The Muscle to Move to the Clinic

R&D DAY | OCTOBER 13, 2021, 8 a.m. ET

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 Therapeutics, Inc.'s (the "Company") strategy, future operations, prospects, plans and objectives of management, the expected timeline for submitting investigational new drug applications, the potential advantages of the Company's FORCE platform and programs, expectations regarding the translation of preclinical findings to human disease and plans to conduct additional preclinical studies and clinical trials, the anticipated design of clinical 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. The Company 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, the initiation and completion of preclinical studies and clinical trials; uncertainties as to the availability and timing of results from preclinical studies; the timing of and our ability to submit and obtain regulatory approval for investigational new drug applications; whether results from preclinical studies will be predictive of the results of later preclinical studies and clinical trials; the Company's ability to obtain sufficient cash resources to fund the Company's foreseeable and unforeseeable operating expenses and capital expenditure requirements; the impact of the COVID-19 pandemic on the Company'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 the Company's views as of the date of this presentation. The Company anticipates that subsequent events and developments will cause its views to change. However, while the Company 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 the Company'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.

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A

OUR MISSION

Life-transforming therapies

for patients with serious muscle diseases

Dyne – Building the Leading Muscle Disease Company

Proprietary FORCE Platform

- Modern oligo therapeutics for muscle diseases
- Overcoming challenge of muscle delivery
- Plug-and-play therapeutics for multiple targets in skeletal, cardiac and smooth muscle diseases

Rare Muscle Disease Focus

- Robust pipeline: DM1, DMD, and FSHD
- Set standard for evaluating PD in DM1 disease model
- Significant exon skipping & dystrophin expression in DMD
- Significant market opportunities

Delivering for Patients

- Developing multiple first-in-class or best-in-class therapies
- Precision medicine strategy
- Three INDs planned between Q4 2021 - Q4 2022

Exceptional Team

- Deep knowledge of muscle diseases and novel therapeutic modalities
- World-class scientific advisory board
- Supported by leading healthcare investors

Robust Portfolio Focused on Muscle Diseases

DISEASE	TARGET	DISCOVERY / PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 3	ESTIMATED PATIENTS
Myotonic Dystrophy (DM1)	DMPK	**DYNE-101**	US: **>40,000** Europe: **>74,000**
Duchenne Muscular Dystrophy (DMD)	Exon 51	**DYNE-251**	US: **~12,000-15,000** Europe: **~25,000**
	Exon 53		
	Exon 45		
	Exon 44		
Facioscapulohumeral Muscular Dystrophy (FSHD)	DUX4	**DYNE-301**	US: **~16,000-38,000** Europe: **~35,000**

Pipeline Expansion Opportunities

Rare Skeletal

Cardiac

Metabolic

Driving To the Clinic with Three INDs Anticipated by YE 2022

DMD

In vitro:

- Enhanced exon skipping

In vivo:

- Robust, durable exon skipping and dystrophin expression in *mdx* model
- Transformative exon skipping in NHP cardiac and skeletal muscles
- NHP GLP tox results support advancement to the clinic

IND: Q4 2021

DM1

In vitro:

- *DMPK* KD, reduction in nuclear foci, splicing correction

In vivo:

- Correction of splicing & reversal of myotonia in HSA^{LR} model
- Robust knockdown of toxic nuclear *DMPK* in hTfR1/DMSXL model, foci reduction & correction of splicing
- Well tolerated in NHP Non-GLP toxicology dose-range finding study

IND: Q1 2022

FSHD

In vitro:

- Reduced expression of key DUX4 biomarkers

In vivo:

- Enhanced tissue distribution in NHP

IND: H2 2022

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

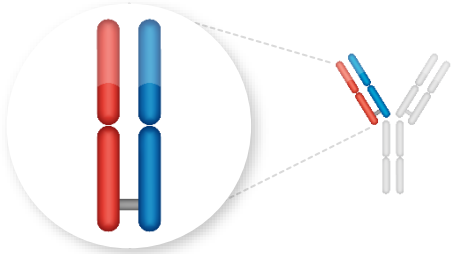
Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

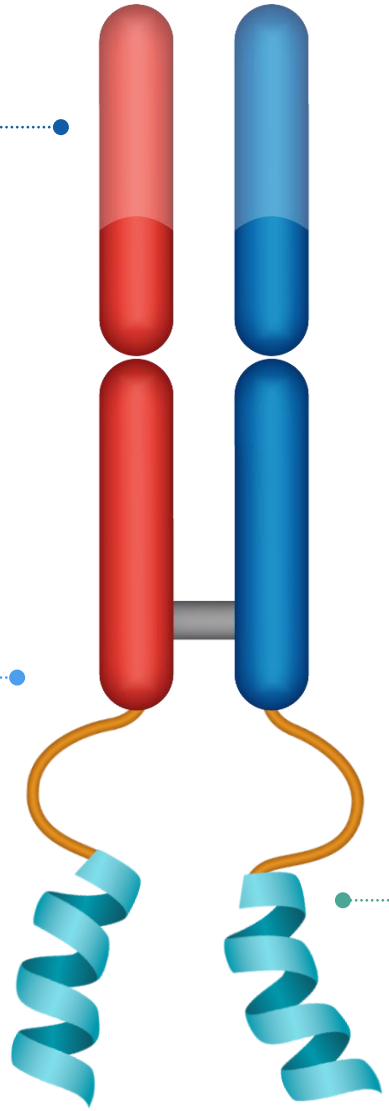
Q&A

Dyne FORCE™ Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



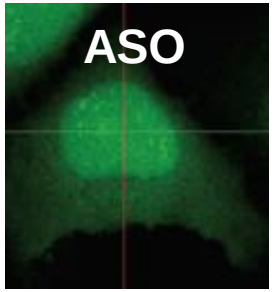


LINKER

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

PAYLOAD

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

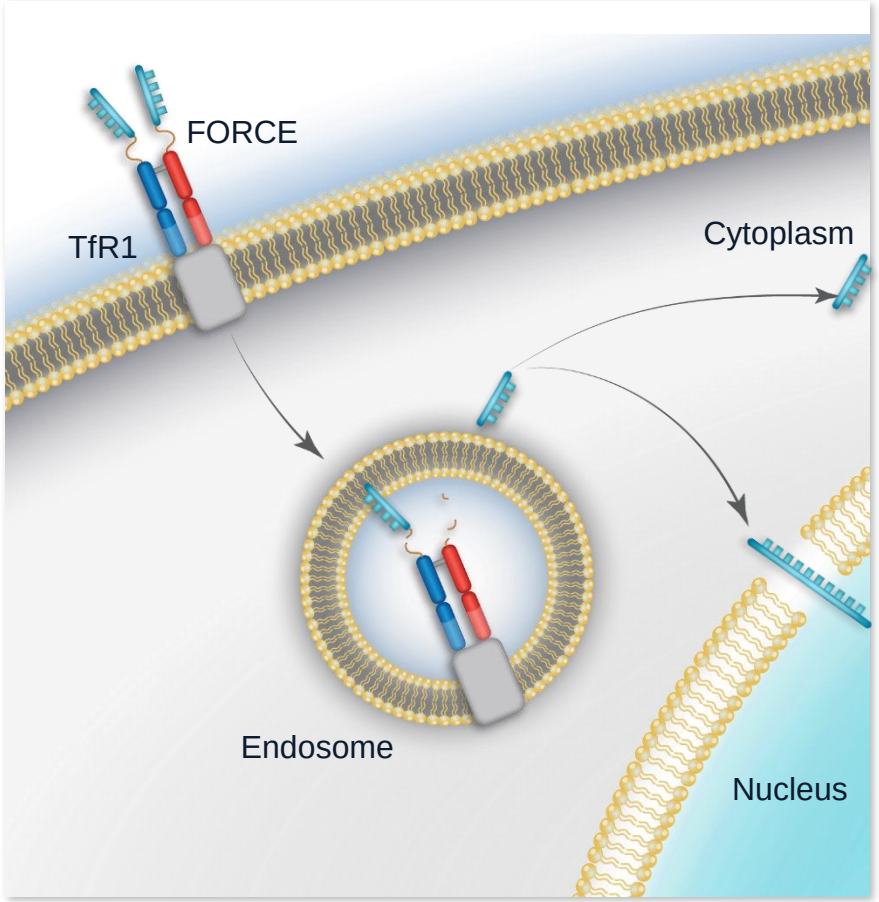


Nuclear localization

Cytoplasmic localization

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

FORCE Platform Designed to Deliver Transformative Therapies

Solve the Challenge of Muscle Delivery

Leverages TfR1 expression on skeletal, cardiac and smooth muscle

Drive Disease Modification

Rationally select payloads to target genetic basis of disease

Enhance Tolerability

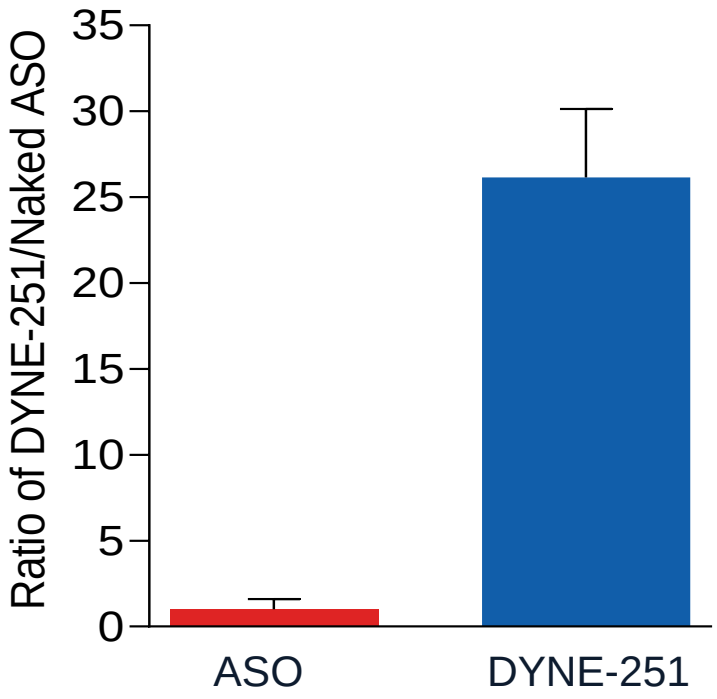
Targeted delivery potentially broadens therapeutic window and limits systemic drug exposure

Leverage Modularity to Realize Full Potential of FORCE

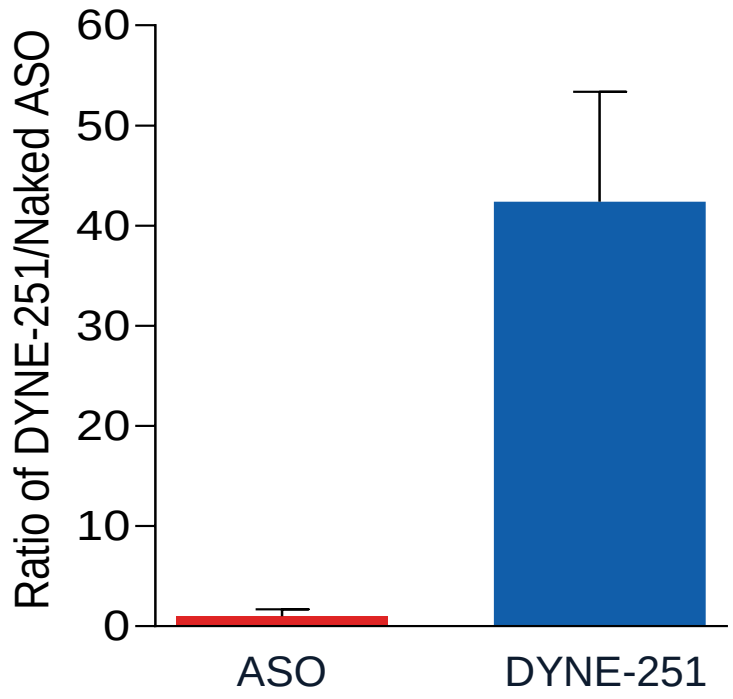
Identified potent siRNA payloads against multiple cardiac and metabolic targets

FORCE Overcame Limitations of ASO Delivery to Muscle in NHP

Heart



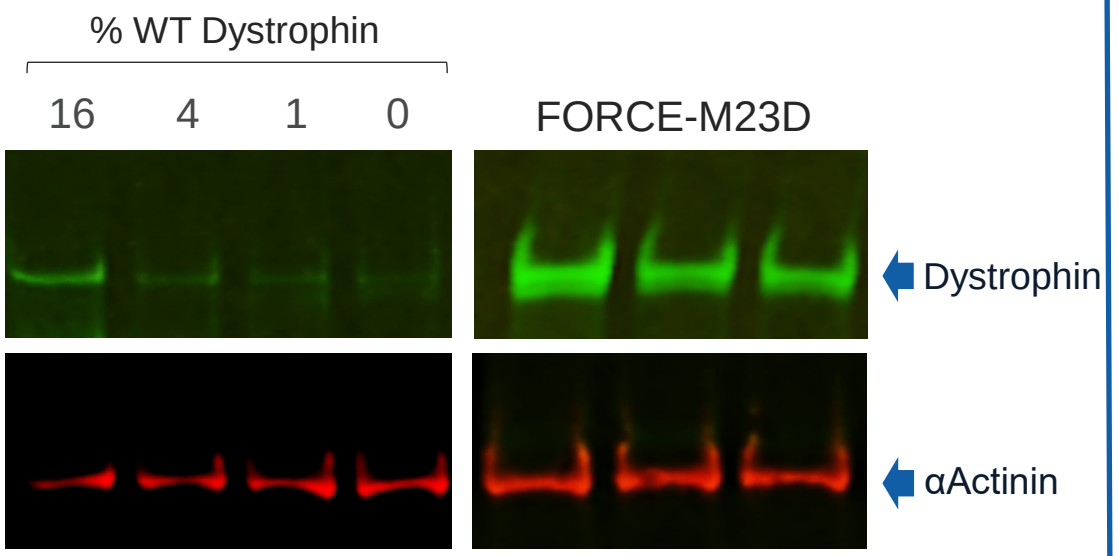
Diaphragm



Note: Results after repeat IV dose of naked ASO or DYNE-251 in male cynomolgus monkeys, 2 x 30 mg/kg on day 0 and day 7, analyzed day 28; n = 4 – 5

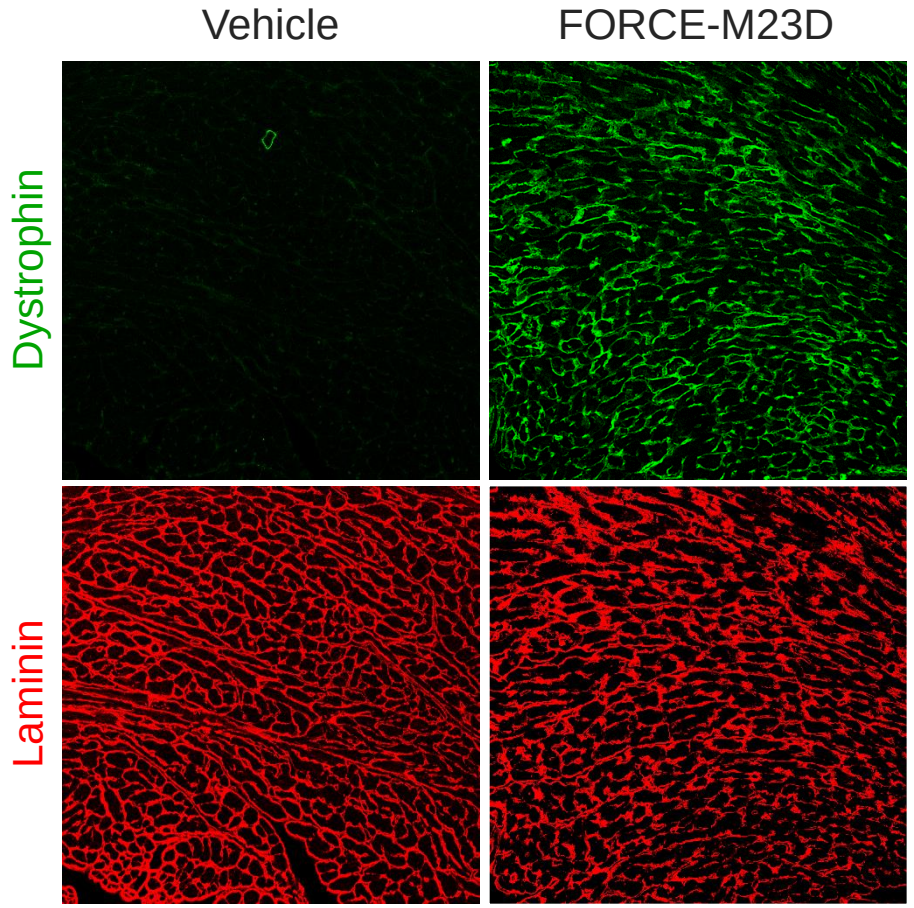
DMD: FORCE Achieved Robust Dystrophin Expression Localization to Sarcolemma in Heart

Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose



78% of wild-type dystrophin

Dystrophin Localization to Sarcolemma

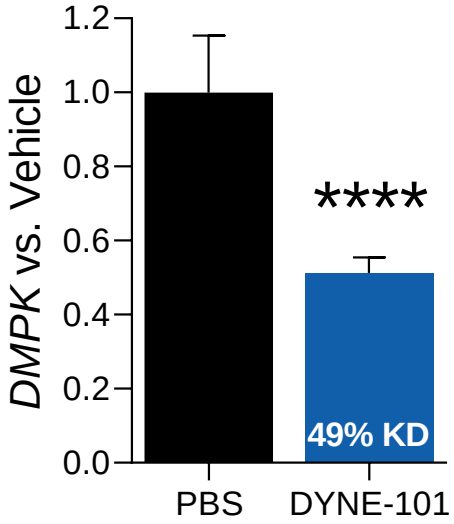


~80% dystrophin-positive fibers

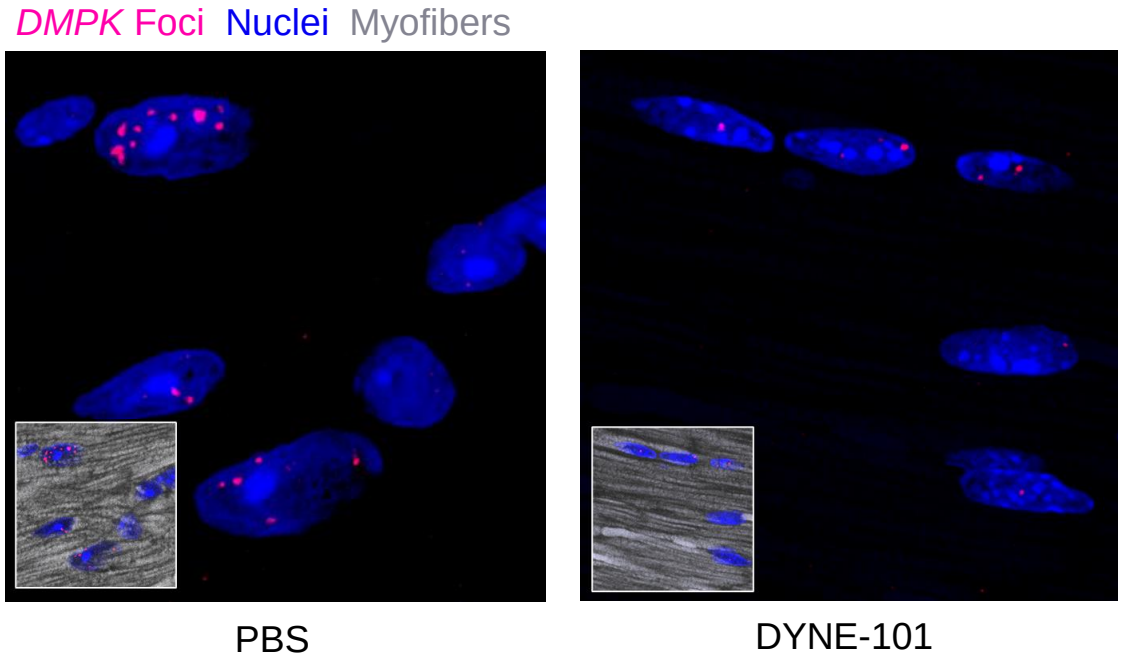
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis on week 4.

DM1: DYNE-101 Reduced Nuclear Foci and Corrected Splicing of Toxic Human *DMPK* in hTfR1/DMSXL Model

Toxic Human *DMPK* RNA KD

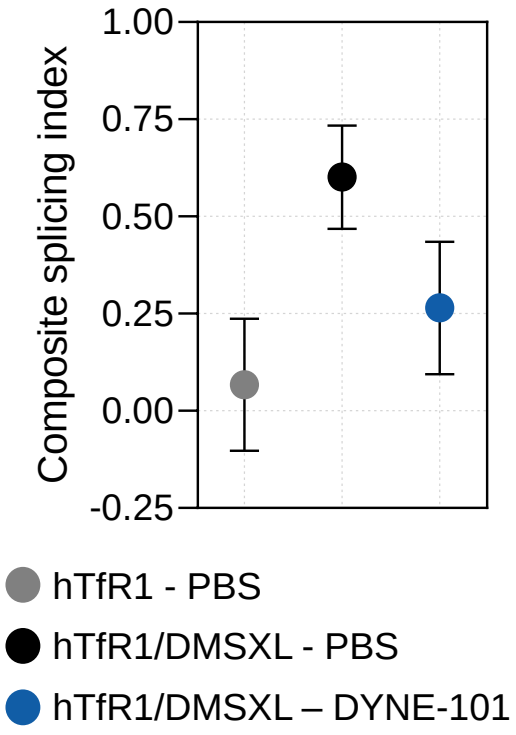


Toxic Human *DMPK* Foci Reduction



DYNE-101 reduces foci area by 49%*

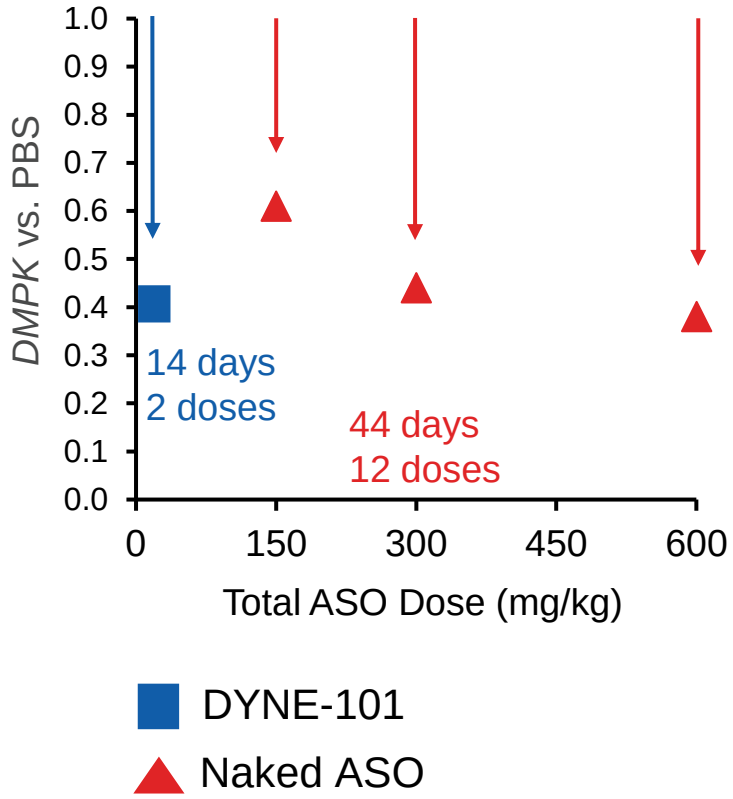
Splicing Correction



Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28.
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are mean ± SD, n = 6 - 7.; * p <0.05; **** p < 0.0001

FORCE Targeted Delivery to Muscle Tissue Enhanced Potency and Tolerability

Toxic Human *DMPK* KD in Heart of DMSXL mice



FORCE Offers Potential for Wide Therapeutic Window

DM1 mouse model DMSXL

- 15-30-fold lower dose required for ~60% *DMPK* KD by FORCE vs naked ASO

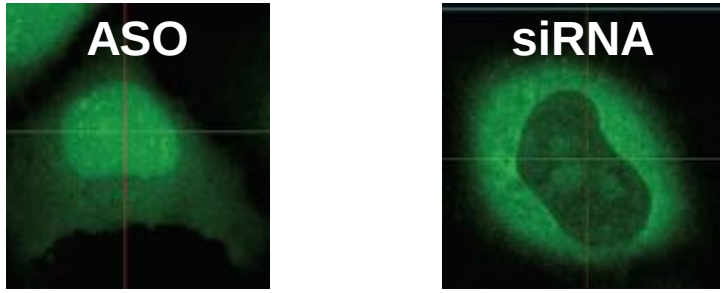
DM1 Non-GLP NHP Toxicology

- No adverse findings in DRF study in cynomolgus monkeys up to maximal feasible dose

Note: Naked ASO from published data (Pandey et al, 2015) in DMSXL model; Dyne data from hemizygous hTfR1/DMSXL model and WT NHP.

