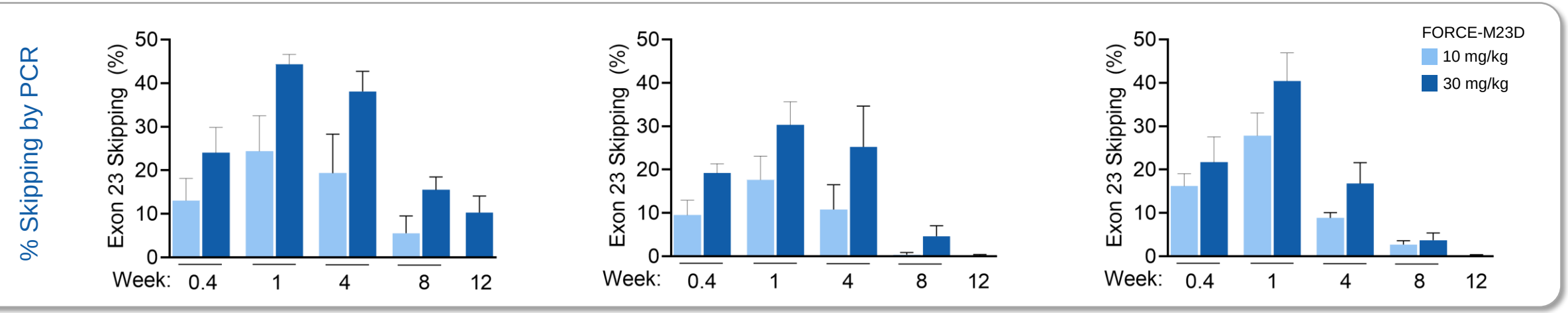
PCR, polymerase chain reaction; WB, western blot; IF, immunofluorescence

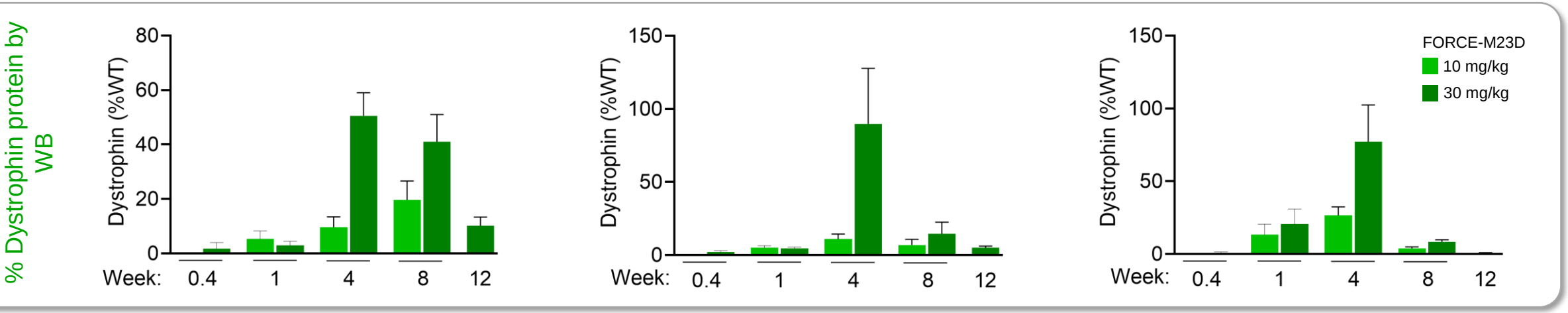
FORCE-M23D achieved robust and durable skipping and expression of dystrophin in muscle of *mdx* mice

Quadriceps

Diaphragm

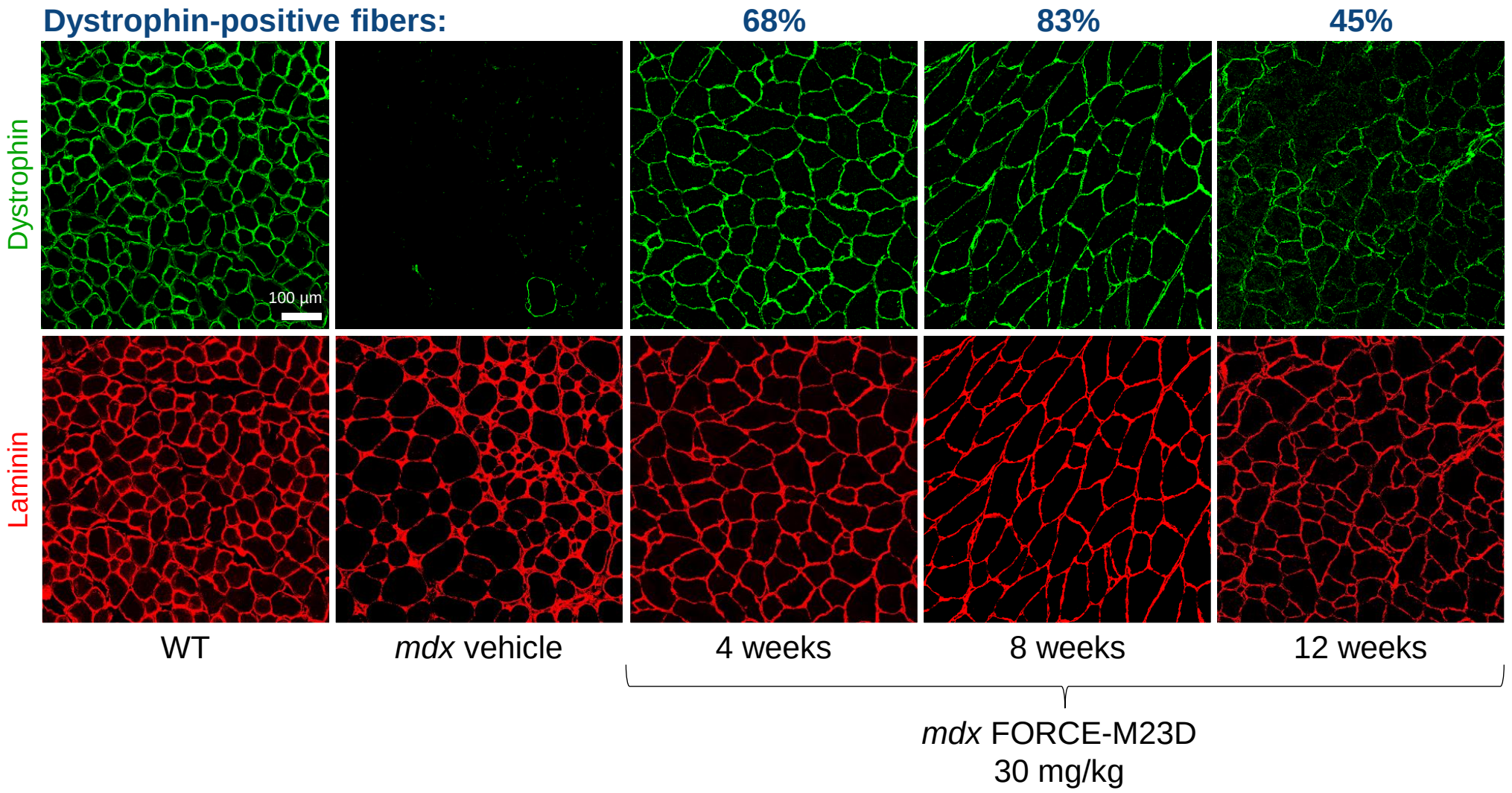
Heart





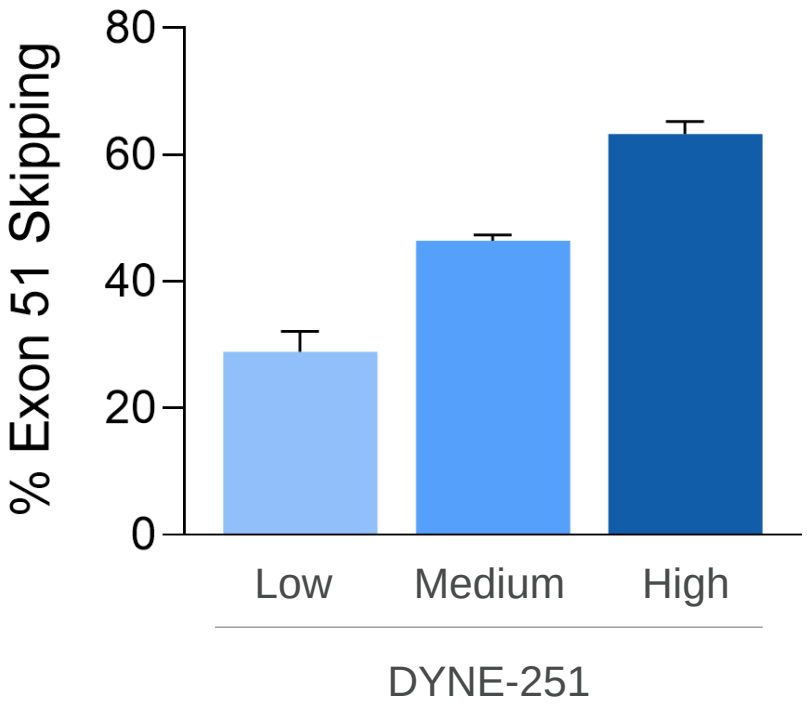
Note: Single IV dose of FORCE-M23D in *mdx* mouse model on day 0. Data are mean ±SD; N = 4 - 5 per cohort for quadriceps and heart and 3-5 per cohort for diaphragm.