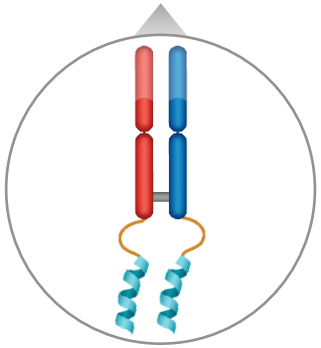
Leveraging Platform Modularity to Realize Full Potential of FORCE, Including siRNA Payloads for Cytoplasmic Targets

Subcellular distribution of ASO and siRNA



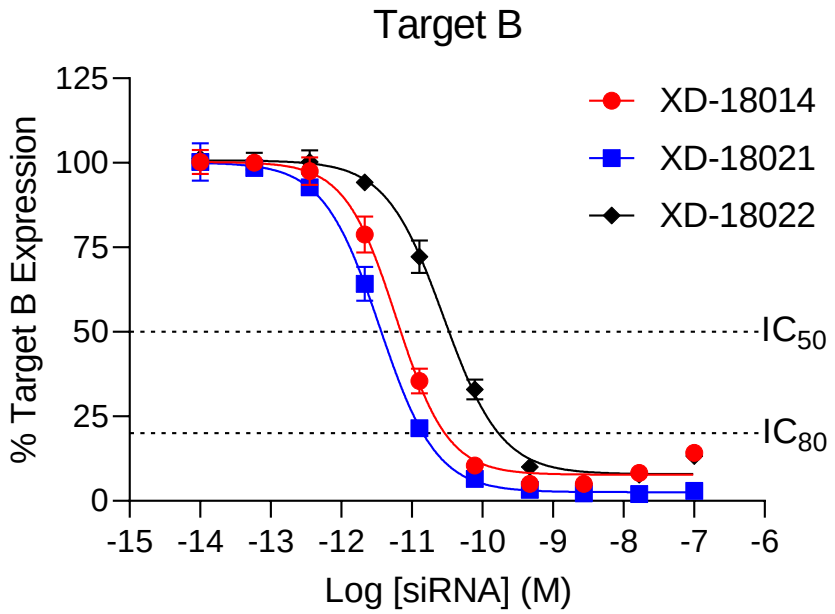
Nuclear localization

Cytoplasmic localization



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

Engineered proprietary siRNA payloads



Identified potent **siRNA** payloads against multiple cardiac and metabolic targets

Localization graphic adapted from: Ohrt et al: NAR , 2006, v.34, p.1369

Building a Global DMD Franchise of Transformative Therapies

mdx model

- Robust, durable exon skipping and dystrophin expression

NHP

- Transformative exon skipping in NHP cardiac and skeletal muscles

Safety

- NHP GLP tox results support advancement to the clinic

Current Approved Exon 51 Therapies Only Increased Dystrophin Production

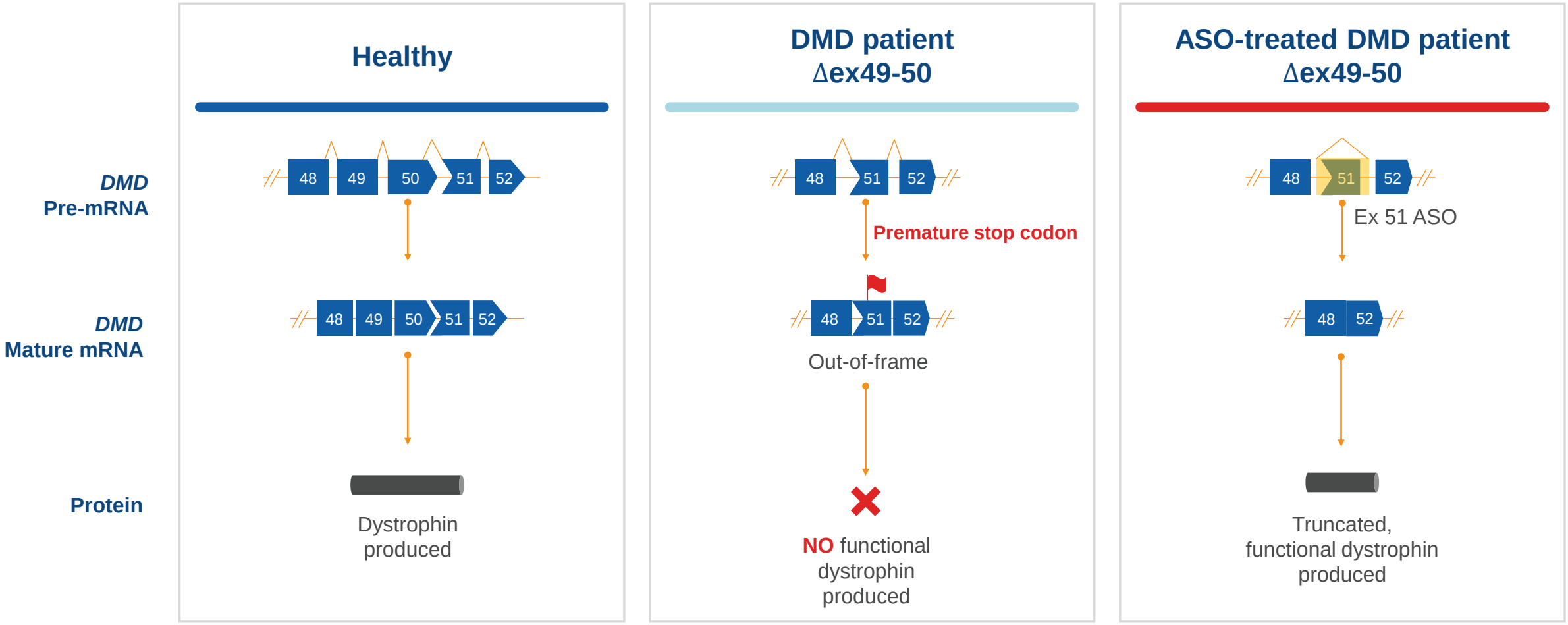
<1%

OUR APPROACH

Best-in-class Targeted Exon Skipping

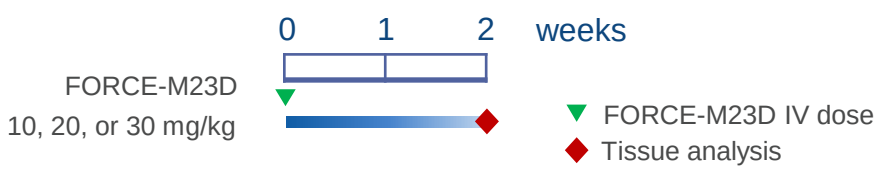
Increase dystrophin expression and enable less frequent dosing to potentially **stop or reverse disease progression**

ASO-Mediated Exon Skipping: Mechanism for Disease Correction



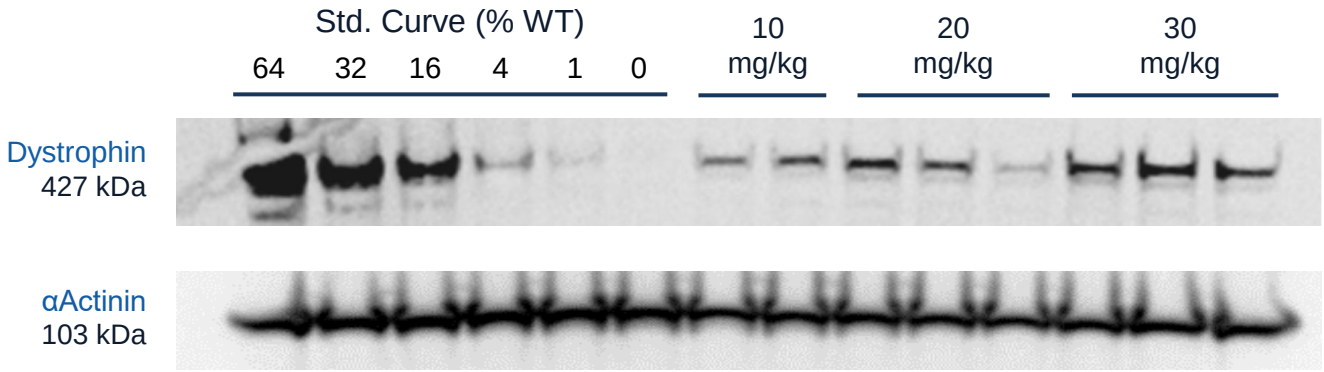
Adapted from Lim KRQ., et al. *Drug Des Devel Ther* 2017;11:533.

FORCE Dose-Dependently Increased Dystrophin Expression



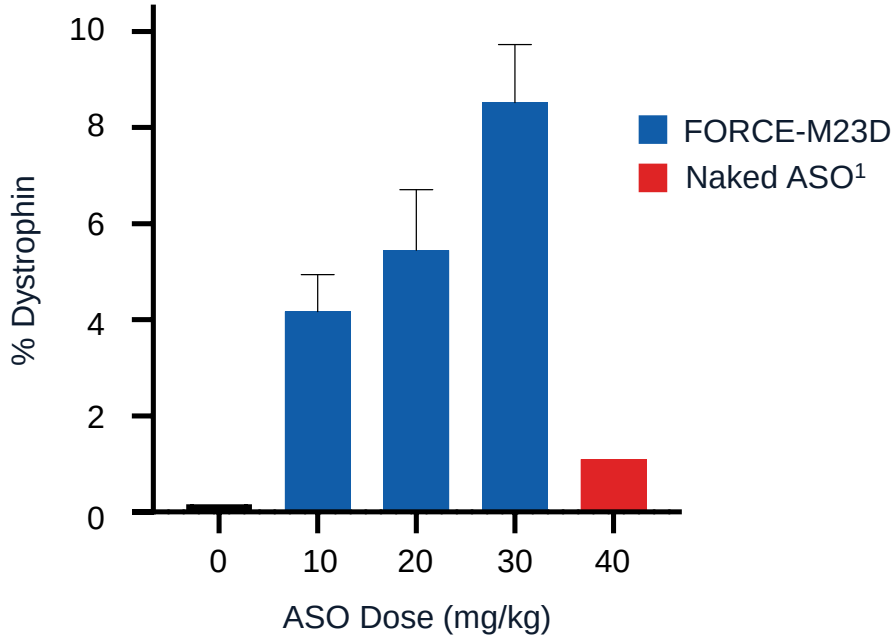
Quadriceps

Dose-Dependent Increase in Dystrophin Expression



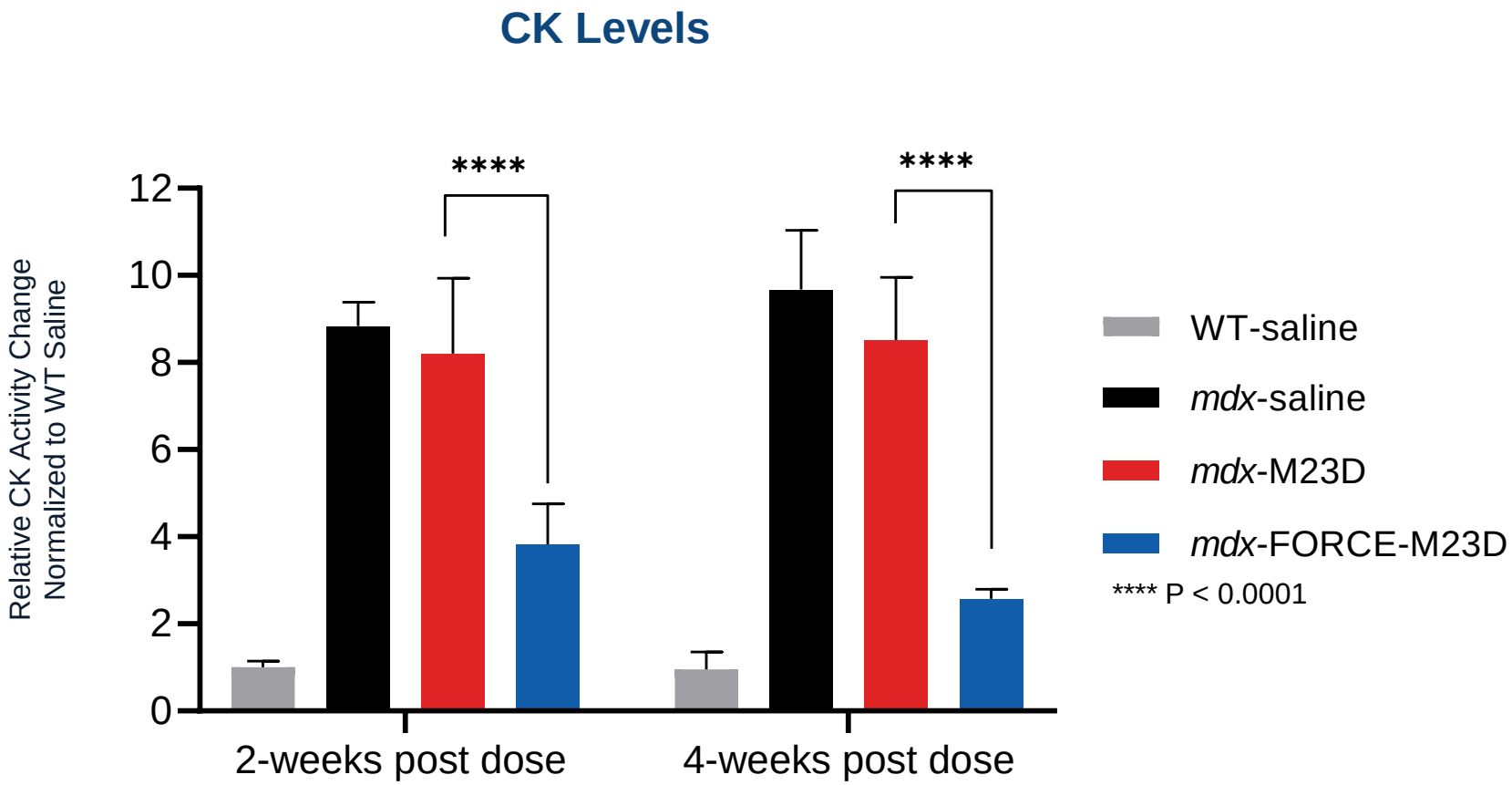
Standard curve - Used pooled WT protein and pooled mdx protein,
% indicates amt. of WT spiked into sample

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 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 significantly reduced serum CK after a single dose

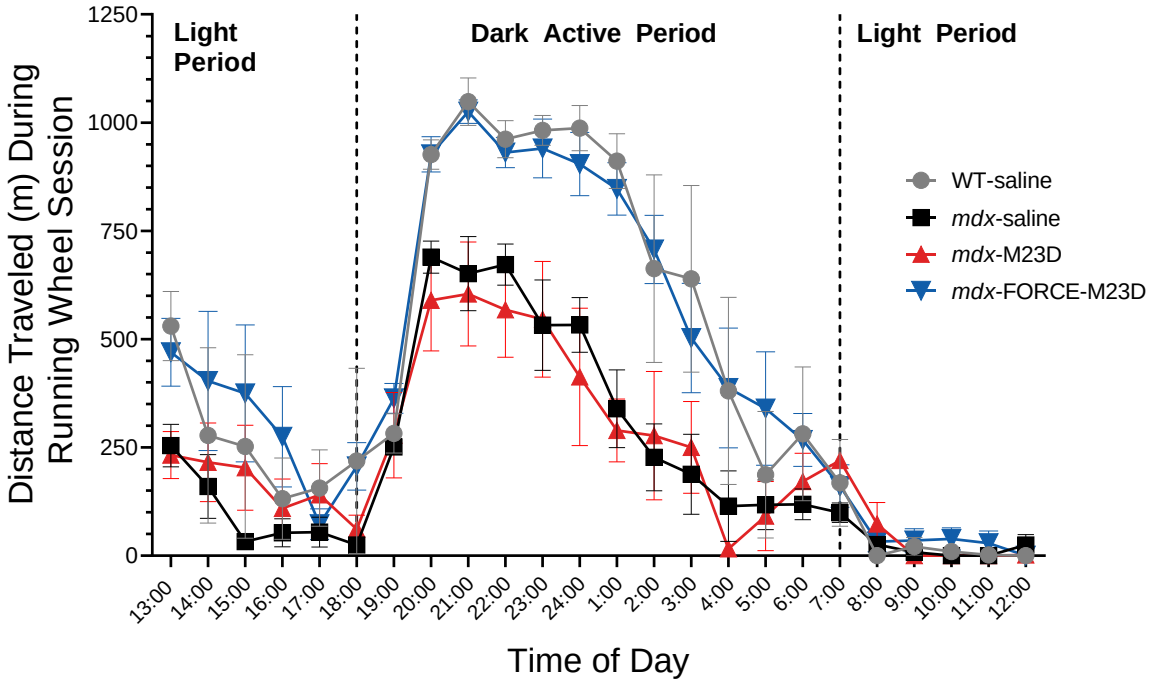
Note: single 30 mg/kg dose of FORCE-M23D in *mdx* model. Statistical analysis comparison to naked mdx-M23D group one-way using ANOVA followed by post-hoc Dunnett's test.

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

FORCE Demonstrated Functional Benefit with a Single Dose

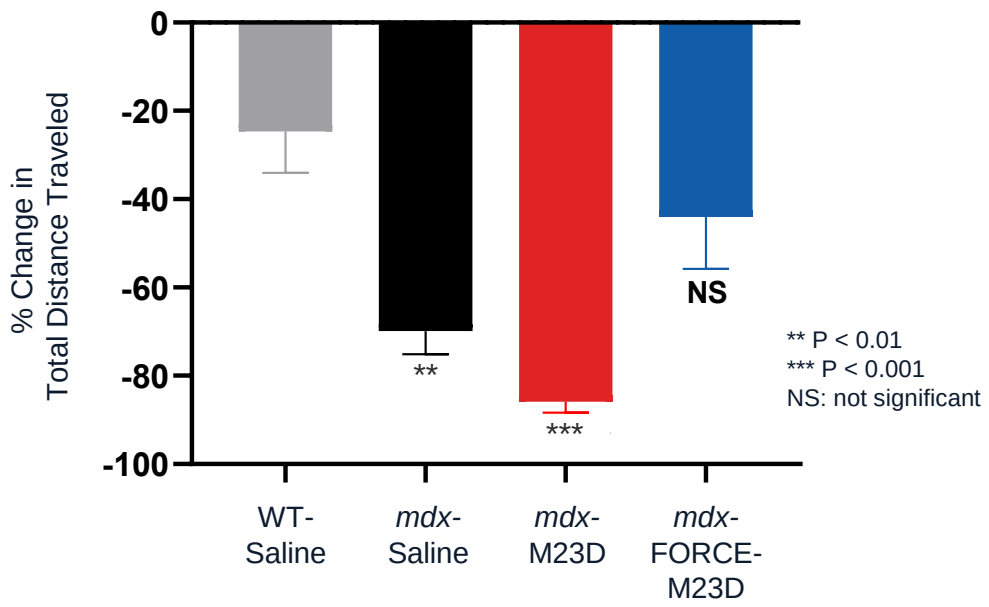
Distance Traveled in Home Cage Running Wheel

(Assessed 4 weeks after treatment)



Distance Traveled in Open Field Following Hind Limb Fatigue Challenge

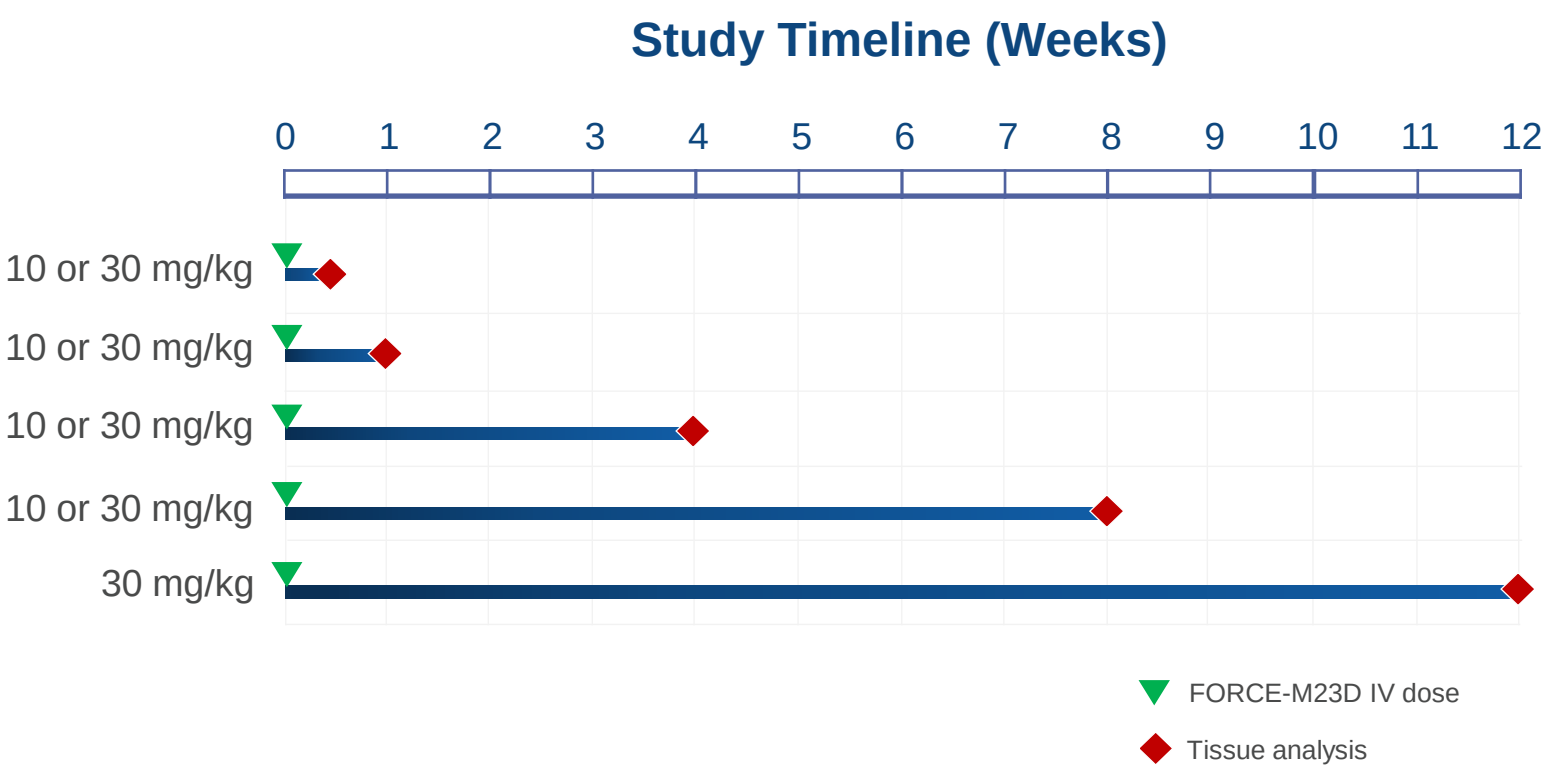
(Assessed 2 weeks after treatment)



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.

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

Study Evaluated Dynamic of FORCE on Dystrophin Expression up to 12 Weeks After a Single Dose



Endpoints

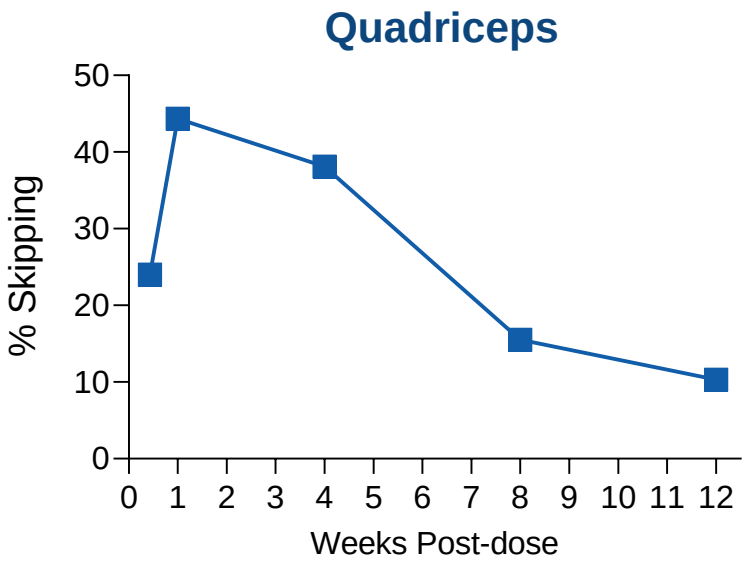
- ASO muscle concentration
- Exon skipping by PCR
- Dystrophin protein by WB
- Dystrophin localization by IF

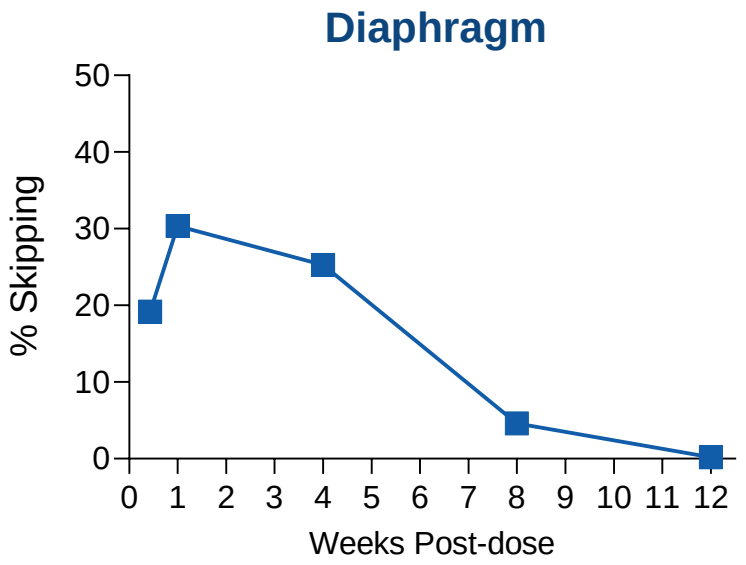
Tissues analyzed

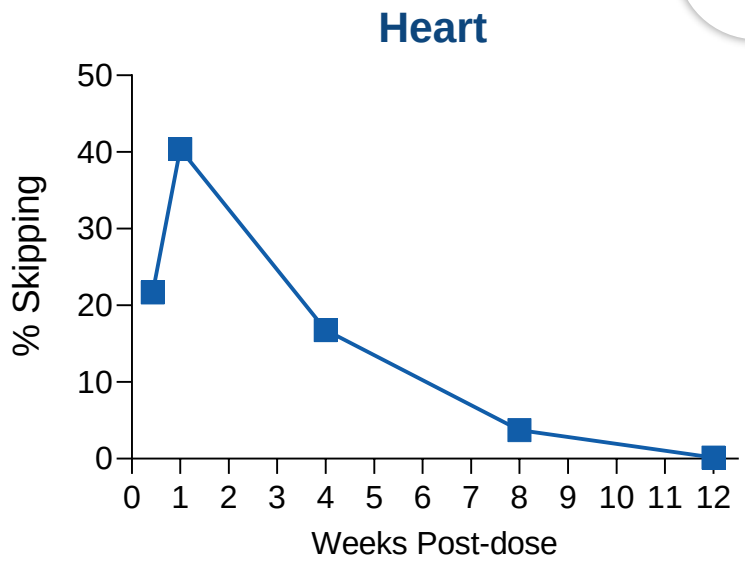
- Quadriceps
- Diaphragm
- Heart

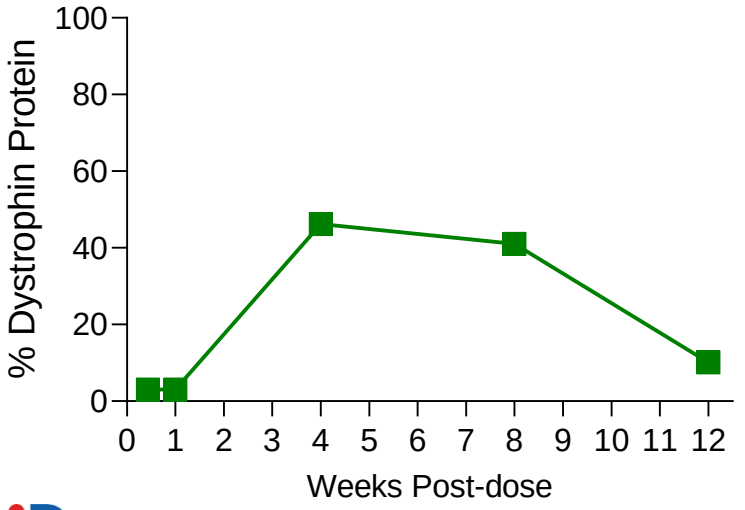
PCR, polymerase chain reaction; WB, western blot; IF, immunofluorescence

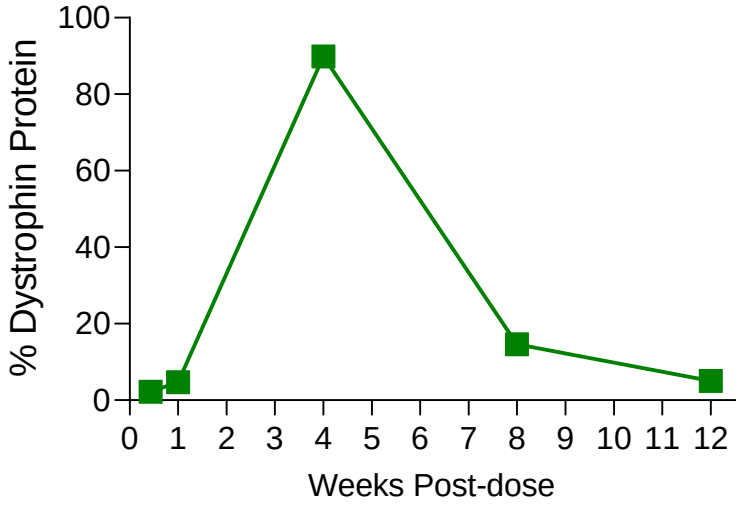
FORCE Achieved Robust and Durable Skipping and Dystrophin Expression in Cardiac and Skeletal Muscle

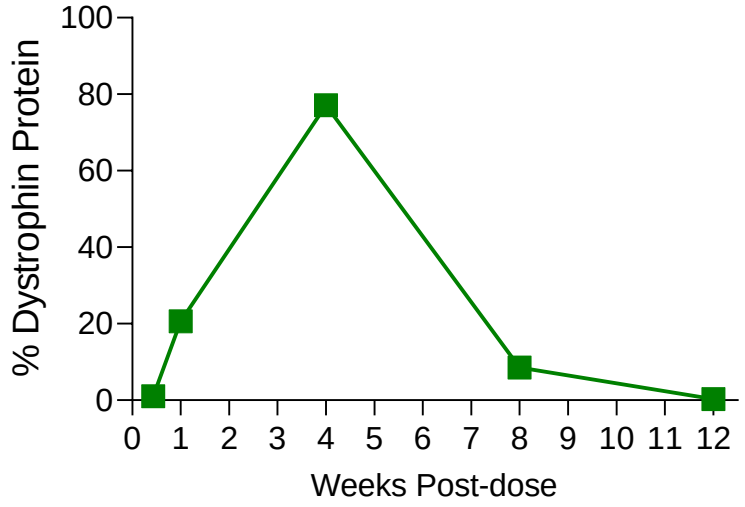








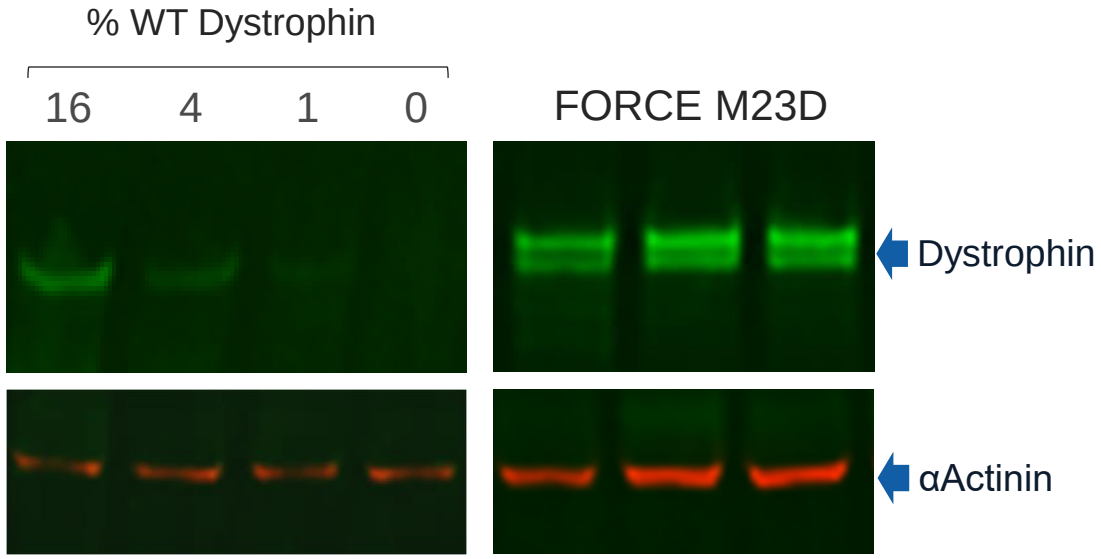




Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; N = 3 - 5 per cohort.

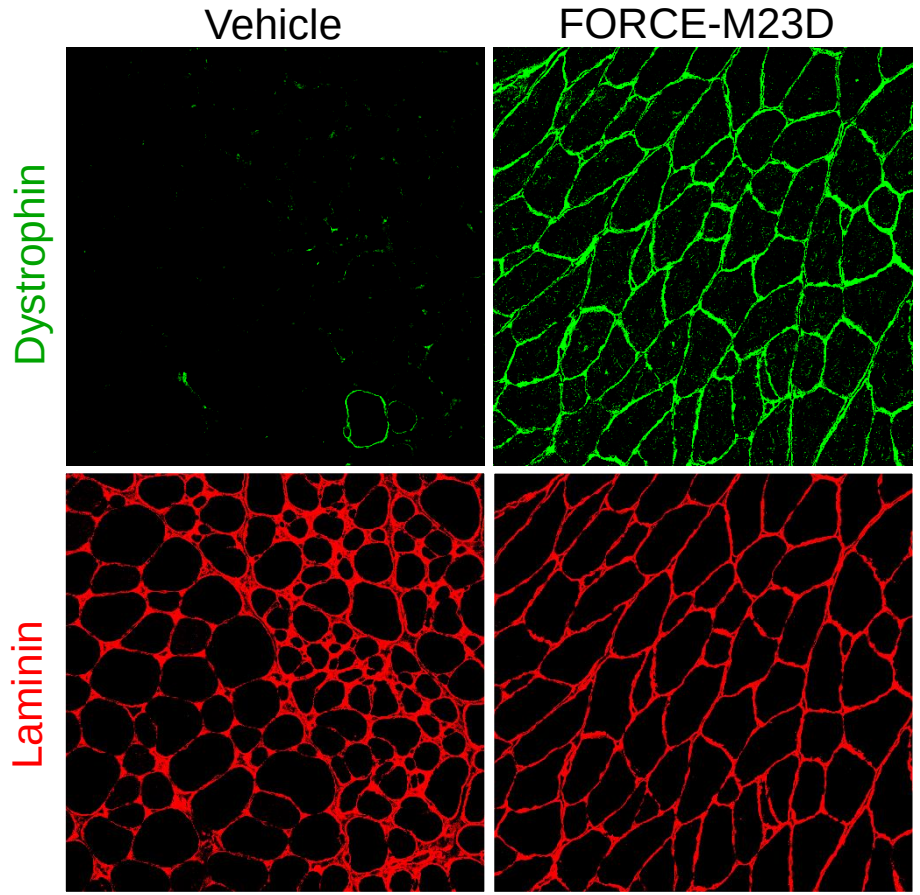
FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Quadriceps at 8 Weeks

Dystrophin Expression by WB
30 mg/kg 8 Weeks Post-Dose



41% of wild-type dystrophin

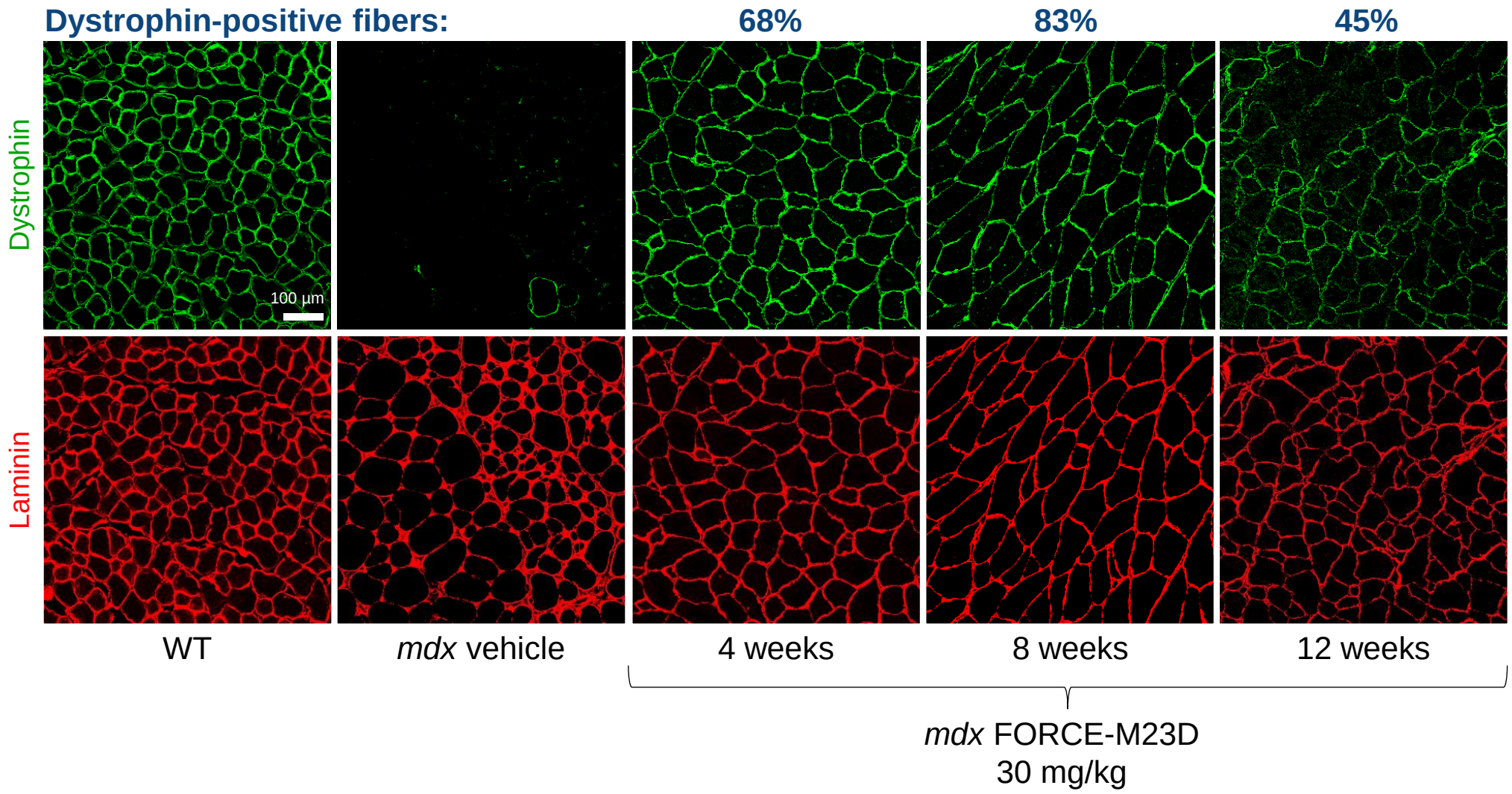
Dystrophin Localization to Sarcolemma



83% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis on week 8.

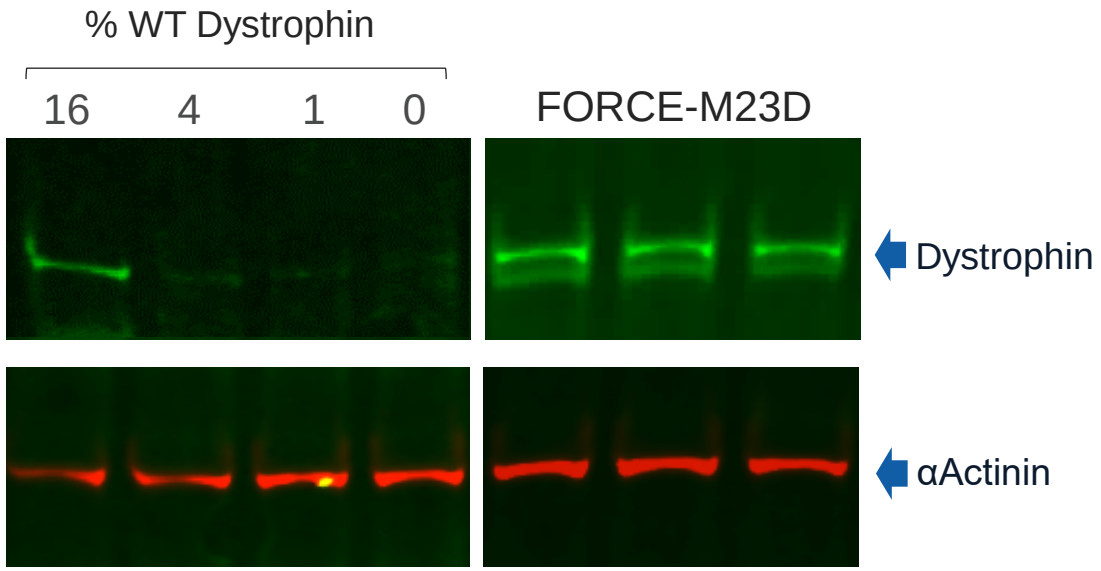
FORCE Achieved Durable Dystrophin Localization to Sarcolemma in Quadriceps



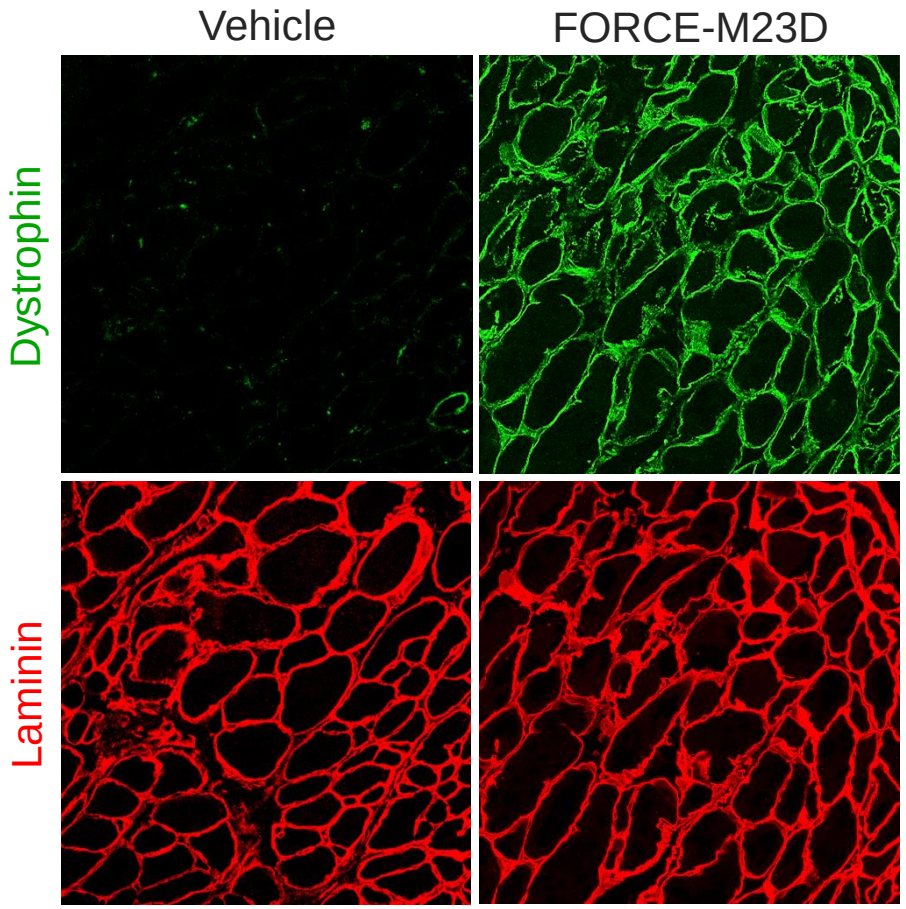
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis at specified time intervals.

FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Diaphragm at 4 Weeks

Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose



Dystrophin Localization to Sarcolemma



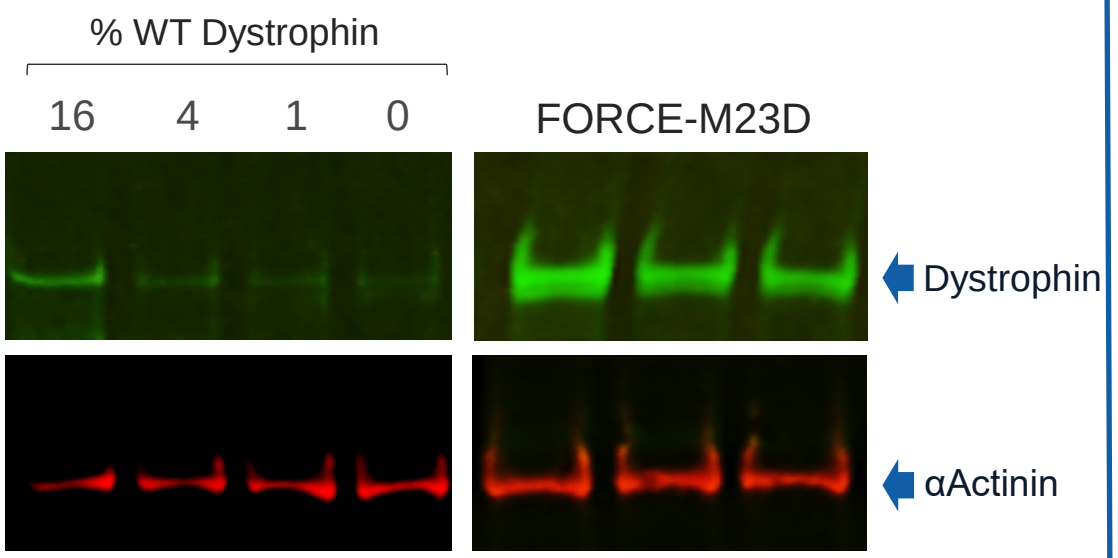
90% of wild-type dystrophin

~80% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis on week 4.

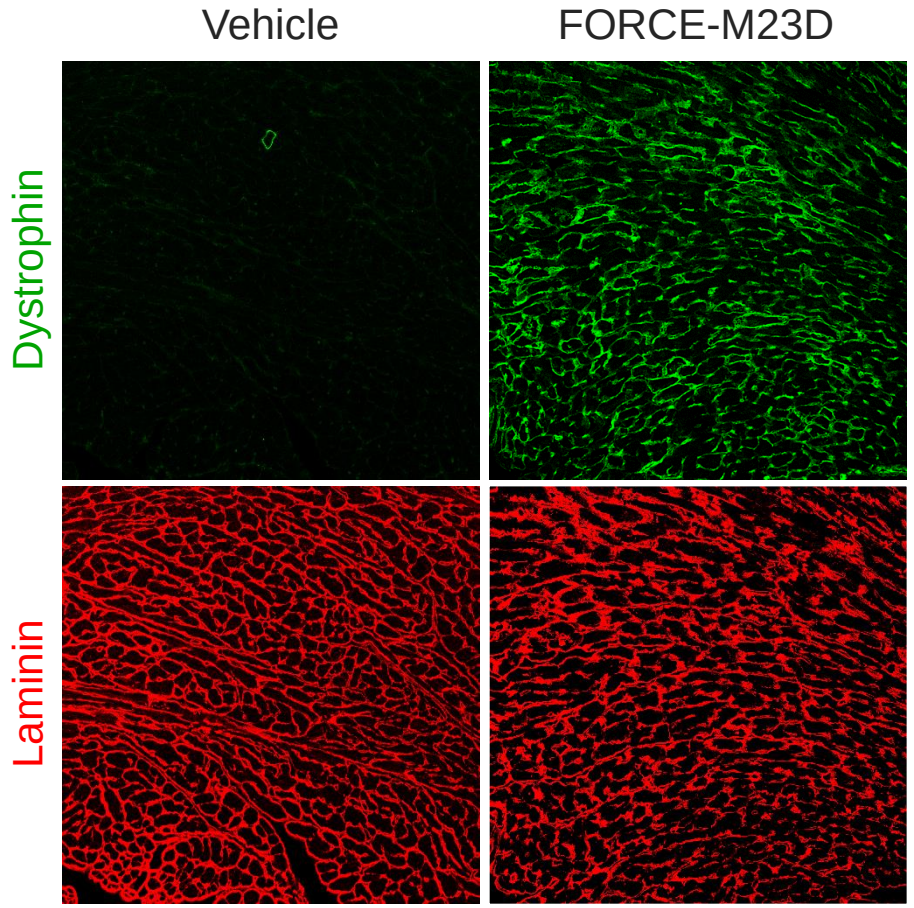
FORCE Achieved Robust Dystrophin Expression and Localization to Sarcolemma in Heart at 4 Weeks

Dystrophin Expression by WB
30 mg/kg 4 Weeks Post-Dose



78% of wild-type dystrophin

Dystrophin Localization to Sarcolemma



~80% dystrophin-positive fibers

Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0, analysis on week 4.

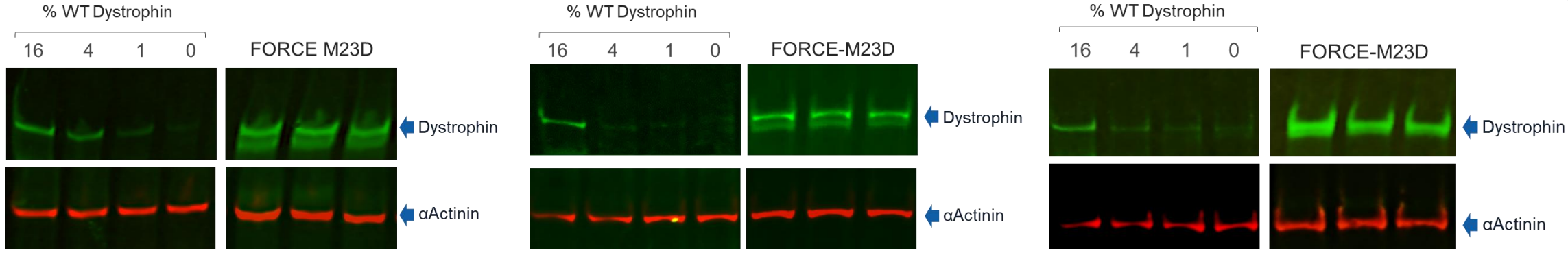
FORCE Achieved Robust and Durable Dystrophin Expression and Sarcolemma Localization in Muscle

Quadriceps

Diaphragm

Heart

Dystrophin expression by WB

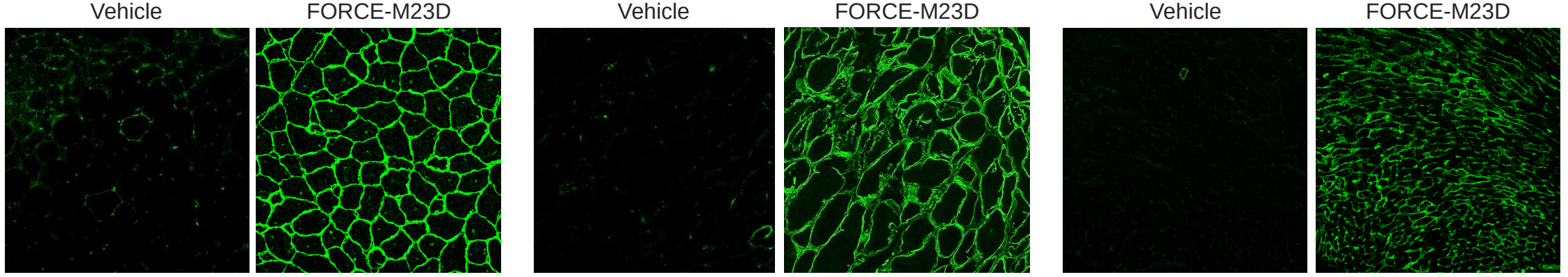


46% of wild-type dystrophin

90% of wild-type dystrophin

78% of wild-type dystrophin

Dystrophin localization to sarcolemma



68% dystrophin-positive fibers

~80% dystrophin-positive fibers

~80% dystrophin-positive fibers

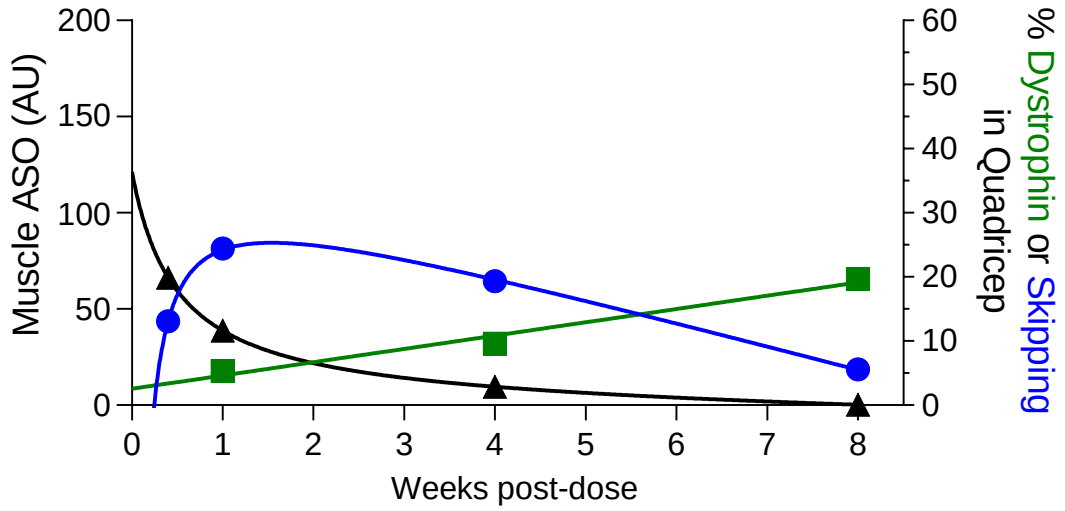
Note: Single IV 30 mg/kg dose of FORCE-M23D in *mdx* mouse model on day 0; analysis on week 4 for all muscles. N= 3 - 5 per cohort.

FORCE Distinctive Pharmacokinetic Profile Delivered Substantial and Durable Dystrophin Expression with a Single Dose

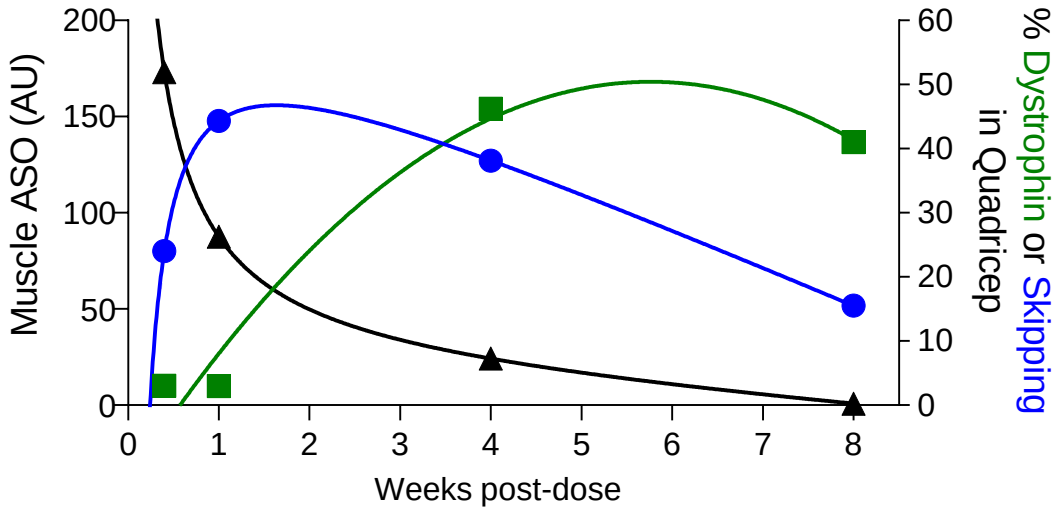
Pharmacokinetics | **Pharmacodynamics**

Muscle ASO concentration → Exon skipping → Dystrophin restoration

FORCE-M23D 10 mg/kg



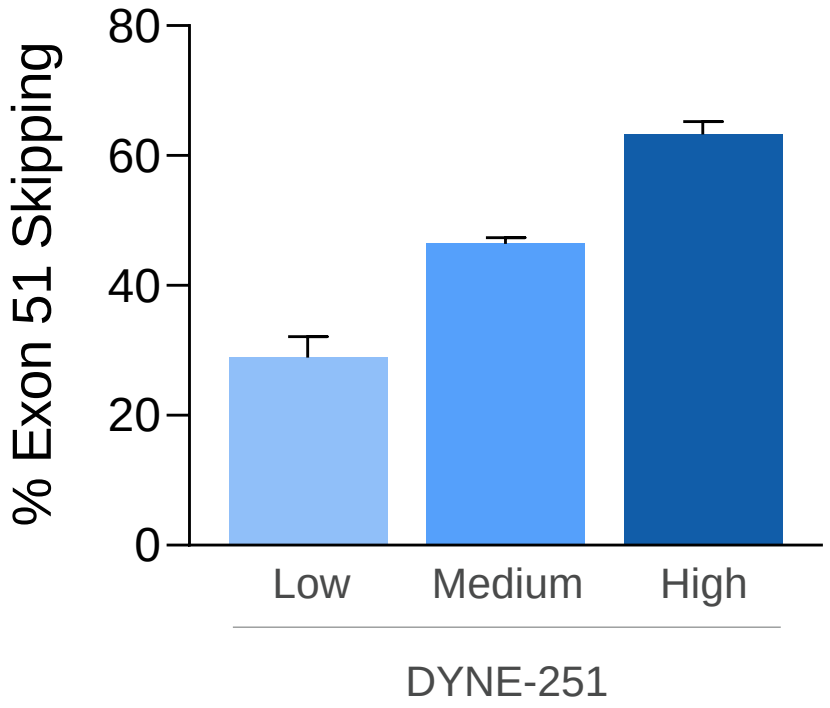
FORCE-M23D 30 mg/kg



Muscle ASO | Skipping | Dystrophin

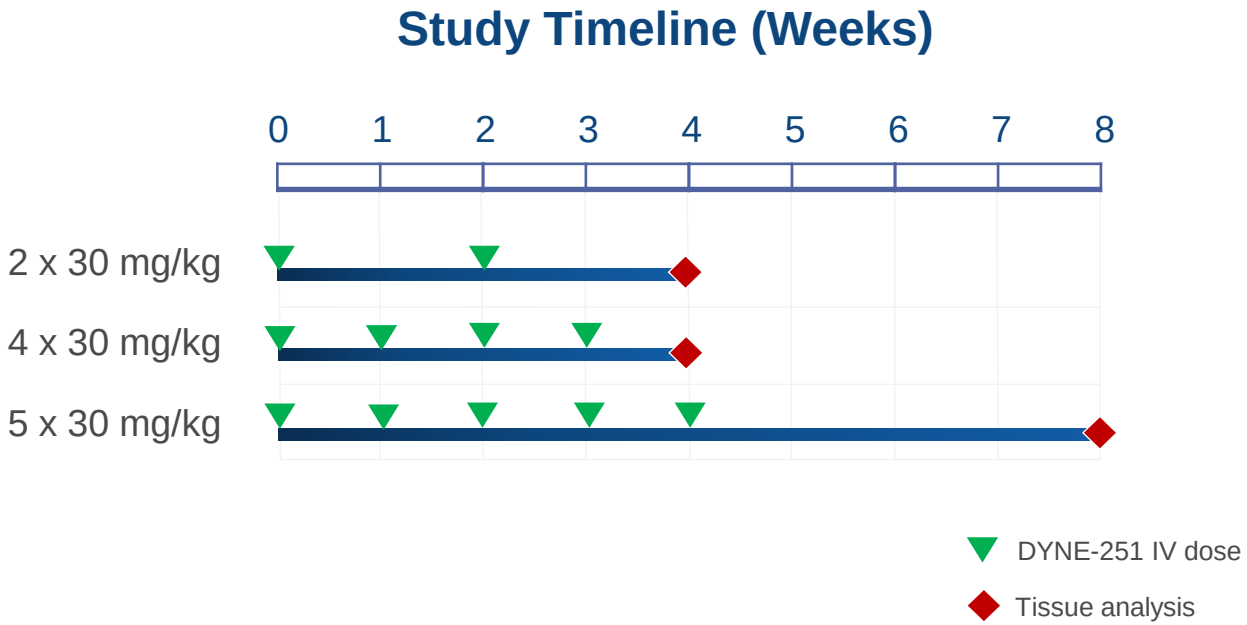
Note: Single IV dose of FORCE-M23D in *mdx* mouse model on day 0. N = 3 - 5 per cohort. ASO levels expressed as arbitrary units (AU).