FORCE-M23D achieved durable dystrophin localization to sarcolemma in quadriceps



Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis at specified time intervals.

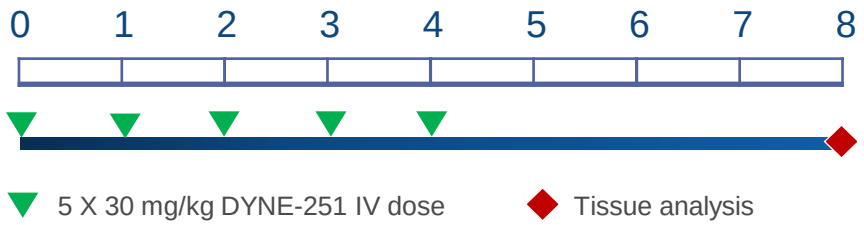
DYNE-251 achieved robust and dose-dependent exon 51 skipping in DMD patient myotubes



Note: DYNE-251 exposure in DMD patient myotubes for 10 days. N = 3.

DYNE-251 achieved robust exon skipping in cardiac and skeletal muscles of NHPs

Study Timeline (Weeks)



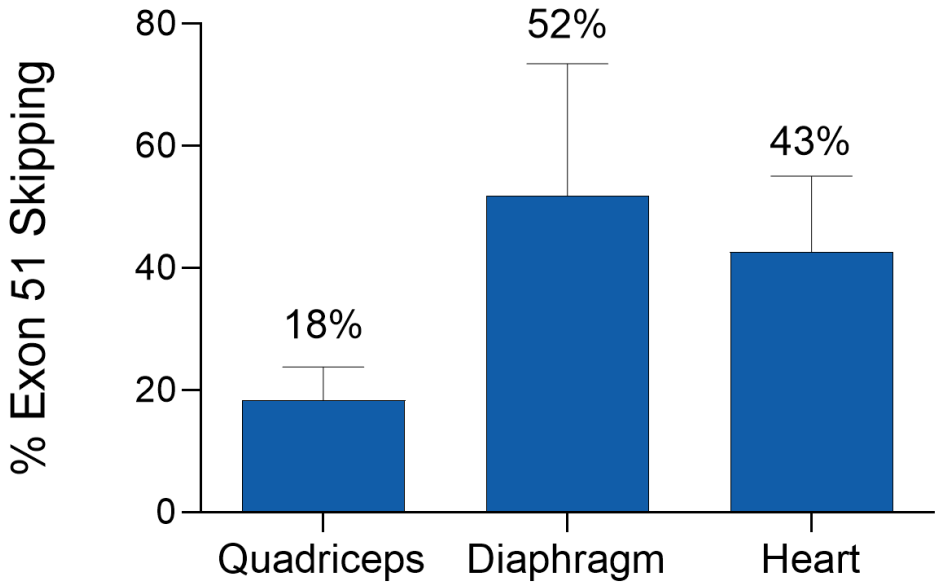
Endpoints

- Exon 51 skipping by PCR

Tissues analyzed

- Quadriceps
- Diaphragm
- Heart

Exon 51 Skipping in WT NHPs



Note: Five weekly IV doses of 30 mg/kg PMO-equivalent of DYNE-251 in WT NHP, analysis 8 weeks post-first dose.

DYNE-251 NHP GLP Toxicology Results Demonstrate Favorable Safety Profile

5-Week GLP Toxicology Study

- No dose limiting toxicity observed after five weekly doses up to a maximally feasible dose
- No changes in cardiac, respiratory, neurologic or ophthalmic endpoints
- No effect on kidney function
- No effect on liver function
- No effect on coagulation
- NOAEL was identified at the highest dose tested

Note: Based on conclusions of report from third-party CRO
NOAEL: No-observed-adverse-effect level

DMD program summary

mdx Model

- **Achieved robust and durable** exon skipping in skeletal and cardiac muscle
- **Dose-dependently increased dystrophin** expression up to 90% of WT based on western blot and ~80% dystrophin-positive fibers
- **Reduced serum CK levels**
- **Demonstrated functional benefit** in multiple standardized assessments

DYNE-251

- **Robust and dose-dependent exon skipping** in patient DMD patient myotubes (exon 51)
- **Transformative exon skipping in NHP** cardiac and skeletal muscles
- **Favorable safety profile in NHP GLP tox study**

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