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.

Dose Regimen Study in NHPs to Inform Clinical Dose



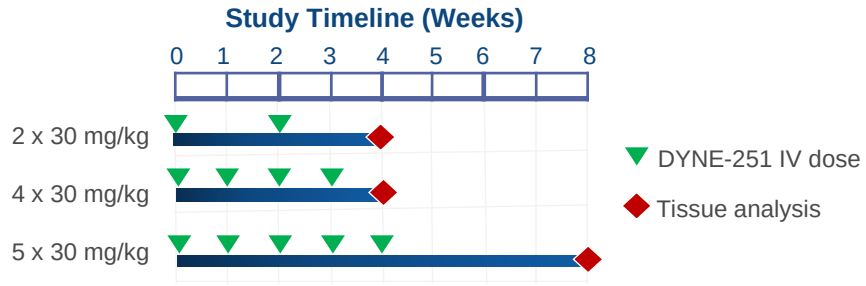
Endpoints

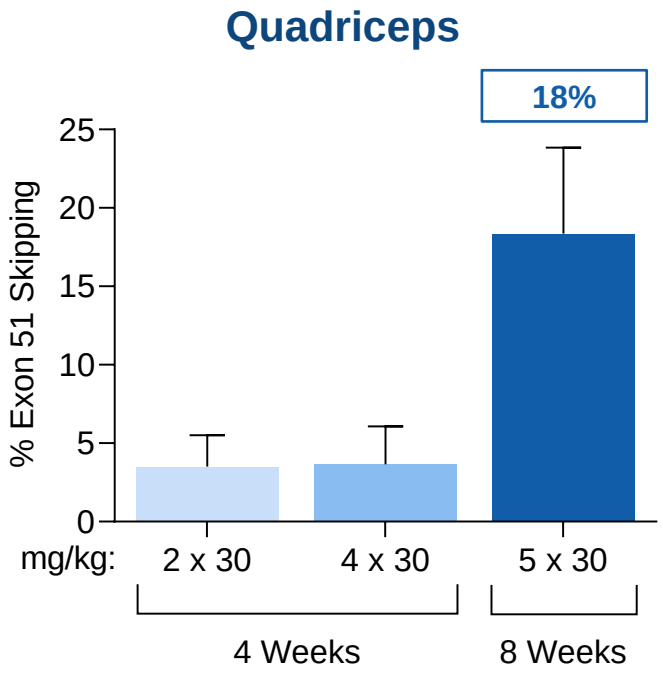
- Exon skipping by PCR

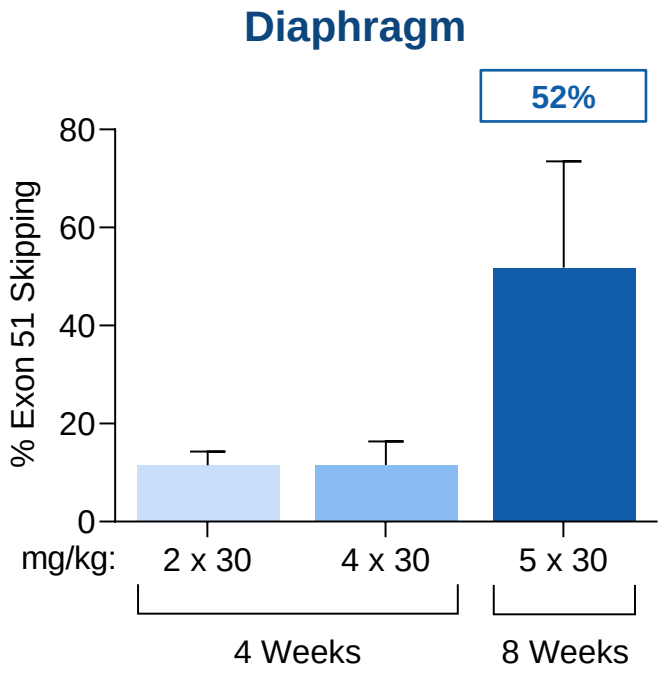
Tissues analyzed

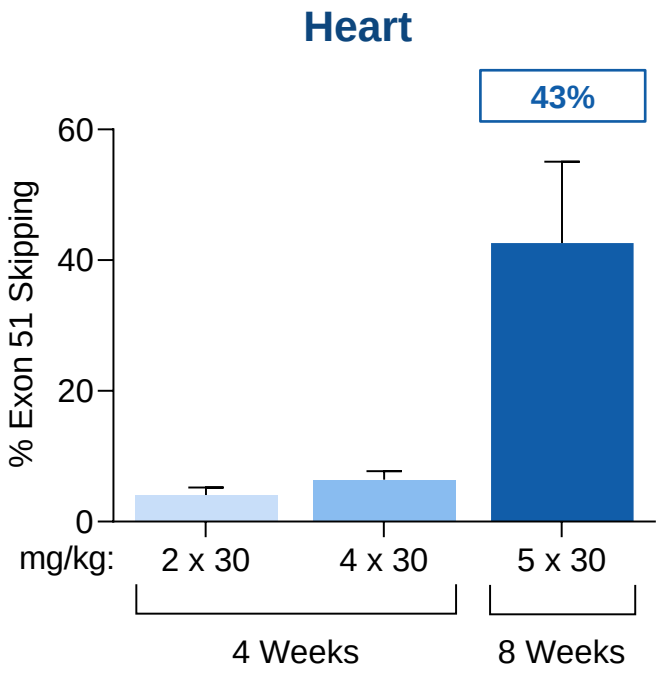
- Quadriceps
- Diaphragm
- Heart

DYNE-251 Achieved Robust Exon Skipping in NHP Skeletal and Cardiac Muscles









Note: Data are means ± SD. N = 3 - 5 per cohort.

DYNE-251 NHP GLP Toxicology Results Demonstrate Favorable Safety Profile That Support Advancement to Clinic

- 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

NOAEL: No-observed-adverse-effect level

DMD Program Summary

Validating Data

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**

Potential Advantages

- **Established** clinical and regulatory path
- **Opportunity to accelerate DMD franchise** expansion (exon 53, exon 45, exon 44) to reach additional patient populations

DYNE-251 IND submission planned in Q4 2021

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A

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**

DMD Clinical Development Plan Informed by Extensive Duchenne Community Engagement

Global, Multi-disciplinary KOL Input

- Overall design for the MAD study in patients with DMD amenable to exon 51 skipping
- Patient population, biomarker and functional endpoints, and key safety considerations
- Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

Global Advocacy Leaders, Patient and Caregiver Input

- Considerations for trial selection
- Clinical trial protocol and visit schedule
- Minimizing patient burden during trial conduct
- Ensuring support and education to patients and families

KOL input includes U.S. and European thought leaders across: pediatric & adult neurology; physical medicine and rehabilitation; cardiology, physical therapy. Advocacy leaders, patient and caregiver input includes U.S. and European advocacy leaders, young men with DMD, caregivers for individuals living with DMD.

DMD Community Has Urgent Need for Improved Treatment Options

"The endpoint I'm looking for is to halt the progression of the disease. I don't want to lose any more function."

"Time is not on our side… We just feel a huge sense of urgency to get the best set of treatments…"

"We would love to have someone recognize that stability for this community is something we would love to achieve. Yes, we would love a cure for our boys, but sometimes just stopping progression would be great."

Proposed Clinical Trial to Evaluate DYNE-251 in Patients with DMD

MULTIPLE ASCENDING DOSE (MAD) | **LONG-TERM EXTENSION (LTE)**

Design

- Multiple Ascending Dose
- Placebo Controlled
- Global
- LTE

Population

- Patients with symptomatic DMD and mutation amenable to exon 51 skipping therapy
- Ages 4 to 16 years
- ~30-40 male participants
- Ambulant and non-ambulant

Endpoints*

- Safety and tolerability
- PK/PD
- Dystrophin by Western Blot
- Measures of muscle function
  - Upper and lower limbs
  - Respiratory

Planned IND Submission in Q4 2021

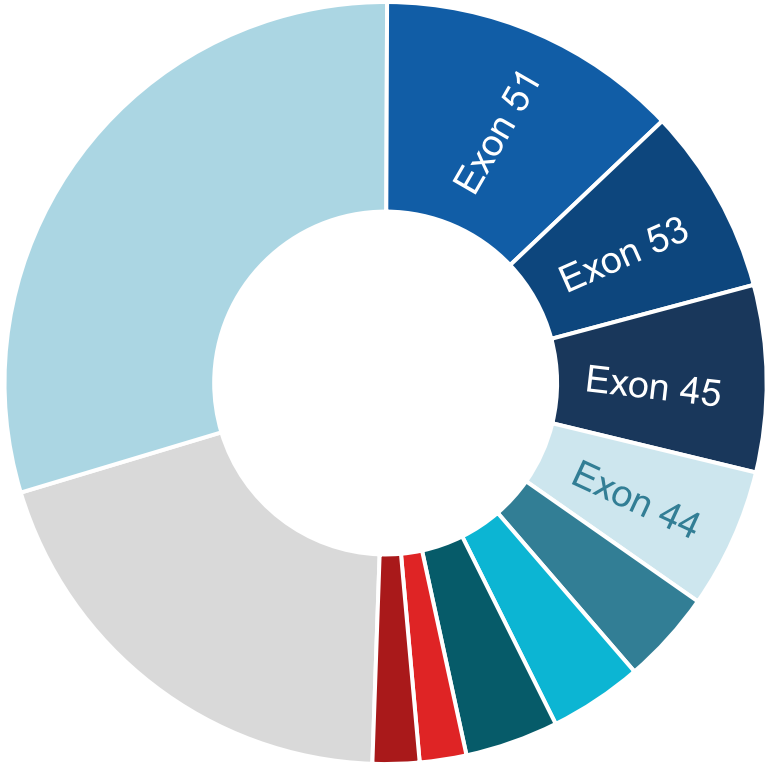
* Proposed endpoints include primary, secondary and exploratory

Dyne Committed to Developing Global DMD Franchise

Approximately

80% of patients

have genotypes amenable to exon skipping



- Exon 51 – **13%**
- Exon 53 – **8%**
- Exon 45 – **8%**
- Exon 44 – **6%**
- Exon 50 – **4%**
- Exon 52 – **4%**
- Exon 43 – **4%**
- Exon 55 – **2%**
- Exon 8 – **2%**
- Other exon skips – **~30%**
- May not be amenable to exon skipping – **~20%**

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A

Duchenne Muscular Dystrophy: Current Unmet Needs & Emerging Therapies

John W. Day, MD, PhD

Professor, Departments of Neurology and Pediatrics
Director, Division of Neuromuscular Medicine
Stanford University School of Medicine

Disclosures

In addition to funding from NIH/NINDS, MDA, CureSMA, SMA Foundation and the Myotonic Dystrophy Foundation, in the past 12 months I have had the following financial relationships with the manufacturers of commercial products or providers of commercial services at least indirectly related to this presentation:

- Research grants support – AMO, Astellas Gene Therapies, Avidity, Biogen, Cytokinetics, Ionis, Novartis Gene Therapies, Sanofi/Genzyme, Roche, Sarepta, Scholar Rock

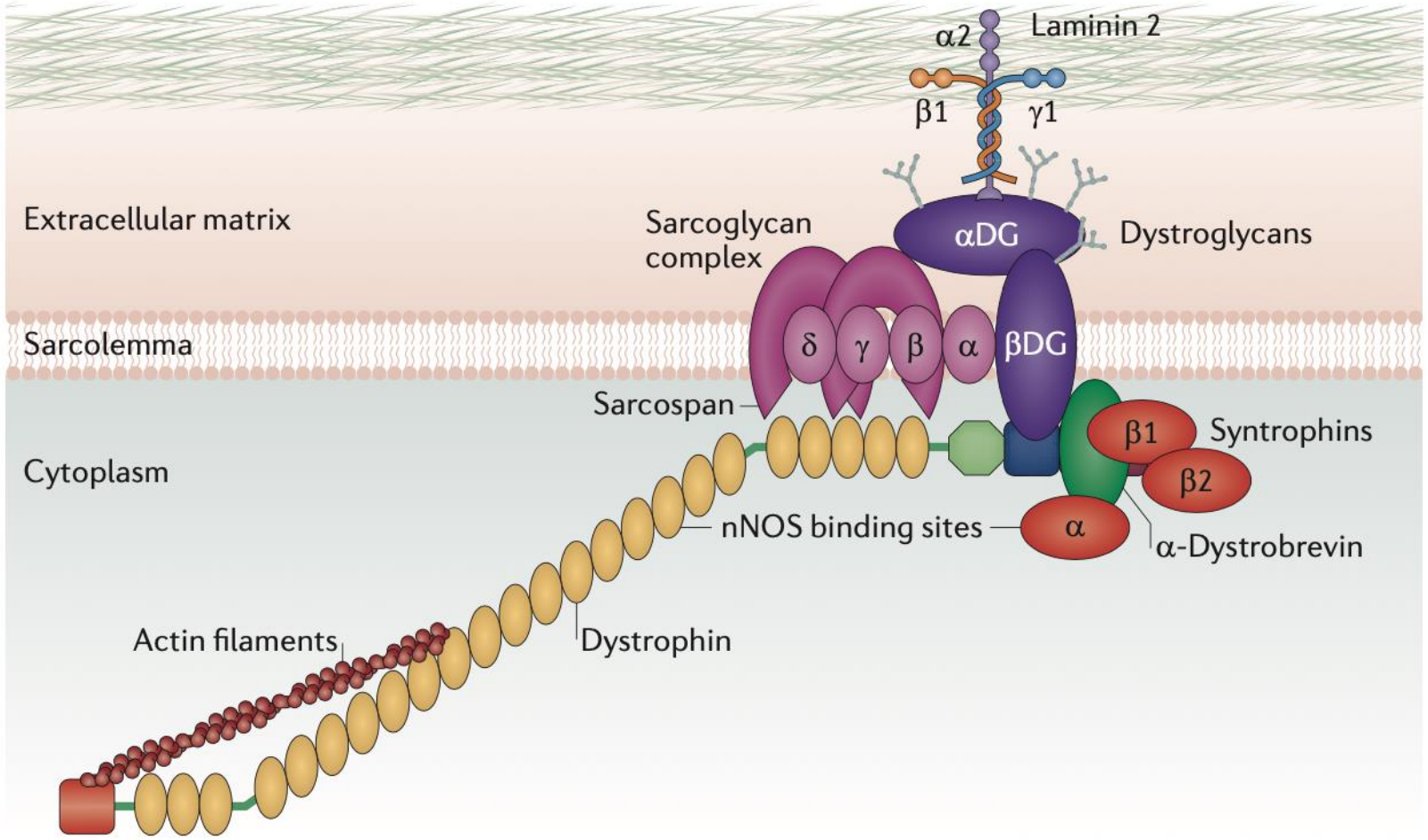
- Consultant or Advisor – Affinia, AMO, Avidity, Biogen, Cytokinetics, Novartis, Novartis Gene Therapies, PepGen, Roche, Sarepta

Dystrophinopathies: Clinical categorization

- DMD:
  - Symptom onset age > 2 years
  - CK 50-100X normal
  - Lower limb and pelvic girdle weakness
  - Loss of ambulation by early teens
  - Cardiopulmonary complications leading to death
- 1:3500 to 5000 live male births
- >12,000 boys registered in MDA clinics

- BMD:
  - Classic: loss of ambulation > age 12
  - Alternatively
    - “intermediate” MD LOA 12 -15y
    - BMD LOA > age 15y
  - Adult LGMD
  - Myalgias
  - Isolated Cardiomyopathy

Role of Dystrophin in Muscle Function



Fairclough RJ, et al. *2013*

Duchenne vs Becker

Type of Dystrophinopathy	Clinical Features	Biopsy Findings	Genetic Mutation
Duchenne	LOA ≤12y	No Dystrophin	Null
Becker	LOA ≥15y	Reduced or Abnormal Dystrophin	In Frame

- Size of deletion does not correlate well with phenotype
- Out-of-frame deletions are DMD ~90% of the time
- In-frame deletions are more likely to result in translation of a protein with partial function

Dystrophin Genotype – Phenotype

MUTATION CLASS	DMD	IMD	BMD	Unknown (B/DMD)	Manifesting Carrier[b]	Carrier (all phenotyp) [a]	Total	%
DELETION	283	15	55	107	3	14	**477**	42.9%
in	*30*	*2*	*36*	*17*	*1*	*2*	***88***	
out	*243*	*13*	*18*	*88*	*1*	*12*	***375***	
other	*10*	*0*	*1*	*2*	*1*	*0*	***14***	
STOP	176	4	30	46	4	34	**294**	26.5%
UGA	*60*	*1*	*13*	*20*	*3*	*15*	***112***	
UAG	*71*	*0*	*11*	*13*	*0*	*4*	***99***	
UAA	*45*	*3*	*6*	*13*	*1*	*15*	***83***	
SUBEXONIC	70	0	10	32	1	14	**127**	11.4%
FS Ins	*22*	*0*	*1*	*7*	*1*	*6*	***37***	
FS Del	*46*	*0*	*4*	*23*	*0*	*8*	***81***	
FS Ins/Del	*1*	*0*	*2*	*2*	*0*	*0*	***5***	
in-frame deletion	*1*	*0*	*3*	*0*	*0*	*0*	***4***	
DUPLICATION	87	7	10	8	5	5	**122**	11.0%
SPLICE	22	3	7	18	2	12	**64**	5.8%
MISSENSE	2	1	6	6	0	0	**15**	1.4%
PSEUDOEXON	0	2	2	0	0	2	**6**	0.5%
POTENTIAL	2	0	0	3	0	1	**6**	0.5%
OTHER	0	0	0	0	0	0	**0**	0.0%
TOTAL MUTATIONS	642	32	120	220	15	82	**1111**	100.0%

Flanigan, et al., *Hum Mutation*, 2009

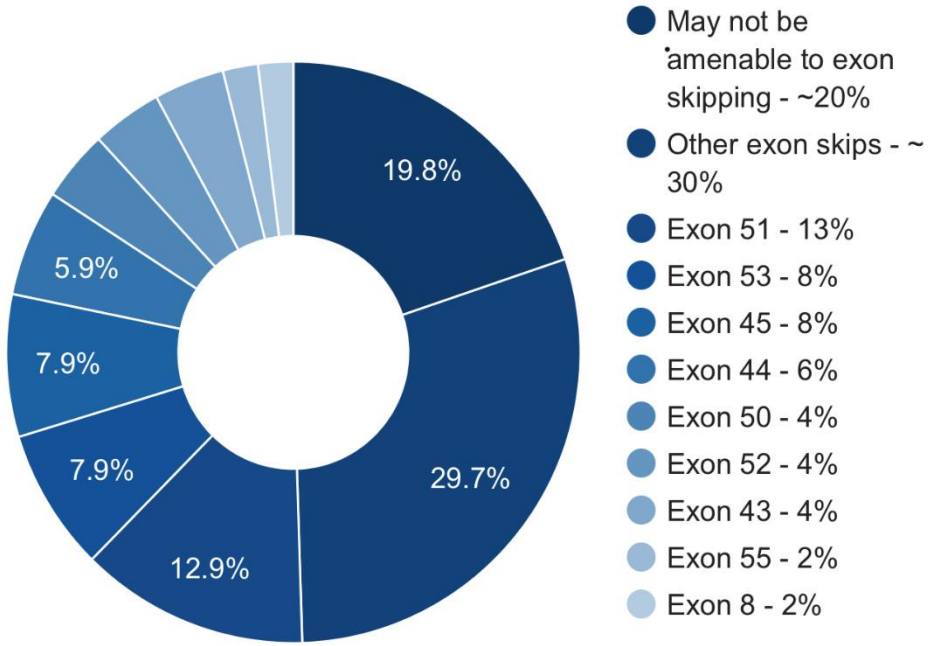
Exon skippable deletions ~80% of Duchenne

Distribution of mutations in an unselected cohort

(*Dent et al; AJMG, 2005*)

Mutation Type	DMD	BMD	Carrier	Total
≥1 exon deletion	32	13		45 (66%)
Premature Stop	5	3	1	9 (13%)
Missense	1	2		3 (4%)
Frameshift insertion or deletion	1		1	2 (3%)
≥1 exon duplication	3	1		4 (6%)
No mutation detected	3	2		5 (7%)
Total	45	21	2	68

Skippable DMD mutations



Currently available methodology can detect 93%-96% of dystrophinopathy mutations from blood samples

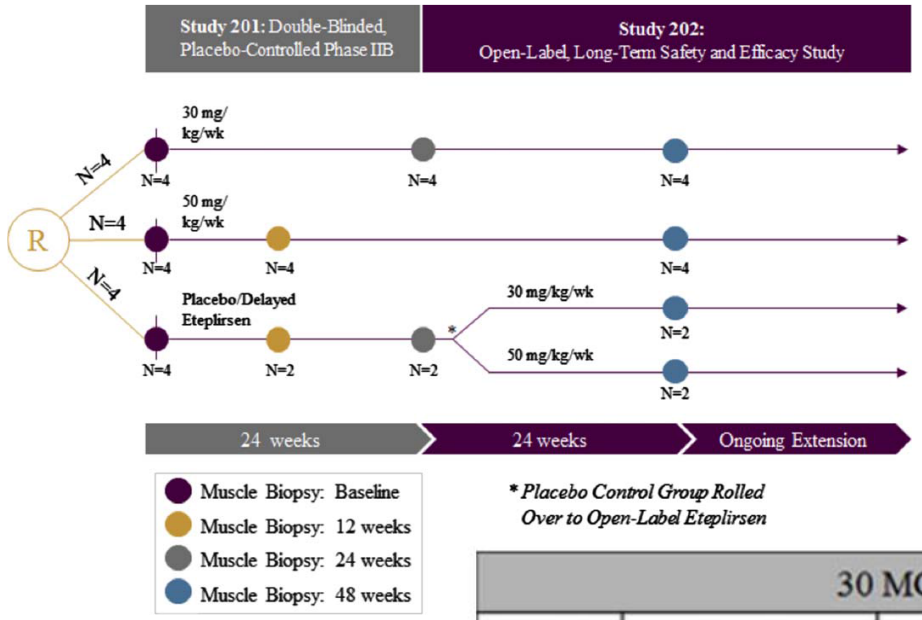
(Yan et al, *Hum Mutat* 2004)

https://www.cureduchenne.org/cure/exon-skipping/

Emerging Therapies

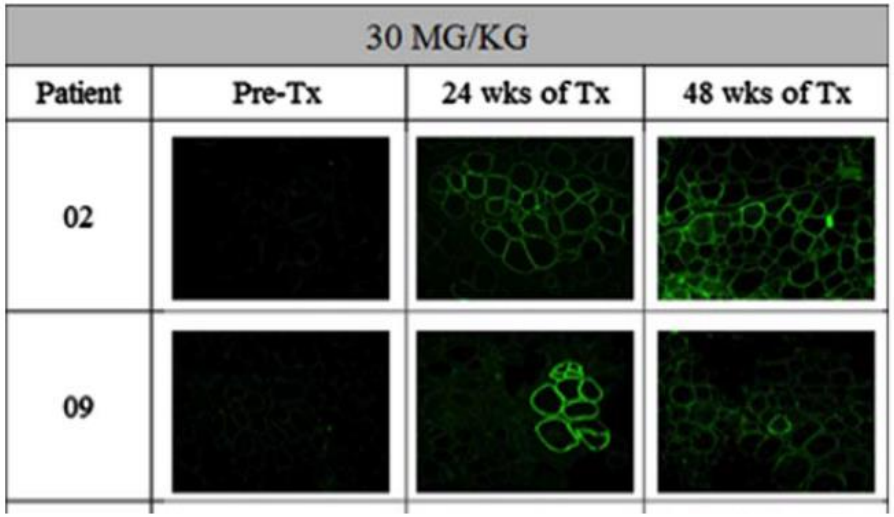
- Exon skipping
- Gene replacement
- CRISPR/Cas9 gene editing

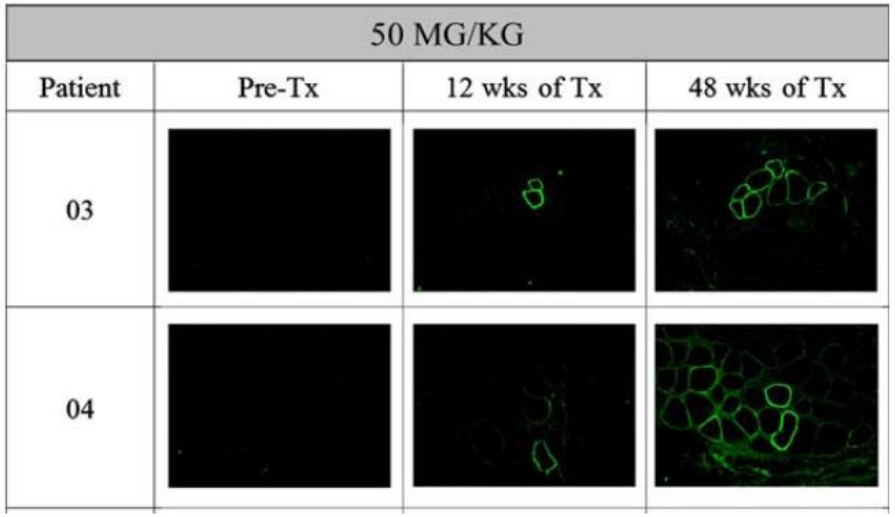
Eteplirsen for treatment of 51 skip-amenable patients with DMD



Eteplirsen for the Treatment of Duchenne Muscular Dystrophy

Jerry R. Mendell, MD,[1,2,3,4] Louise R. Rodino-Klapac, PhD,[1,4] Zarife Sahenk, MD, PhD,[1,2,3,4] Kandice Roush, RN,[5] Loren Bird, RN,[5] Linda P. Lowes, PhD,[4] Lindsay Alfano, PT,[4] Ann Maria Gomez, MD,[1,4] Sarah Lewis, HT, ASCP,[1,4] Janaiah Kota, PhD,[1,4] Vinod Malik, PhD,[1,4] Kim Shontz, BA, MS,[1,4] Christopher M. Walker, PhD,[1,4,6] Kevin M. Flanigan, MD,[1,2,3,4] Marco Corridore, MD,[7] John R. Kean, MD,[4,7] Hugh D. Allen, MD,[1,4] Chris Shilling, MS,[1,3,4] Kathleen R. Melia, PhD,[8] Peter Sazani, PhD,[8] Jay B. Saoud, PhD,[8] Edward M. Kaye, MD,[8] and the Eteplirsen Study Group





Mendell et al, *Annals of Neurology* 2013

Table 2. Western Blot Results: EXONDYS 51-Treated (Week 48) vs Pre-treatment Baseline (% Normal Dystrophin) (Study 301)

Patient Number	Baseline % normal dystrophin	Week 48 % normal dystrophin	Change from Baseline % normal dystrophin
1	0.13	0.26	0.13
2	0.35	0.36	0.01
3	0.06	0.37	0.31
4	0.04	0.10	0.06
5	0.17	1.02	0.85
6	0.37	0.30	-0.07
7	0.17	0.42	0.25
8	0.24	1.57	1.33
9	0.11	0.12	0.01
10	0.05	0.47	0.43
11	0.02	0.09	0.07
12	0.18	0.21	0.03
Mean	0.16	0.44	0.28; p=0.008

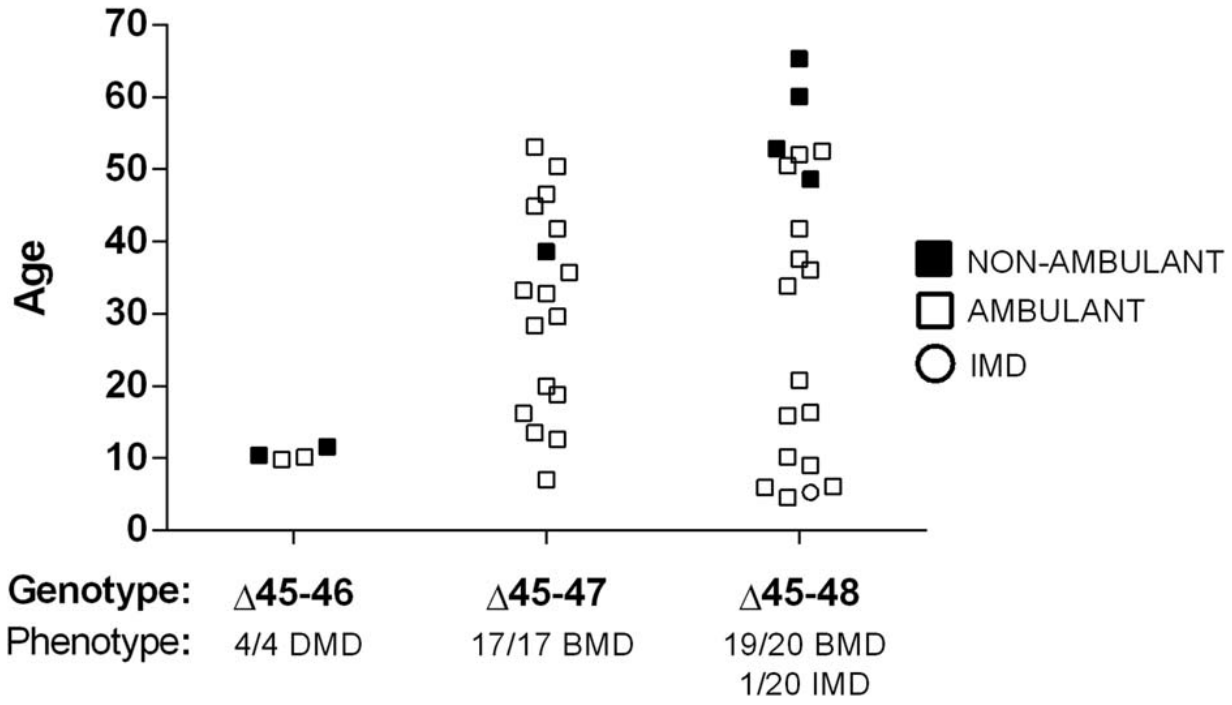
Package Insert, Sarepta Therapeutics (9/2016)

FDA Approved Exon Skipping for DMD

Therapeutic Agent	Mechanism of Action	Chemistry	Route of Administration	Frequency
eteplirsen	exon 51 skipping	PMO	intravenous	weekly
golodirsen	exon 53 skipping	PMO	intravenous	weekly
viltolarsen	exon 53 skipping	PMO	intravenous	weekly
casimersen	exon 45 skipping	PMO	intravenous	weekly

Predicting clinical benefit of therapies

- There is no human correlate to the engineered microdystrophin proteins in trial
- In contrast, exon skipping results in isoforms identical to native BMD-associated isoforms, allowing researchers to predict maximal benefit



DMD exon 45 skip-equivalent genotypes vs age at last ambulation

Findlay *et al, Annals Neurol (*2015); 77:668-674

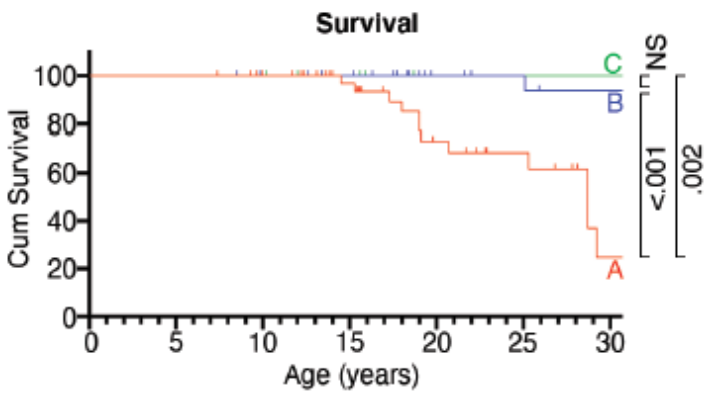
Clinical Effects of Dystrophin Expression

No dystrophin (0%) **Group A (*n* = 42)**	Residual dystrophin (0-5%) **Group B (*n* = 34)**	Residual dystrophin (≥5%) **Group C (*n* = 14)**

Characteristic	Group A	Group B	Group C	*p*
n	42	34	14	
Dystrophin protein quantity, %	0	>0 and <5	≥5	
Canonical splice sites mutations, n (%)	17 (40)	12 (35)	8 (57)	0.374
Pseudoexon and noncanonical splice site mutations, n (%)	7 (17)	16 (47)	4 (29)	0.009
Nonsense mutations in "in-frame" exon, n (%)	18 (43)	6 (18)	2 (14)	0.023
DMD [LoA at <13 yr of age], n (%)	31 (74)	6 (18)	0 (0)	<0.001
IMD [LoA at ≥13 and <16 yr of age], n (%)	4 (10)	1 (3)	0 (0)	0.283
BMD [LoA at ≥16 yr of age], n (%)	1 (2)	21 (61)	8 (57)	<0.001

De Feraudy, Y et al, 2021

Clinical Effects of Dystrophin Expression



Number at risk:

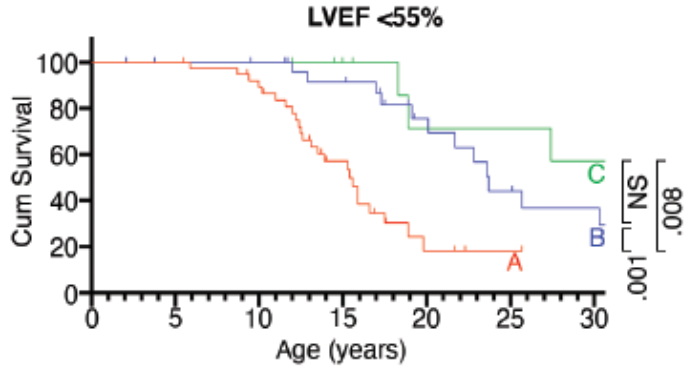
A:	41	41	37	29	16	10	2
B:	34	34	31	27	18	16	14
C:	14	14	14	12	8	8	8

Median age at event (years):

A: 28.7
B: Undefined
C: Undefined

Hazard Ratio (group B/A):

HR = 0.18 (95% CI: 0.07 to 0.48)



Number at risk:

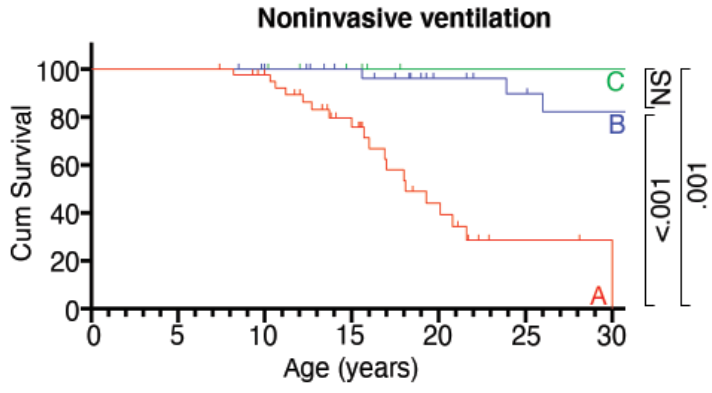
A:	39	39	32	16	3	1	0
B:	28	26	25	21	12	7	5
C:	11	11	11	8	5	5	4

Median age at event (years):

A: 15.4
B: 23.7
C: Undefined

Hazard Ratio (group B/A):

HR = 0.34 (95% CI: 0.17 to 0.65)



Number at risk:

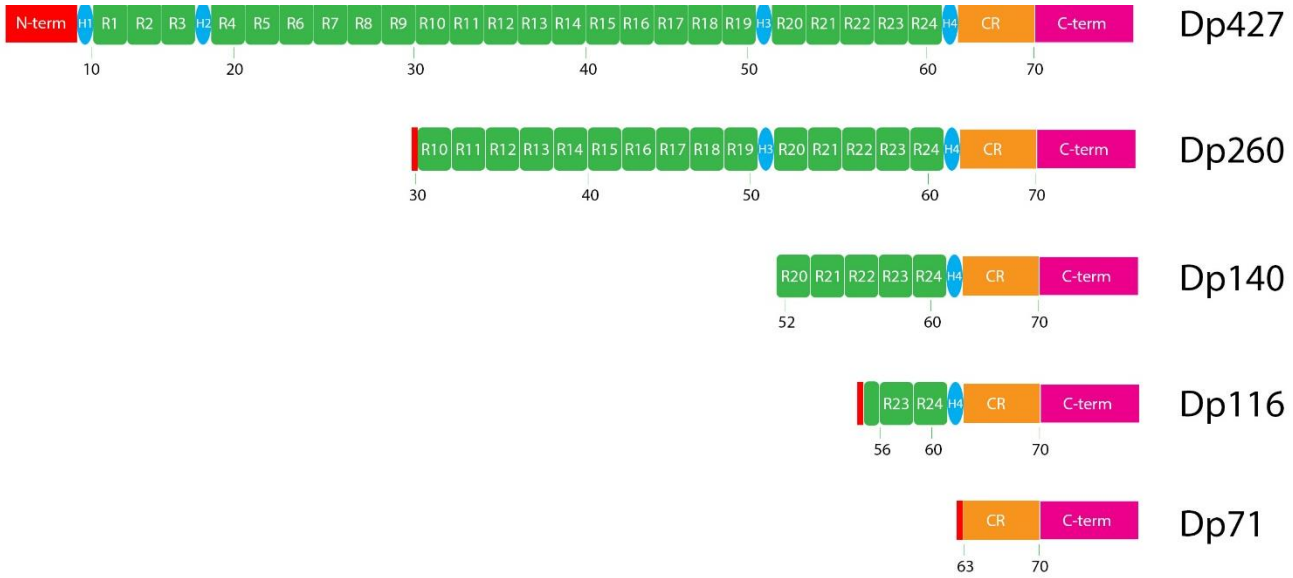
A:	41	41	36	20	9	2	0
B:	32	32	29	25	17	14	11
C:	13	13	13	10	7	7	7

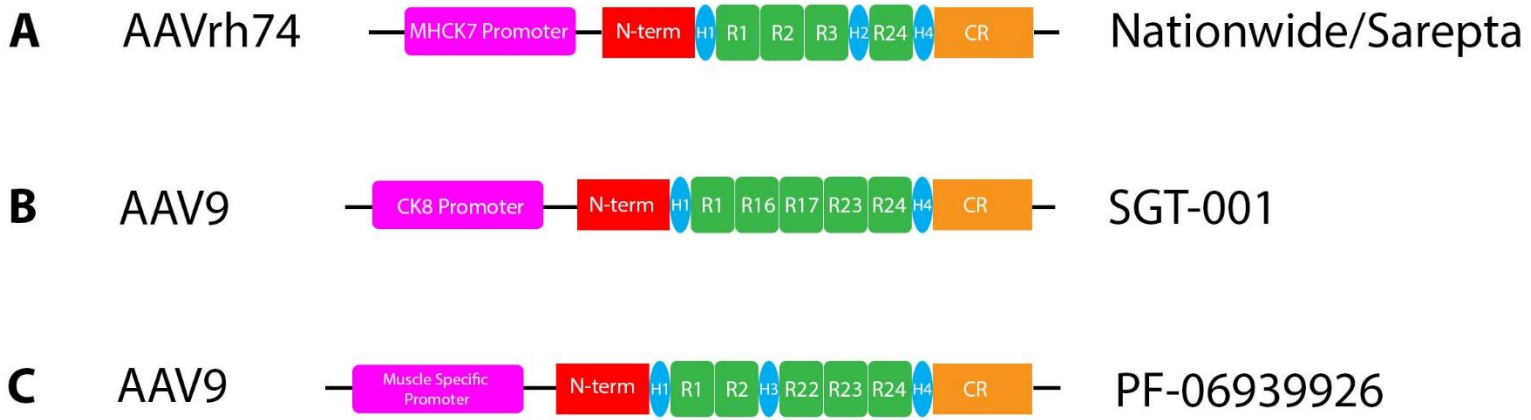
Median age at event (years):

A: 18.1
B: Undefined
C: Undefined

De Feraudy, Y et al, 2021

AAV Gene Therapy for DMD





Shieh P., *Neurotherapeutics* (2018)

Unknowns about AAV Gene Replacement

- How to treat subjects with AAV antibodies
- How to retreat all subjects
- Trans-gene reaction if part of micro-dys protein is novel
- Risks of high AAV viral load
- Distribution: muscle; muscle fiber; myonuclei
- Duration: Dividing cells; Non-dividing cells
- Transduction of satellite/progenitor cells

Hope for patients

- Next-generation technologies may allow for
  - Durable and titratable therapies, with much less frequent dosing than current treatments, for all stages of disease
  - Treating cardiac and pulmonary issues which lead to significant morbidity and mortality
  - Potential to significantly slow or even stop progression
- Goal is to extend patients lives and quality of life

Program

Opening remarks
Joshua Brumm, President & CEO

FORCE™ Platform & DMD Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DMD Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DMD
John Day, M.D., Ph.D., Professor of Neurology and Pediatrics, and Director of the Neuromuscular Division, Stanford Neuroscience Health Center

Q&A

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO

Developing Transformative Therapies for People Living with DM1

DM1 Patient Cells

- *DMPK* KD, reduction in nuclear foci, splicing correction

In Vivo Disease Models

- Correction of splicing & reversal of myotonia in HSA^{LR} model
- Robust KD of toxic nuclear *DMPK* in hTfR1/DMSXL model, foci reduction & correction of splicing

Safety

- Well tolerated in NHP Non-GLP toxicology dose-range finding study

NO approved therapies

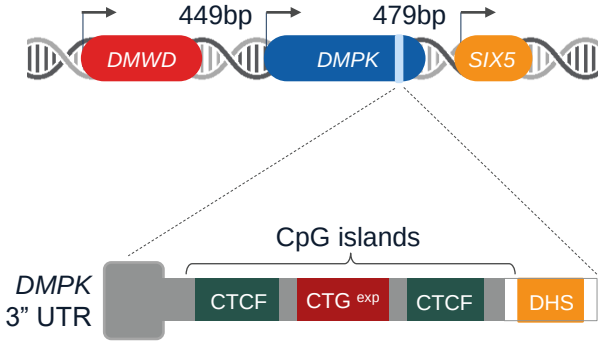
OUR APPROACH

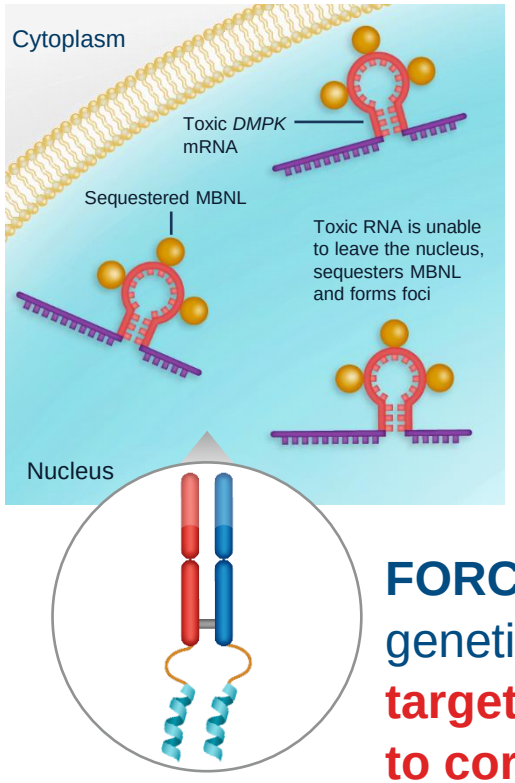
Disease-Modifying Nuclear *DMPK* Knockdown

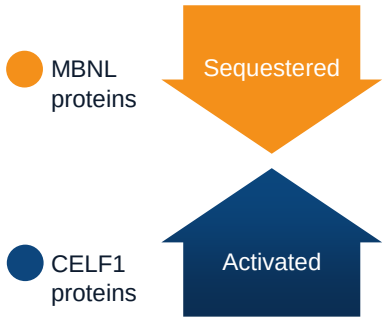
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE Targets the Genetic Basis of DM1 to Correct Splicing

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



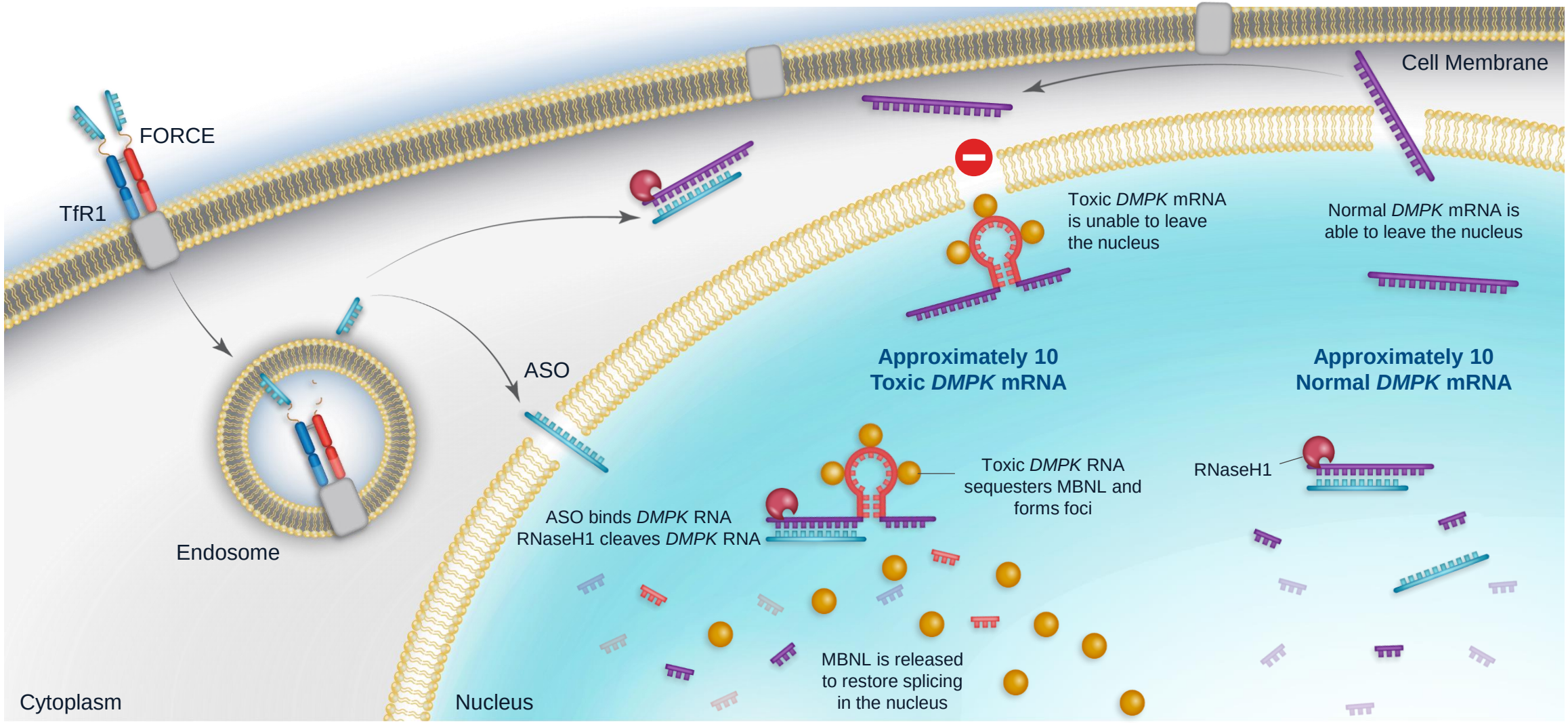




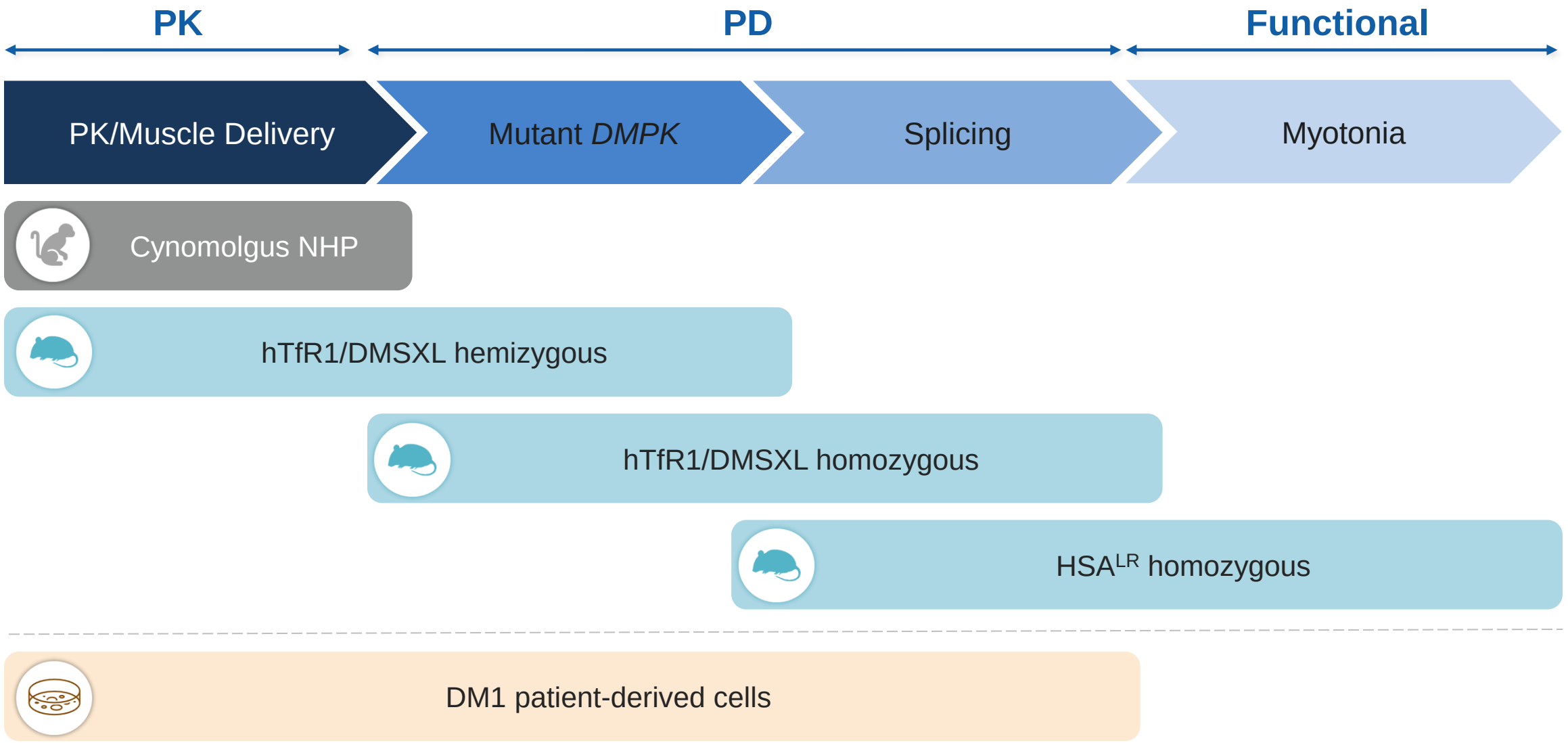
- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

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

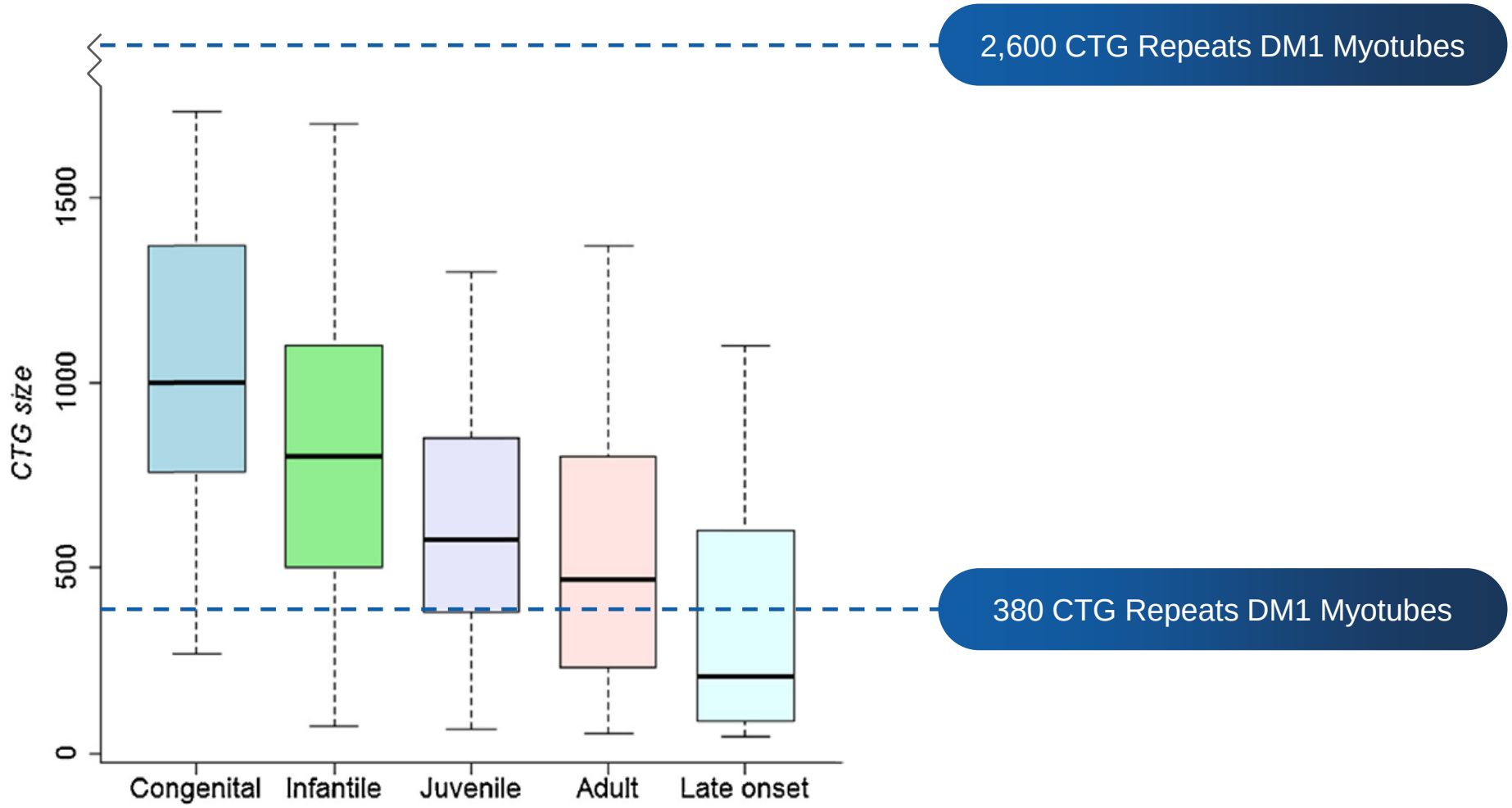
FORCE Targets Toxic Nuclear *DMPK* RNA



Data from Multiple DM1 Models Demonstrate that FORCE Delivers to Muscle and Drives Disease Modification



In Vitro Models Represent DM1 Patient Population With Wide Range of CTG Repeats

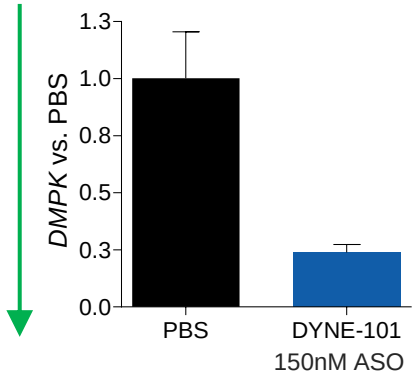


Source: Repeat length data from De Antonito et al. International meeting of the French Society of Neurology, 2016.

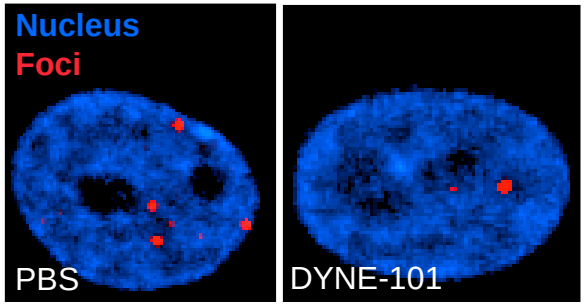
DYNE-101 Demonstrated Robust Dose-dependent *DMPK* KD, Foci Reduction, and Splicing Correction

380 CTG Repeats DM1 Myotubes

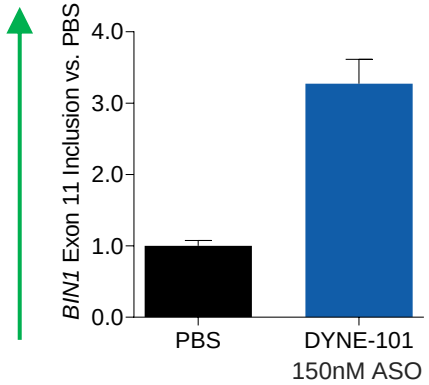
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

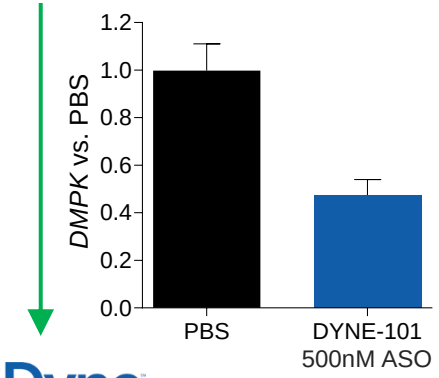


BIN1 mis-splicing correction by qPCR

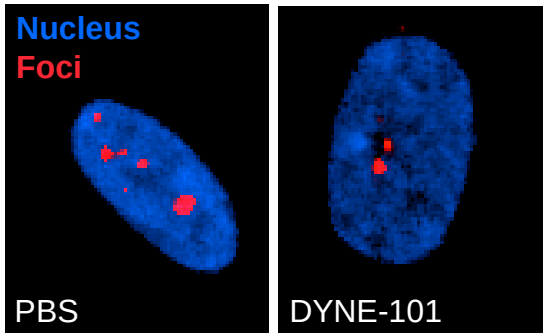


2,600 CTG Repeats DM1 Myotubes

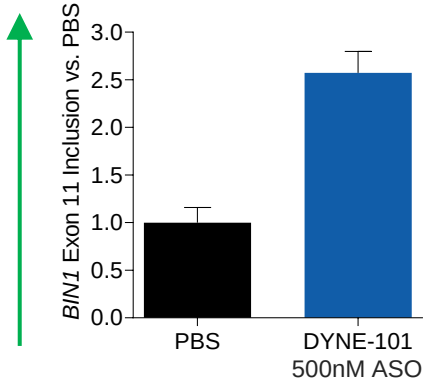
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

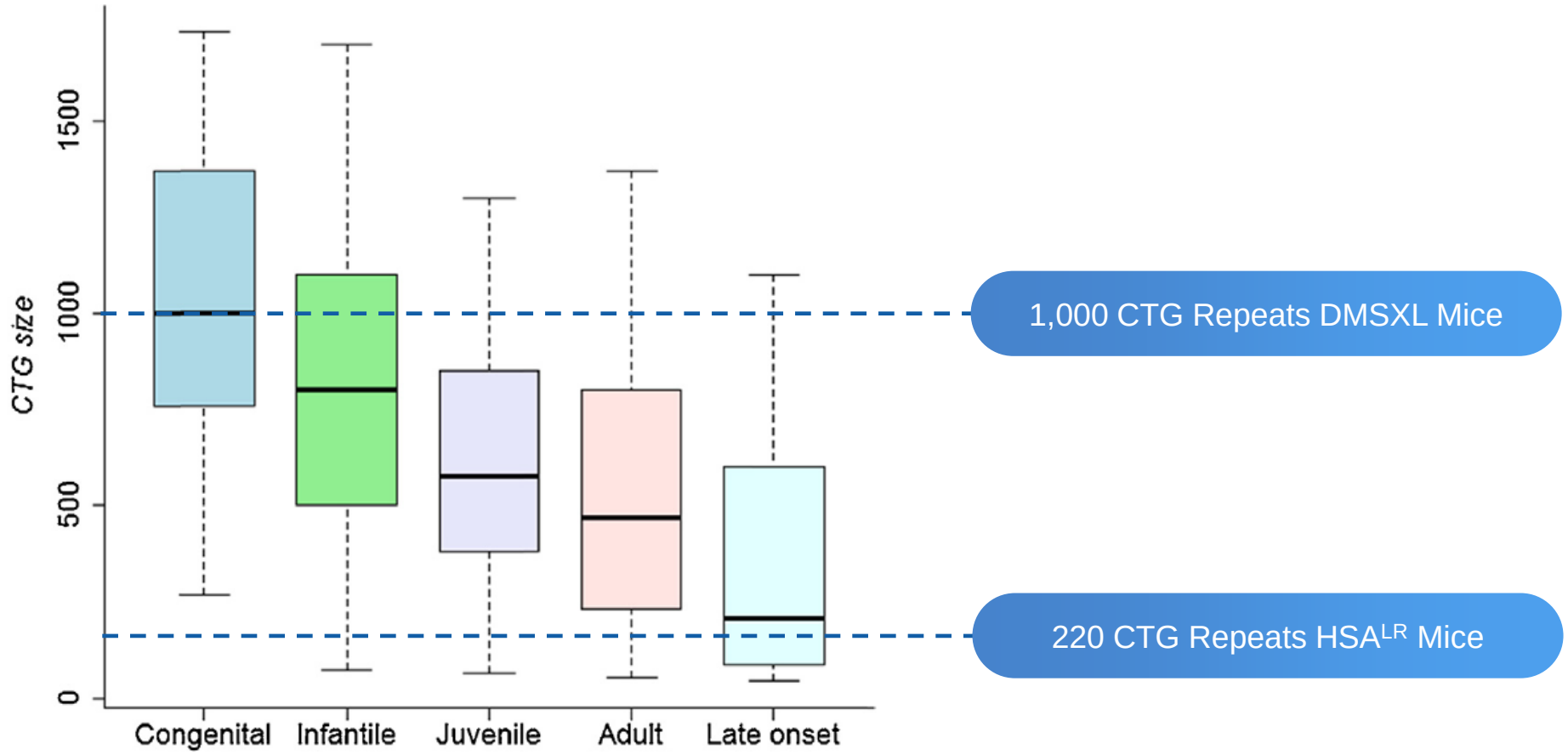


BIN1 mis-splicing correction by qPCR



Note: Data are mean ±SD, n=4. Foci reduction based on foci area corrected for nuclear area

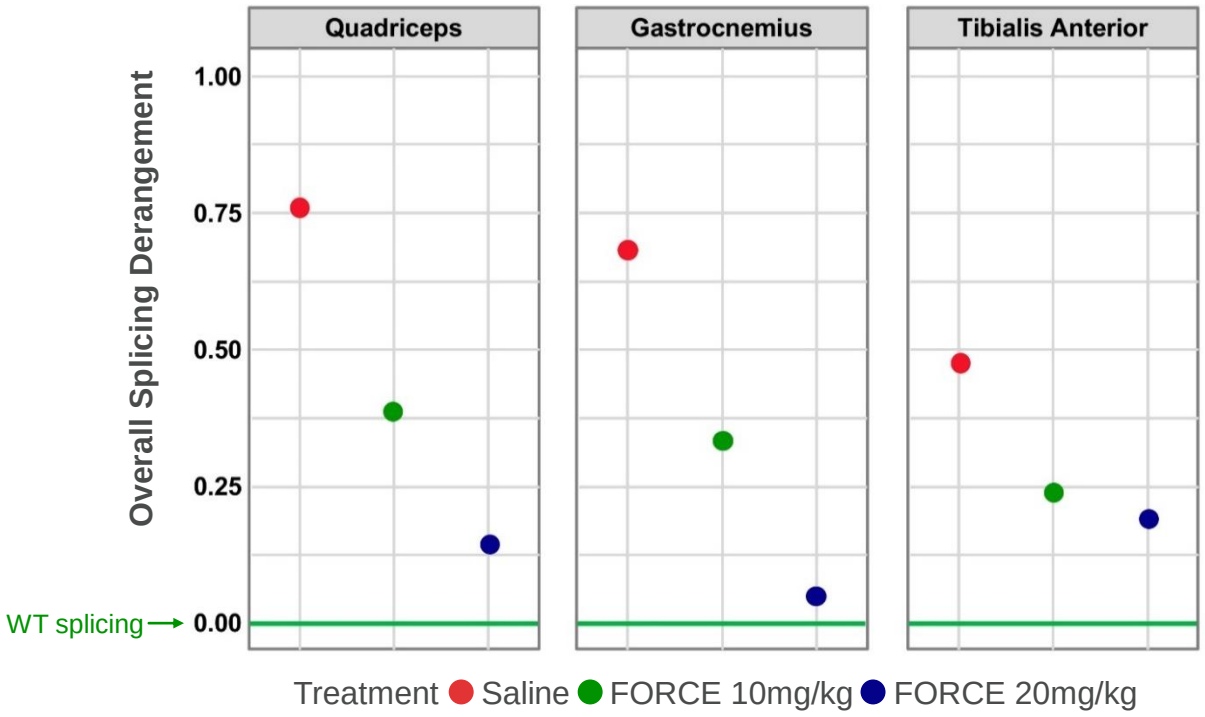
In Vivo Models Represent DM1 Patient Population With Wide Range of CTG Repeats



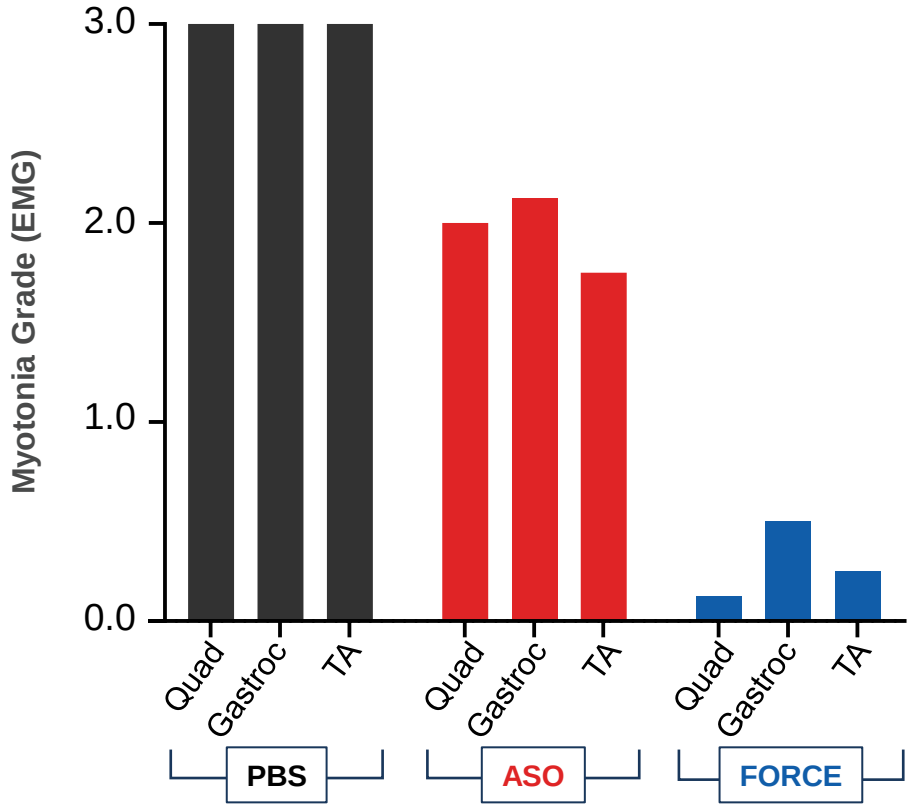
Source: Repeat length data from De Antonito et al. International meeting of the French Society of Neurology, 2016.

FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

Splicing Correction in Multiple Muscles

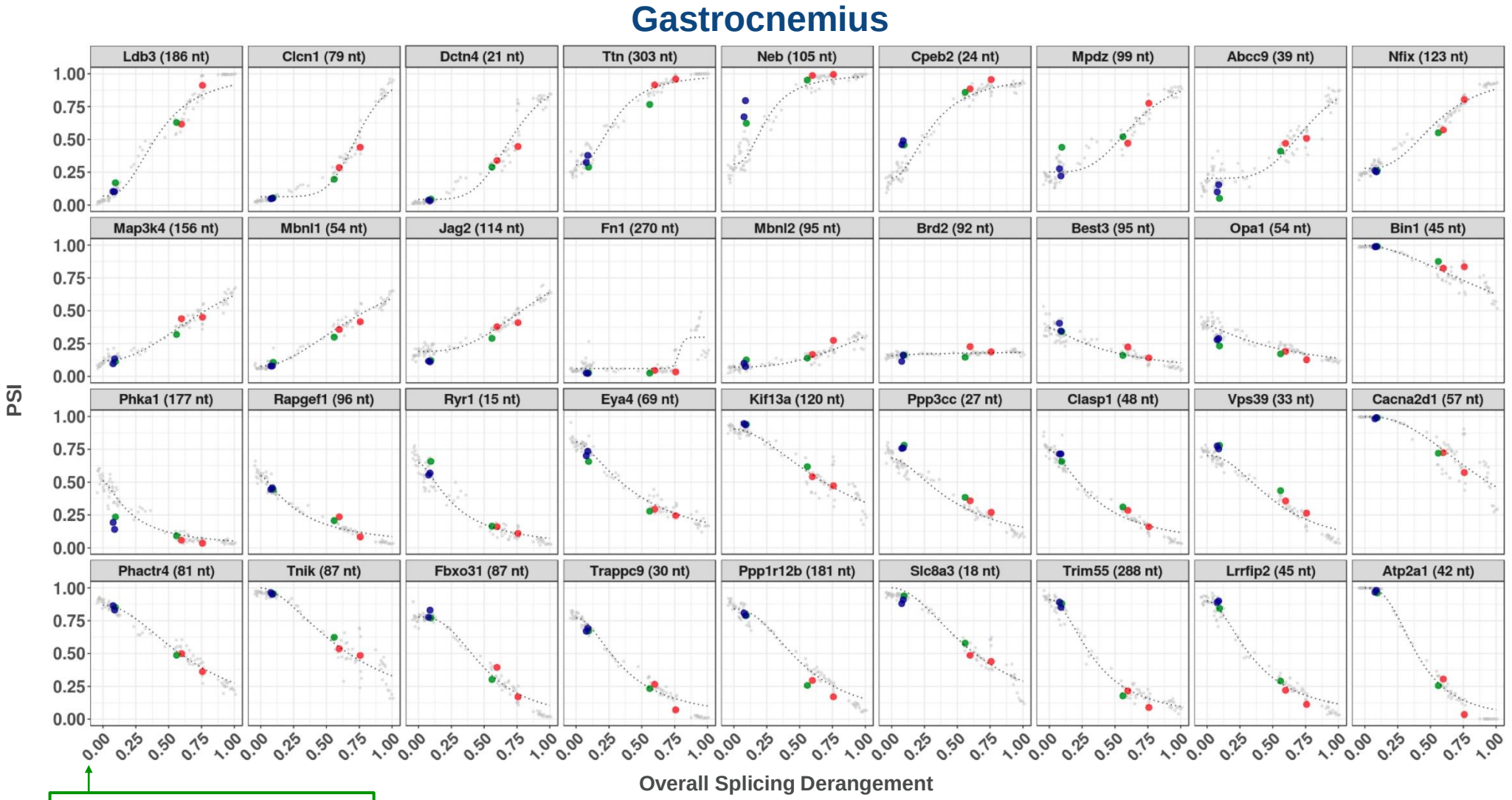


Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose



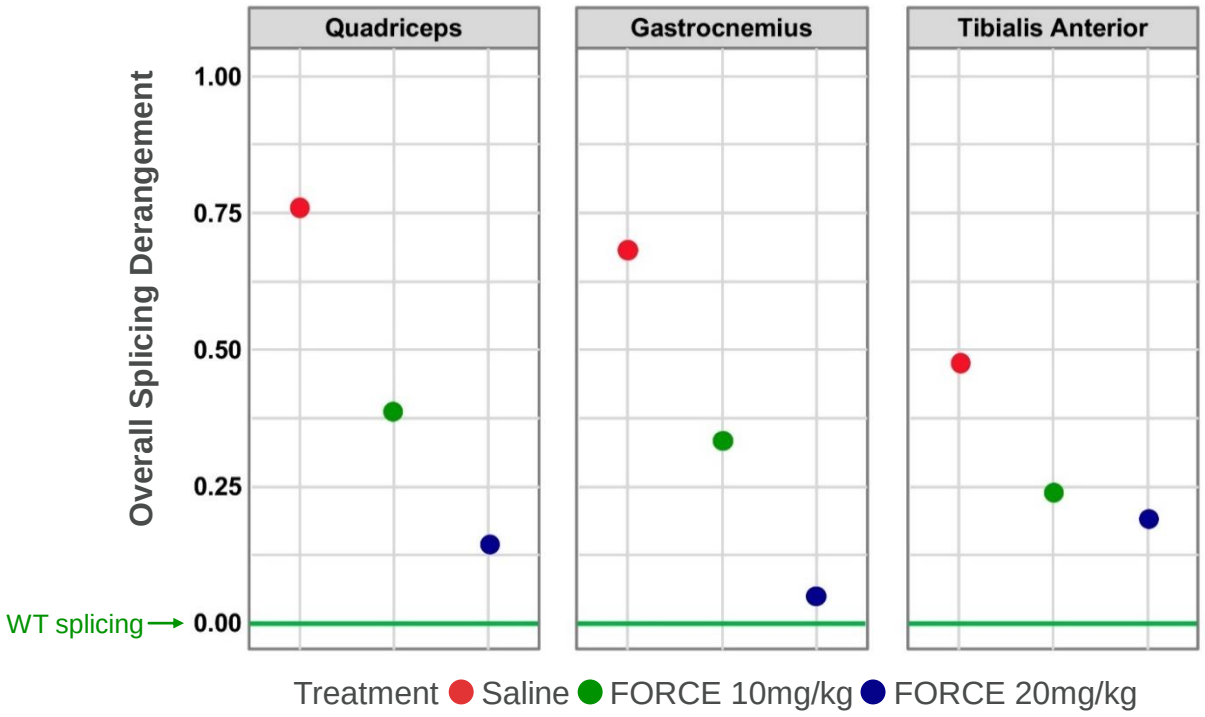
Note: HSA^{LR} mice, single dose 14-day study. Overall splicing derangement indexed to WT level of 0.00. EMG myotonic discharges were graded by a blinded examiner on a 4-point scale: 0, no myotonia; 1, occasional myotonic discharge in less than 50% of needle insertions; 2, myotonic discharge in greater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

FORCE Dose-Dependently Corrected Splicing in Multiple RNAs in HSA^{LR} DM1 Mouse Model After a Single Dose

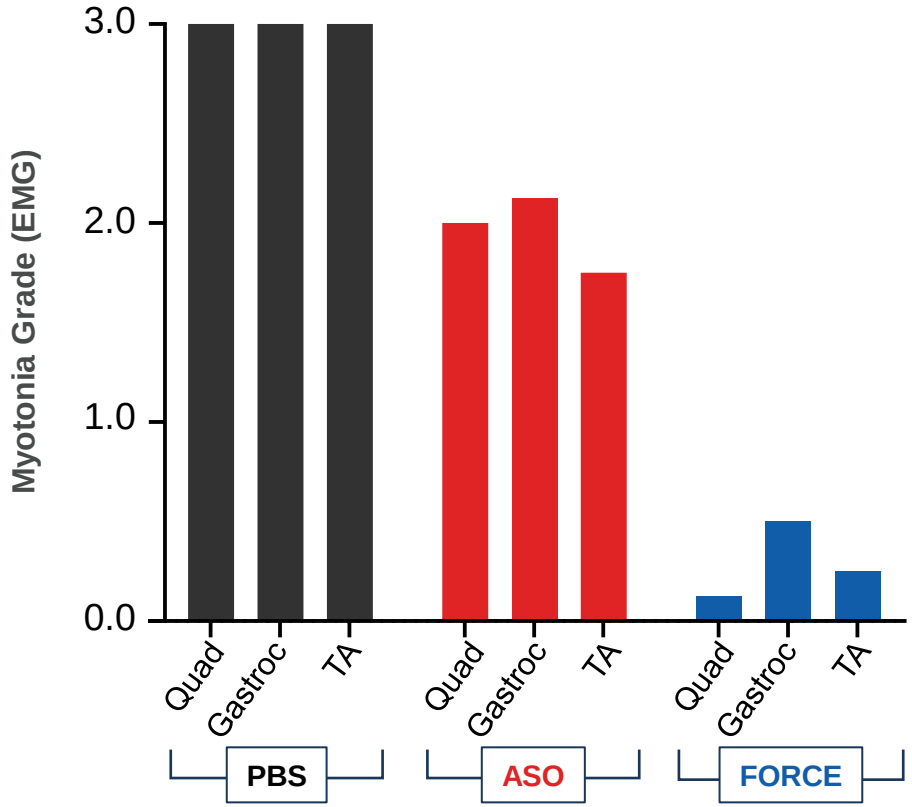


FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

Splicing Correction in Multiple Muscles

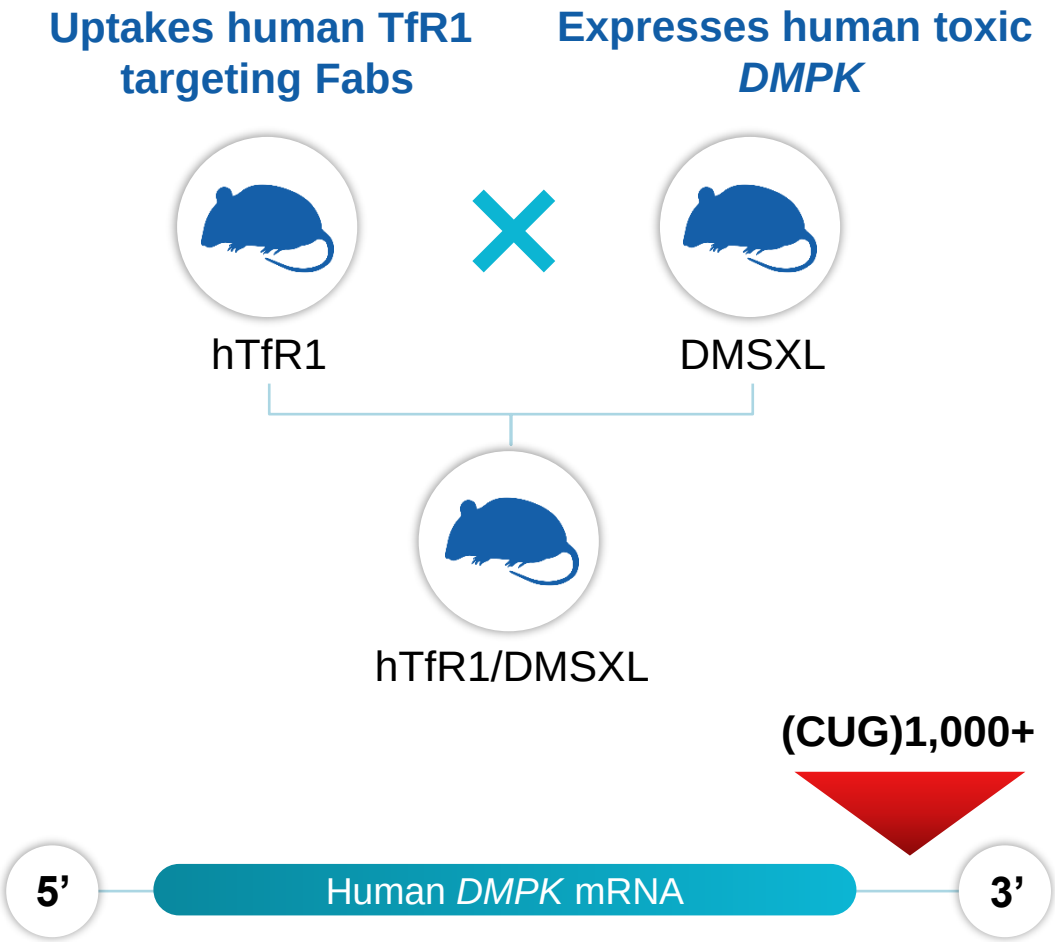


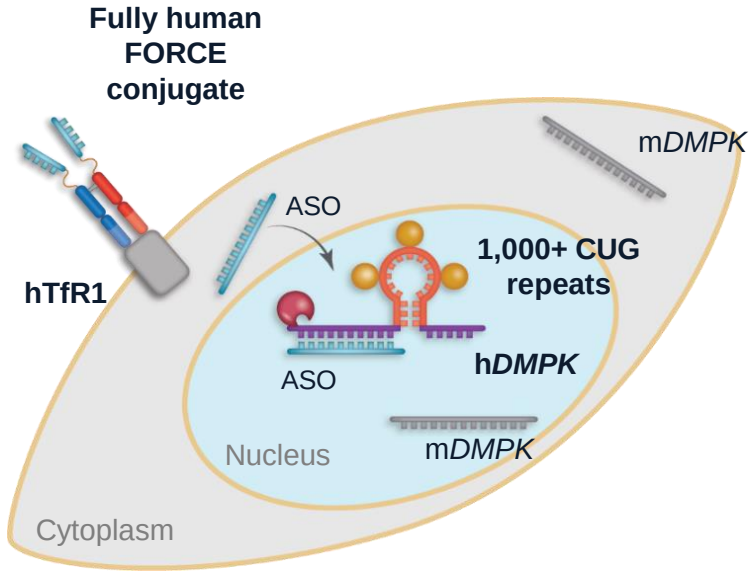
Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose



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

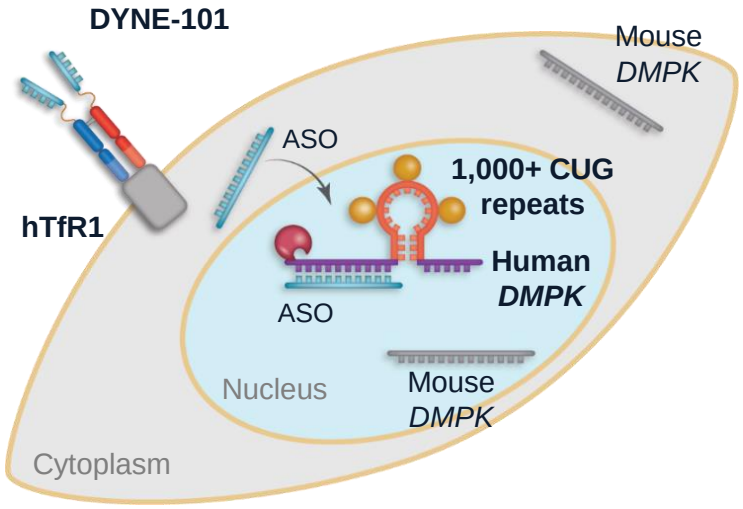




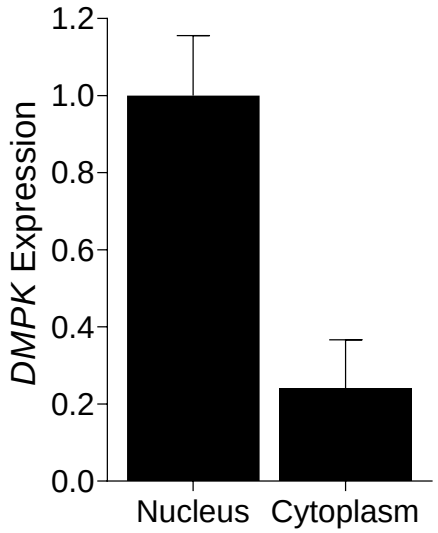
- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

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

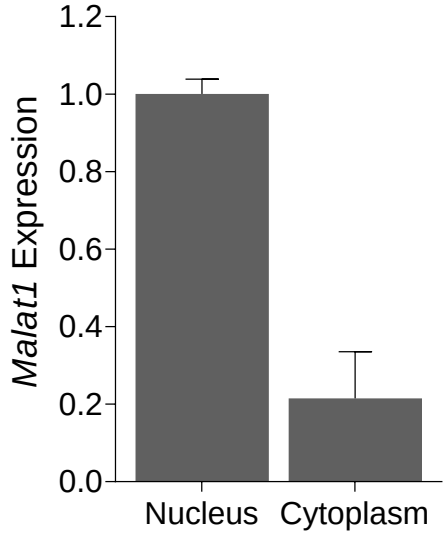
Toxic Human *DMPK* is Trapped in Nuclei in hTfR1/DMSXL Model



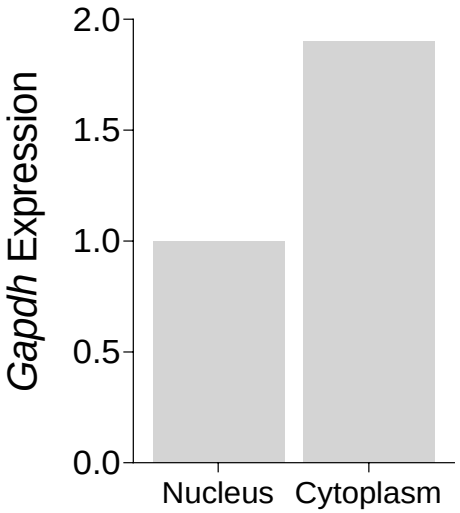
Human Mutant *DMPK* Enrichment in the Nucleus



Malat1 Nuclear Control

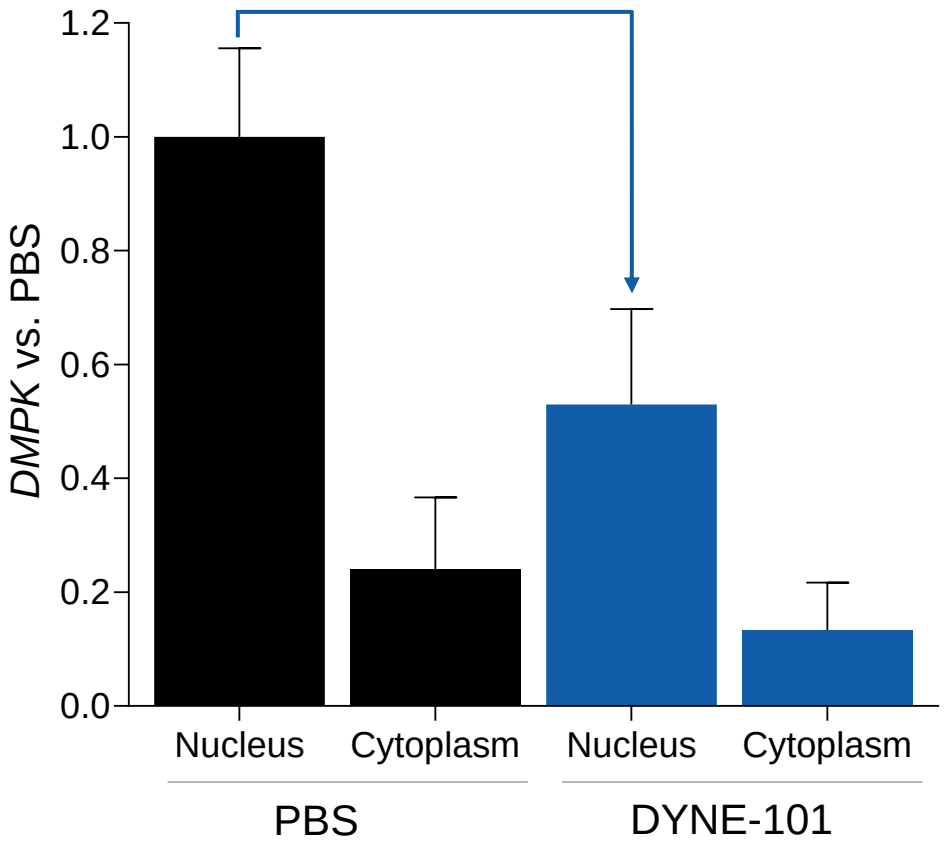


Gapdh Cytoplasmic Control



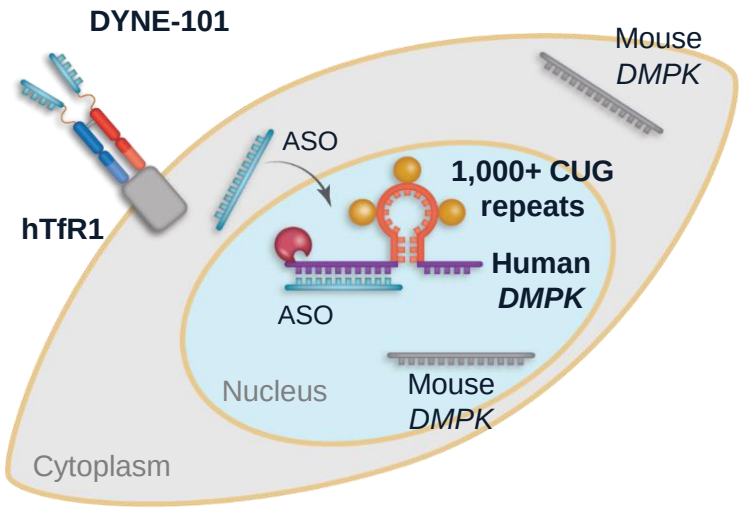
Note: fractions from gastrocnemius of vehicle-treated hTfR1/DMSXL hemizygous model. Data are mean ±SD; n=2

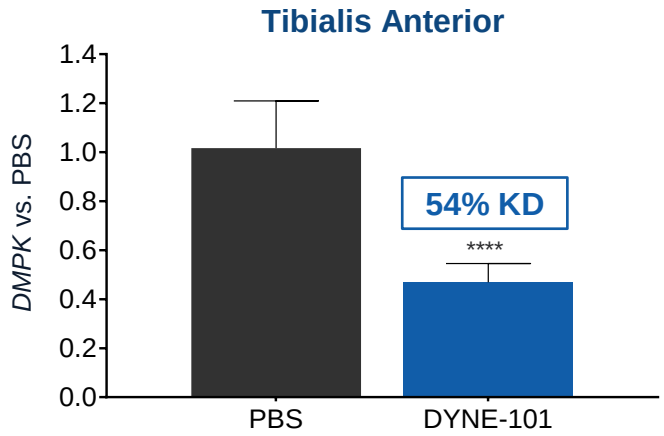
DYNE-101 Achieved Robust Toxic Human *DMPK* KD in Nuclei of hTfR1/DMSXL Model

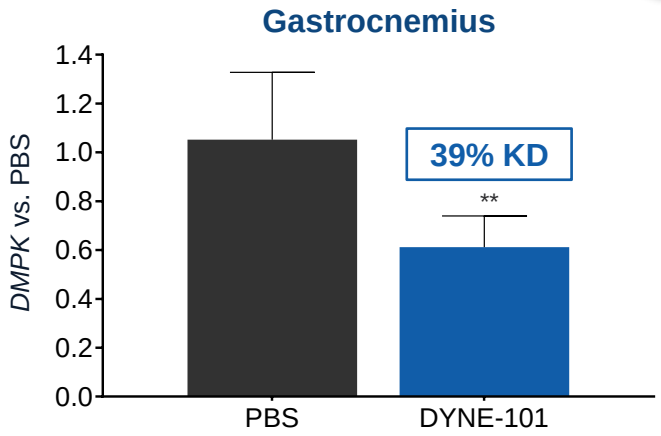


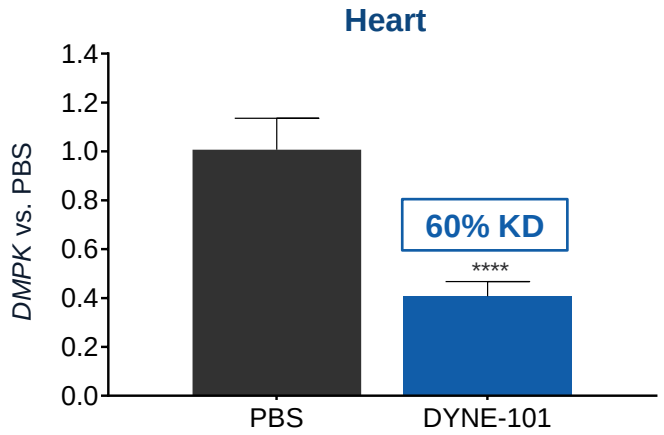
Note: hTfR1/DMSXL hemizygous model. Single IV 10 mg/kg dose on d0, samples from gastrocnemius analyzed d28; Data are mean ±SD; n = 2

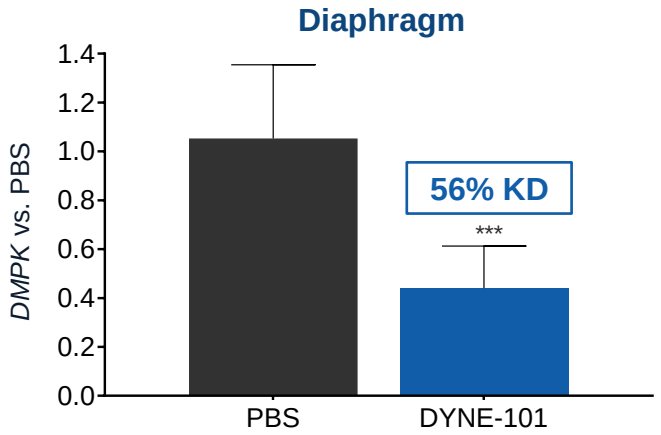
DYNE-101 Demonstrated Robust Toxic Human *DMPK* KD in hTfR1/DMSXL Model











Note: hTfR1/DMSXL hemizygous model. 2 x 10 mg/kg, d0 and d7, analyzed d14; Data are mean ±SD; **p < 0.01,***p < 0.001, ****p < 0.0001, significant by ANOVA; n=6-9

hTfR1/DMSXL Homozygous Model Enables Assessment of Splicing Correction with DYNE-101

Toxic nuclear human *DMPK* → Splicing Defect

hTfR1/DMSXL hemizygous

- **One** copy of the toxic human *DMPK* gene
- **No splicing phenotype**

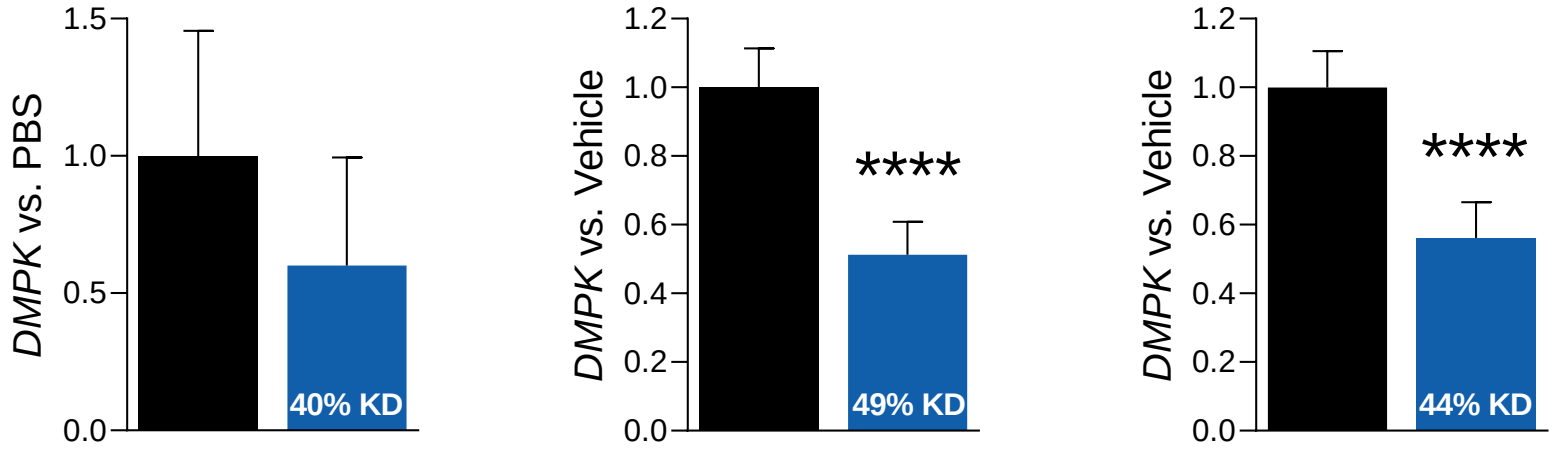
hTfR1/DMSXL homozygous

- **Two** copies of the toxic human *DMPK* gene
- **DM1 splicing phenotype**

DYNE-101 Demonstrated Toxic *DMPK* KD and Splicing Correction in Muscle of hTfR1/DMSXL Homozygous Model

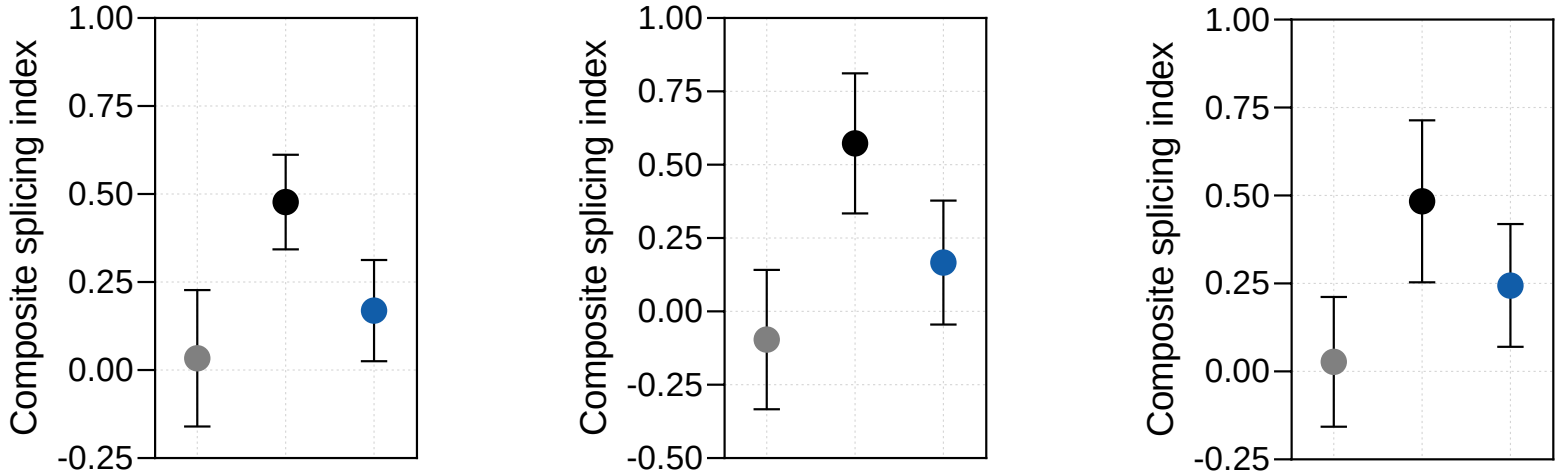
Toxic Human *DMPK* KD

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



Splicing correction

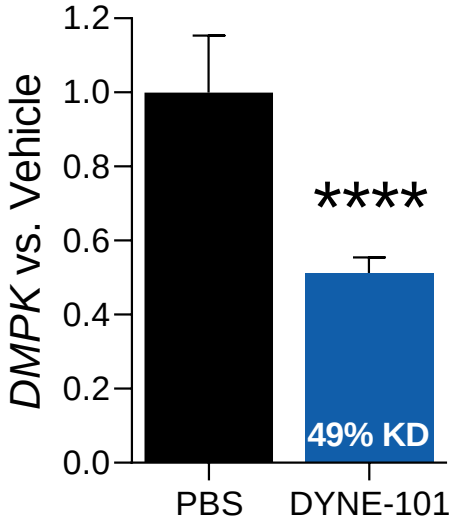
- hTfR1 - PBS
- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101



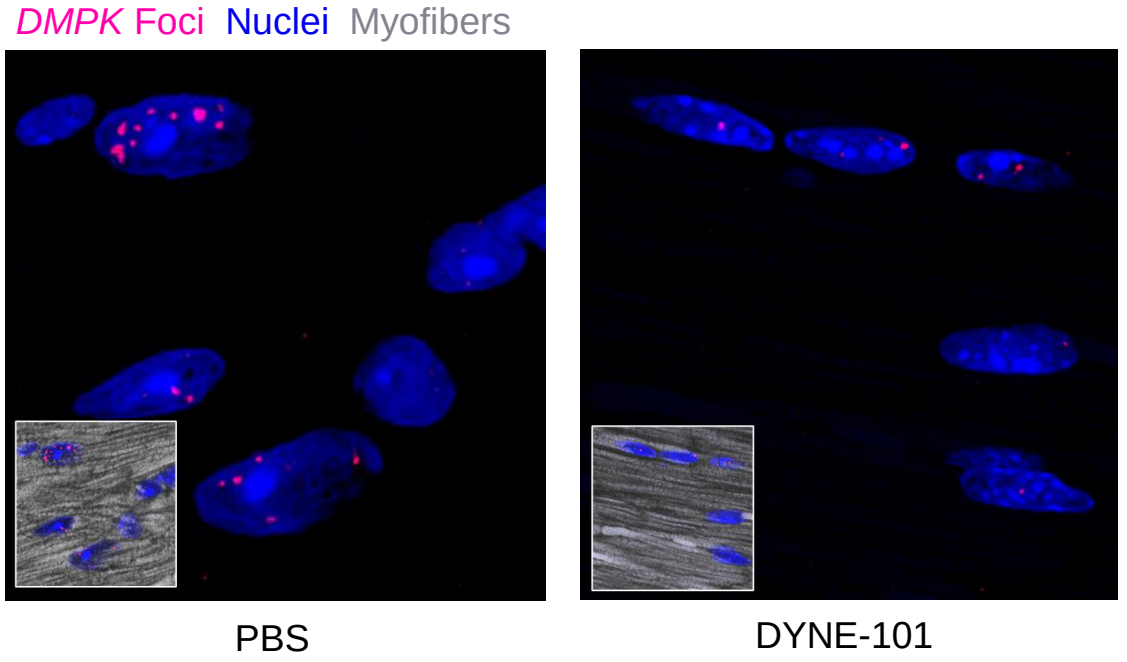
Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28.
Composite splicing indices include *Bin1* E11, *Insr* E11, *Ldb3* E11, *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 mis-splicing measured by qRT-PCR. Data are means ± SD; n = 4–7; **** $p < 0.0001$ by *t*-test.

DYNE-101 Demonstrated Toxic DMPK KD, Foci Reduction and Splicing Correction in Heart of hTfR1/DMSXL Homozygous Model

Toxic Human *DMPK* RNA KD

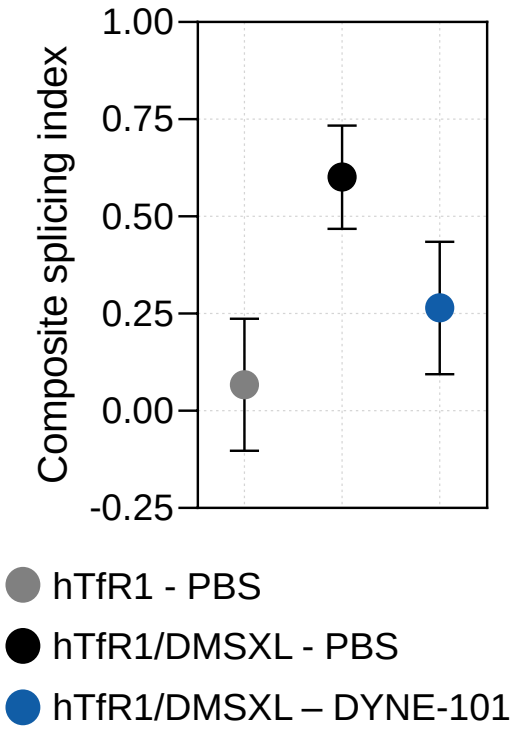


Toxic Human *DMPK* Foci Reduction



DYNE-101 reduces foci area by 49%*

Splicing Correction



Note: hTfR1/DMSXL homozygous model. 2 x 10 mg/kg on d0 and d7, analyzed d28.
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are mean ± SD, n = 6 - 7.; * p <0.05; **** p < 0.0001

hTfR1/DMSXL Mice are a PK/PD Model and Non-Human Primates are a PK and Tolerability Model

Uptakes human TfR1 targeting Fabs

Expresses human toxic DMPK

hTfR1

DMSXL

hTfR1/DMSXL

(CUG) ~1,000

Enables measurement of human toxic nuclear *DMPK* KD

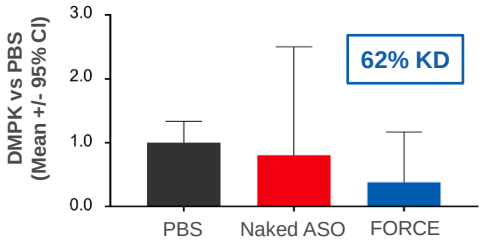
Cytoplasmic normal DMPK

Asian cynomolgus monkey

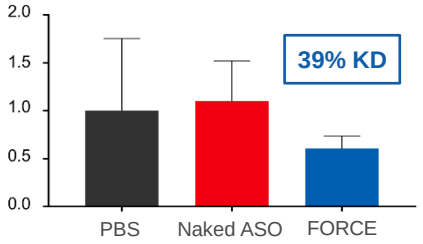
Allows measurement of normal cytoplasmic *DMPK* KD

FORCE Achieved Enhanced Distribution and WT *DMPK* KD Across NHP Skeletal, Cardiac and Smooth Muscles

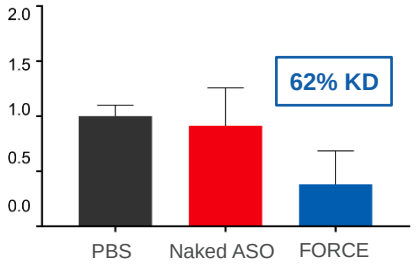
Gastrocnemius



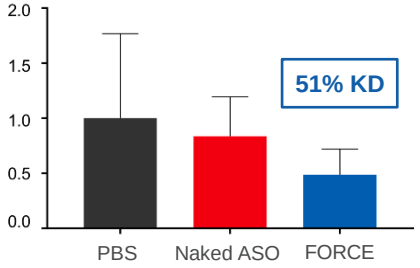
Soleus



Deep Flexor

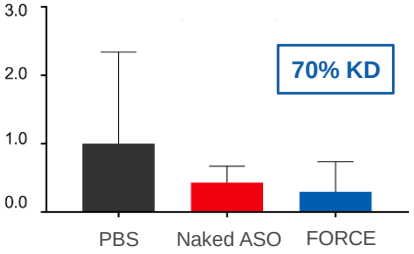


Bicep

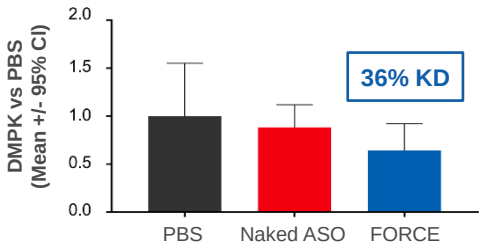


Ileum

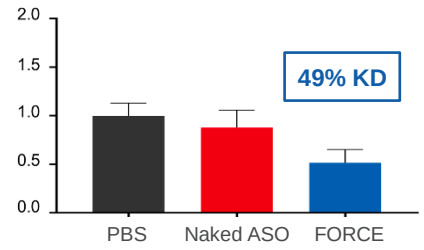
(Near Cecum)



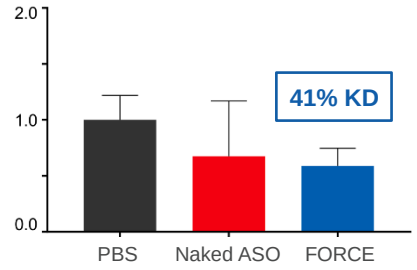
Heart-left Ventricle



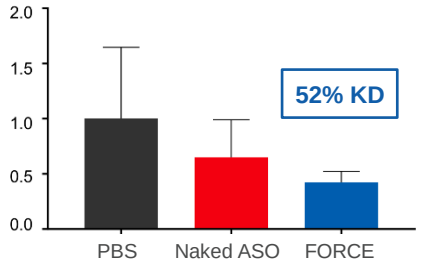
Diaphragm



Masseter

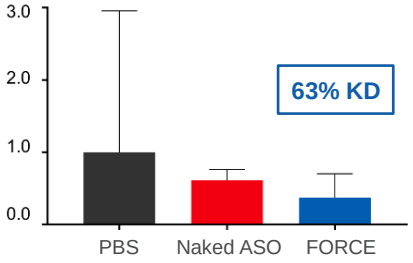


Quadricep



Jejunum

(Duodenum Ends)



Note: WT NHP with WT *DMPK* expression, n=3 per group, single dose IV at 10mg per kg for ASO, 14-day study.

DYNE-101 Well Tolerated in NHP Non-GLP Toxicology Dose-Range Finding Study

- No adverse findings in cynomolgus monkeys after repeat ascending doses of DYNE-101
- No effects on body weight with no clinical signs of toxicity
- No test article-related macroscopic observations or organ weight changes
- No effect on kidney and liver function

DM1 Program Summary

Validating Data

- **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
- **Delivered** *DMPK* targeting ASO to mouse and NHP muscle tissues
- **Favorable safety profile in NHP DRF study**

Potential Advantages

- **Tractable development** with rapid path to human PoC
- **Efficient** commercial model, addressable with focused sales force

DYNE-101 IND submission planned in Q1 2022

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Development Plan
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO

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

DM1 Clinical Development Plan Informed by KOL and Patient Community Input

Global, Multi-disciplinary KOL Input

- Overall design for the MAD study in patients over 18 yrs
- Splicing, myotonia, measures of strength & function, key safety considerations
- Natural history data to contextualize clinical trial data for patients and families, clinicians, payers, regulators

Global Advocacy Leaders, Patient and Caregiver Input

- Considerations for trial selection
- Clinical trial protocol and visit schedule
- Minimizing patient burden during trial conduct
- Ensuring support and education to patients and families

KOL input includes U.S. and European thought leaders across: pediatric & adult neurology; physical medicine and rehabilitation; cardiology, physical therapy. Advocacy leaders, patient and caregiver input includes U.S. and European advocacy leaders, young men with DMD, caregivers for individuals living with DMD.

DM1 Clinical Development Plan Informed by Natural History Study

END-DM1 Natural History Study

- 700 adults (age 18-70 years); 2-year follow-up
- Informs biomarker testing methods and endpoint selection for clinical trials
- Access to study data and biological samples

Sponsored by:

Myotonic Dystrophy Clinical Research Network (DMCRN)

Supporters of END-DM1 include Dyne and:

MDA Muscular Dystrophy Association Team Momentum

FDA

Myotonic Dystrophy FOUNDATION

DM1 Community Urgently Needs Treatment Options

"Being so dependent on others for such simple tasks…is extremely frustrating and demoralizing."

"I used to love to dance. I lost so many things I used to love to do."

"Each and every day brings a new challenge for all our children, and those challenges will certainly increase as the disease progresses."

Proposed Clinical Trial to Evaluate DYNE-101 in Patients with DM1

MULTIPLE ASCENDING DOSE (MAD) | **LONG-TERM EXTENSION (LTE)**

Design

- Multiple Ascending Dose
- Placebo Controlled
- Global
- LTE

Population

- Patients with symptomatic DM1
- Ages 18+
- ~40-50 participants

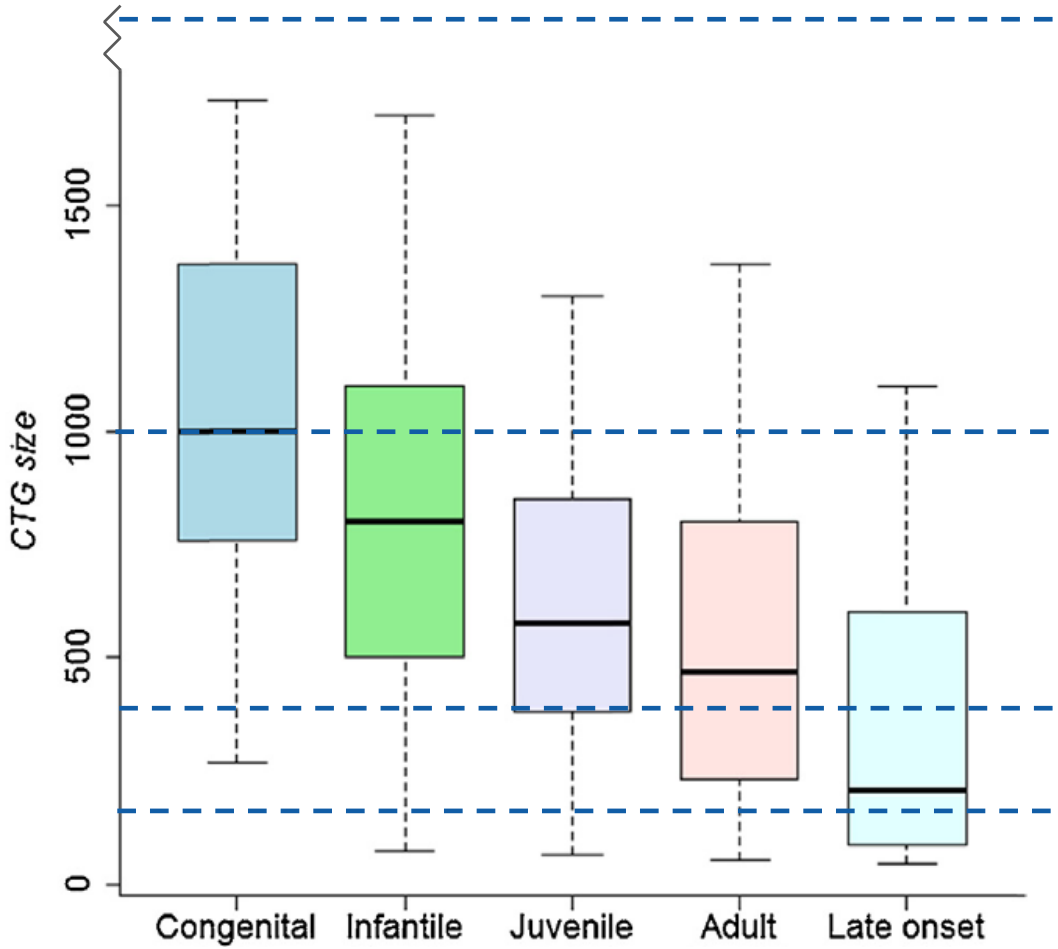
Endpoints*

- Safety and tolerability
- PK/PD
- Splicing Index
- Measures of muscle strength and function
  - Myotonia
  - Ambulation
  - Respiratory

Planned IND Submission in Q1 2022

* Proposed endpoints include primary, secondary and exploratory

Committed to Addressing Full Spectrum of DM1 Population



2,600 CTG Repeats DM1 Myotubes

1,000 CTG Repeats DMSXL Mice

380 CTG Repeats DM1 Myotubes

220 CTG Repeats HSA^{LR} Mice

= Preclinical studies conducted by Dyne

Source: Repeat length data from De Antonito et al. International meeting of the French Society of Neurology, 2016.

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Planning
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

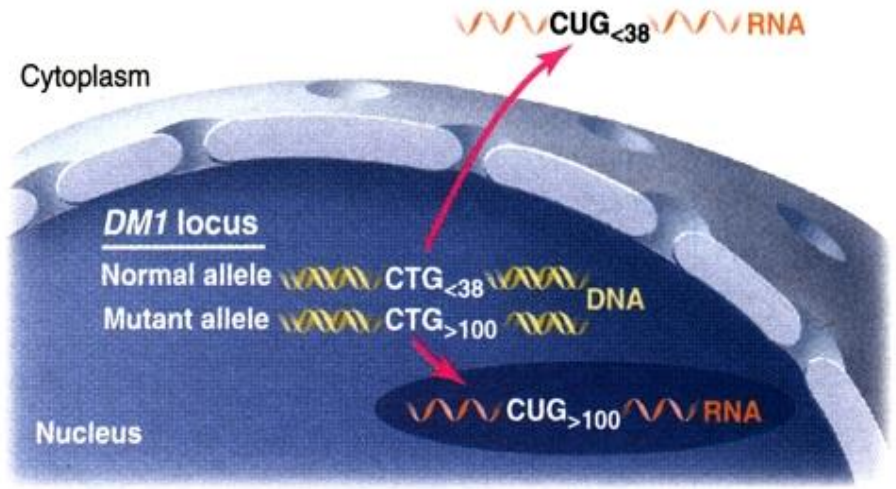
Closing remarks
Joshua Brumm, President & CEO

FROM BENCH TO BED IN MYOTONIC DYSTROPHY

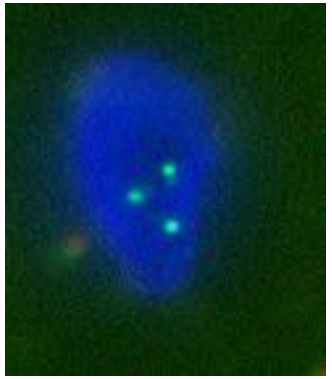
WHERE ARE WE?

Valeria Sansone, MD, PhD
Professor of Neurology, University of Milan
Clinical and Scientific Director of the NEMO Center

DM1: An RNA-mediated Disorder



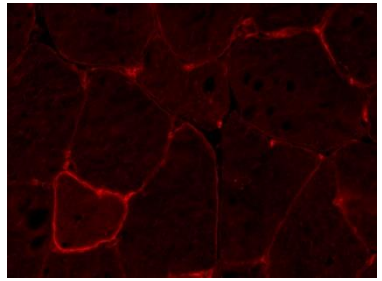
expanded CTG repeat (DNA) → expanded CUG repeat (RNA)



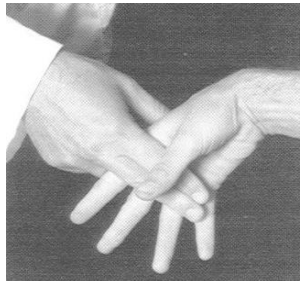
RNA inclusions

DM1 is a spliceopathy

faulty regulation of alternative splicing



loss of CLC-1 chloride channel



myotonia

Aberrant Splicing ➡ Signs & Symptoms

Skeletal muscle

Myotonia:	CLCN1 e7A
Muscle weakness (myopathy):	CACNA1S e29, BIN1 e11, DMD e78, RYR1 e70
Muscle wasting (atrophy):	PKM e10, DMD e78
Respiratory failure:	unknown
Myalgia:	unknown

Cardiac muscle

Conduction defect/block:	SCN5A e6,TNNT2 e5, miR-1

Central nervous system

White/gray matter changes:	unknown
Excessive daytime sleepiness:	unknown
Fatigue:	unknown
Cognitive decline:	MAPT e2, e3, e10
Behavioral changes:	unknown

Gastrointestinal

Difficulty swallowing:	unknown
Constipation, diarrhea:	unknown
Bloating:	unknown

Sensory

Cataracts:	unknown
Ptosis:	unknown
Hearing impairment:	unknown

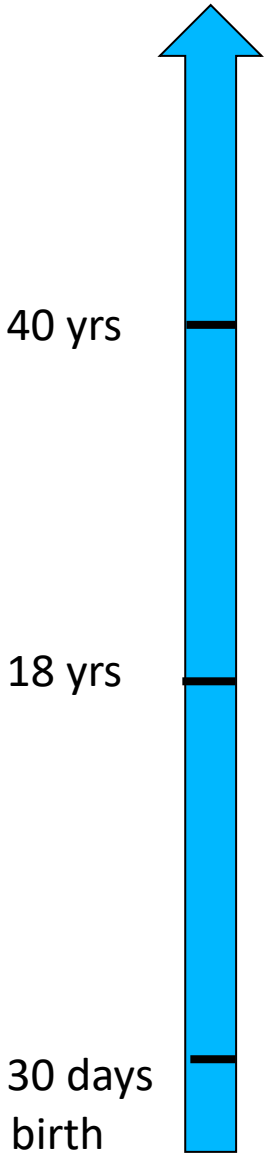
Endocrine

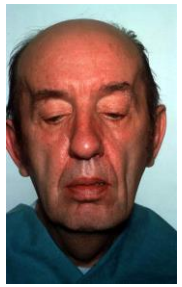
Insulin resistance:	INSR e11
Hypogonadism :	unknown
Hyperparathyroidism:	unknown
Frontal balding:	unknown

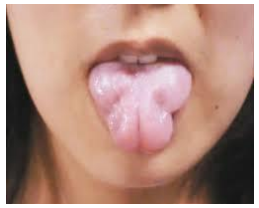
Immune

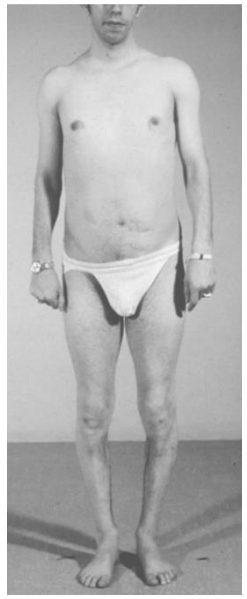
Autoimmune diseases:	unknown
Cancer:	unknown

DM1: Onset At All Ages







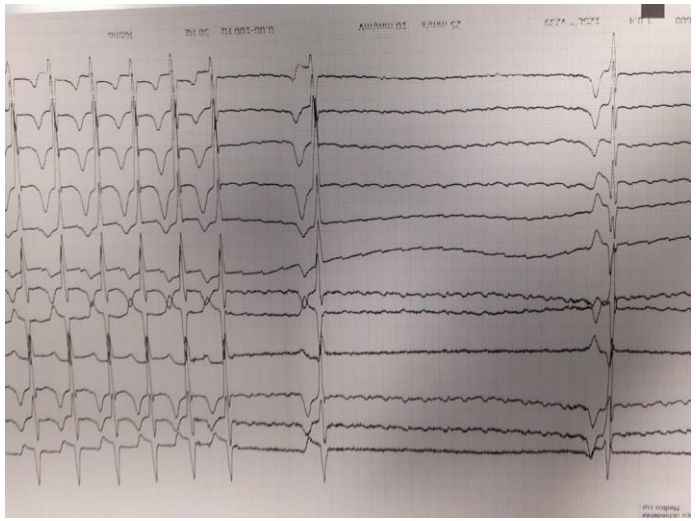


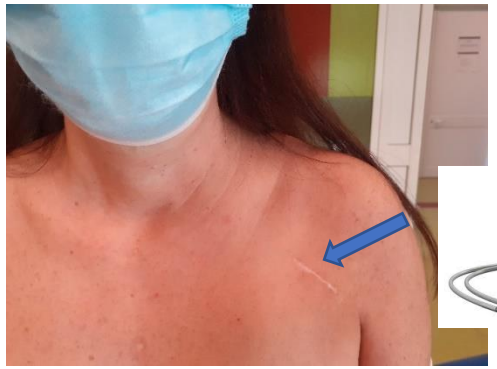
Burden Of Disease

Distal muscle weakness

Stumbles and falls

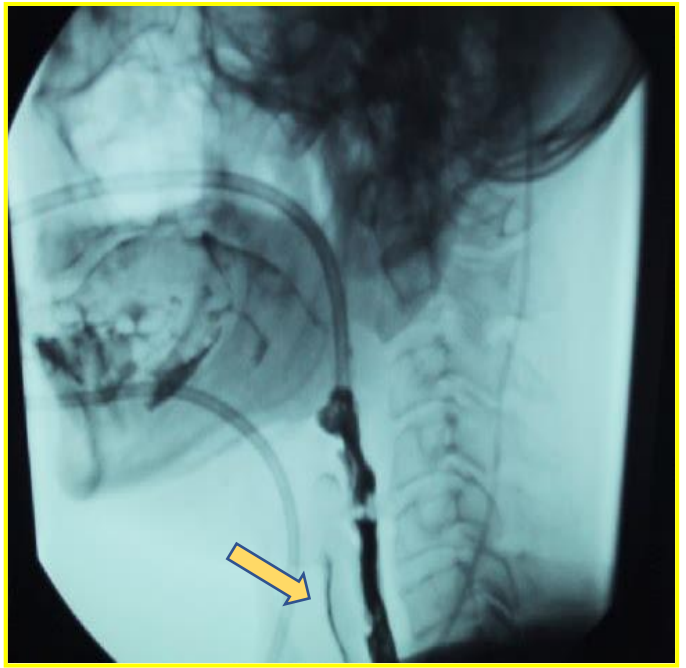
Cardiac arrhythmias





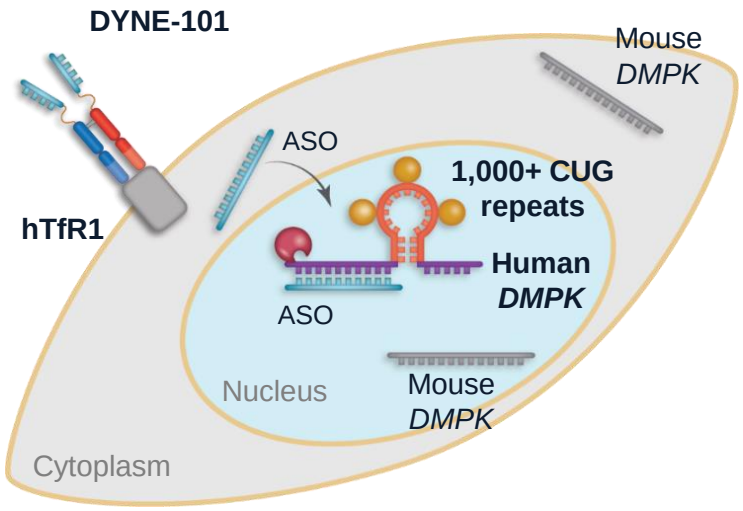
Early PM/ICD implantation

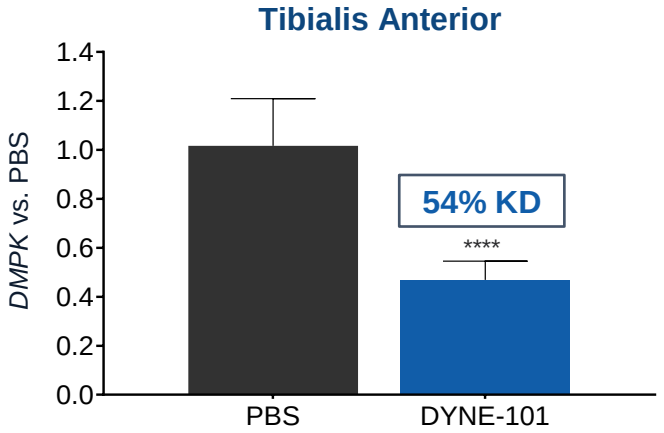
Smooth muscle involvement

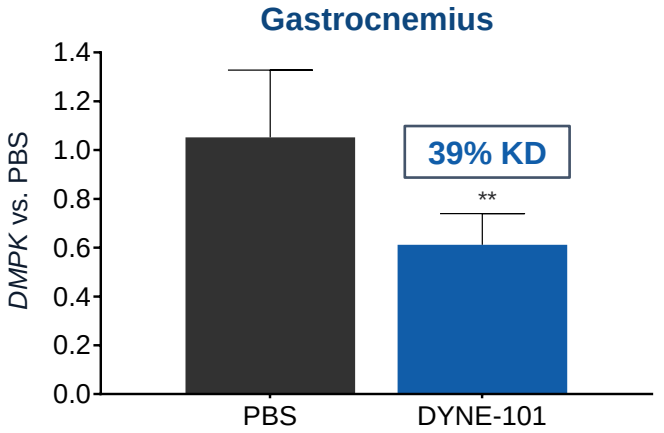


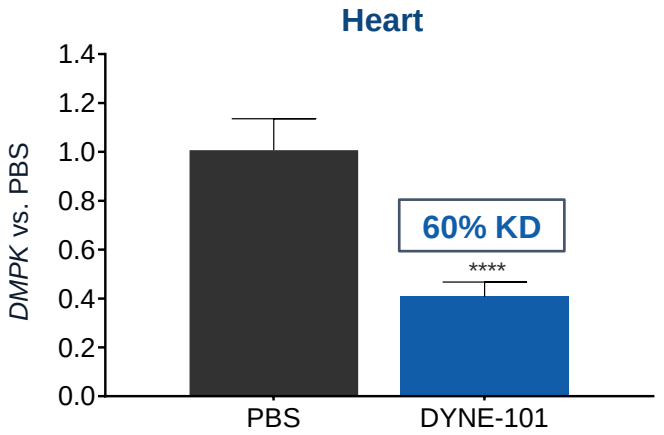
Swallowing difficulties
GI symptoms

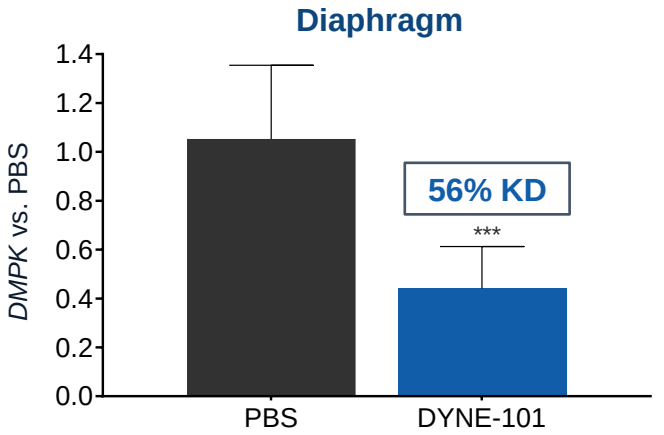
DYNE-101 demonstrated Robust Toxic Human DMPK KD in hTfR1/DMSXL Model







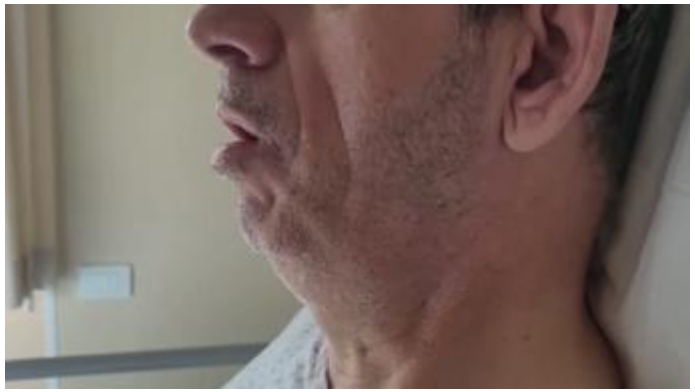




ASGCT 2021; hTfR1/DMSXL hemizygous model. 2 x 10 mg/kg, d0 and d7, analyzed d14; Data are mean ±SD; **p < 0.01,***p < 0.001, ****p < 0.0001, significant by ANOVA; n=6-9

Burden Of Disease

Respiratory muscle weakness



Secretion management
Daytime hypoxia
Hypercapnia

Cognitive & behavioral abnormalities

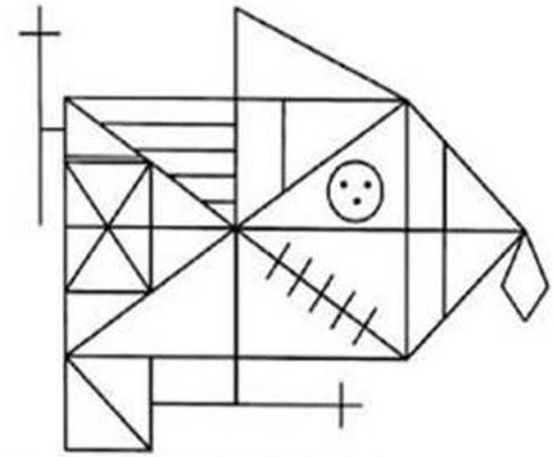
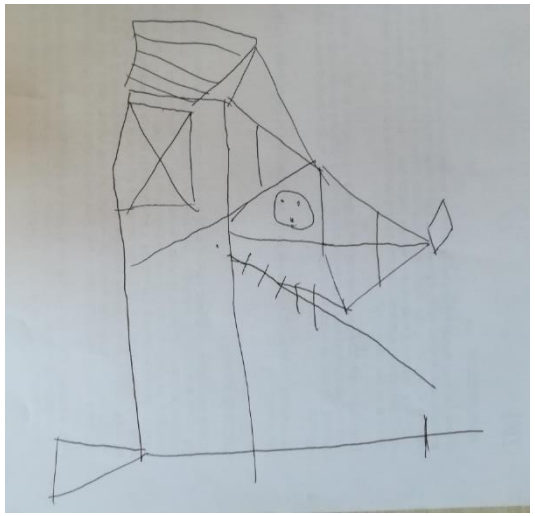


Figura 2. Figura Compleja de Rey-Osterrieth



Central fatigue, apathy,
frontal dysexecutive syndrome,
Excessive Daytime Sleepiness

Unmet Needs

NO TREATMENTS SO FAR

Transcriptional silencing

1. Inhibition of RNA polymerase co-factors
2. Small molecules that bind to GC-rich repeats

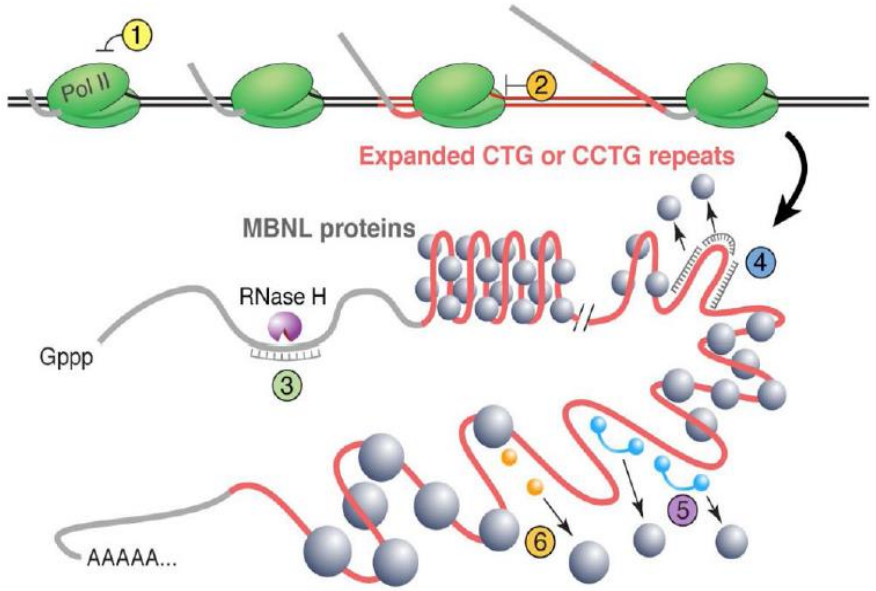
Post-transcriptional silencing

3. Antisense oligonucleotides
4. Small RNAs targeting CUG repeats

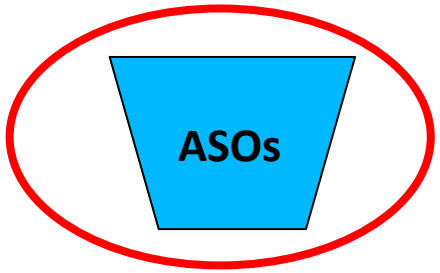
Inhibiting interactions between MBNL and toxic RNA

5. Small molecules - monomers and polymers
6. Peptides

Targeting pathways downstream of RNA toxicity



Thornton C et al. Curr Opin Genetics 2017



FORCE Platform

THE DM-CRN: END-DM1 STUDY:

- *Which patients?*
- *Which outcomes?*

Unmet needs: No Treatment

FORCE Platform

- Durable knockdown of toxic human nuclear *DMPK* RNA in the hTfR1/DMSXL model
- Correction of splicing in the hTfR1/DMSXL model (advantage of the model is to quantify splice products)
- Robust targeted effects on skeletal, diaphragm, cardiac, smooth muscles in preclinical studies

Unmet Needs: Which Patients? Which Outcomes?

Myotonic Dystrophy – Clinical Research Network (DM-CRN)

- 700 Patients
- Multicenter
- International (US & EU) Sites
- Trained staff
- Harmonization of protocols and procedures

Conclusions

WHY IS THIS WORK IMPORTANT?

- DM is the most frequent muscular dystrophy (1:2500 adults)
- Very variable: very severe neonatal form to late onset forms
- Multiple organ involvement
- Very high patient and family burden, social impact, productivity

HOW CAN WE IMPACT ON THIS DISEASE

- Trial readiness
- Target the main domains of impact/disease burden
- Provide access to as many patients as possible worldwide

From Bed To Bench

«What phenomena do clinicians observe that are crying for the attention of laboratory researchers?»

« …need to take the clinical question from the bed to the bench….carrying the answer from the bench back to the bed, and then extending the benefits to the field—to the wider world»

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Planning
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO

Program

DM1 Program Data
Oxana Beskrovnaya, Ph.D., Chief Scientific Officer

DM1 Program Clinical Planning
Wildon Farwell, M.D., MPH, Chief Medical Officer

Perspectives on DM1
Valeria Sansone, M.D., Ph.D., Clinical and Scientific Director, Clinical Center NeMO, Milan; Associate Professor of Neurology, University of Milan

Q&A

Closing remarks
Joshua Brumm, President & CEO

The Muscle to Move to the Clinic

DMD

In vitro:

- Enhanced exon skipping

In vivo:

- Robust, durable exon skipping and dystrophin expression in *mdx* model
- Transformative exon skipping in NHP cardiac and skeletal muscles
- NHP GLP tox results support advancement to the clinic

IND: Q4 2021

DM1

In vitro:

- *DMPK* KD, reduction in nuclear foci, splicing correction

In vivo:

- Correction of splicing & reversal of myotonia in HSA^{LR} model
- Robust knockdown of toxic nuclear *DMPK* in hTfR1/DMSXL model, foci reduction & correction of splicing
- Well tolerated in NHP Non-GLP toxicology dose-range finding study

IND: Q1 2022

FSHD

In vitro:

- Reduced expression of key DUX4 biomarkers

In vivo:

- Enhanced tissue distribution in NHP

IND: H2 2022

Three INDs planned between Q4 2021 - Q4 2022

Targeting the genetic basis of serious muscle diseases to

STOP OR REVERSE DISEASE PROGRESSION

FORCE PLATFORM	**Robust** PIPELINE	**Delivering** FOR PATIENTS	**Exceptional** TEAM