



Building the World's Leading Muscle Disease Company

DM1 PROGRAM WEBCAST EVENT | MAY 14, 2021

Joachim, living with DM1

Program



Opening remarks
Joshua Brumm, President & CEO



FORCE™ platform and DM1 program
Romesh Subramanian, Ph.D., Chief Scientific Officer



hTfR1/DMSXL Model Data
Oxana Beskrovnaya, Ph.D., SVP, Head of Research



Perspectives on DM1 and targeting the genetic basis of the disease
Charles Thornton, M.D., Saunders Distinguished Professor of
Neuromuscular Research at the University of Rochester

Discussion and Q&A

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, 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.

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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



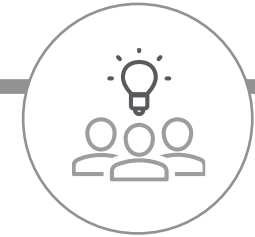
- Robust pipeline: DM1, DMD, and FSHD
- Set standard for evaluating PD in DM1 disease model
- Demonstrated functional benefit in DM1 and DMD models
- Significant market opportunities

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



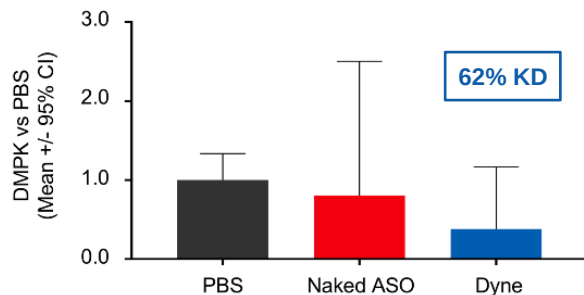
- Deep knowledge of muscle diseases and novel therapeutic modalities
- World-class scientific advisory board
- Supported by leading healthcare investors

Robust Portfolio Focused on Muscle Diseases

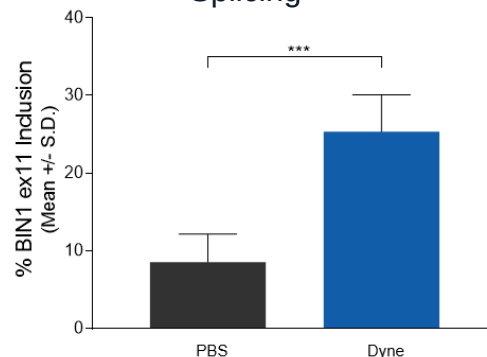
PROGRAM	TARGET	DISCOVERY	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ESTIMATED PATIENTS
Myotonic Dystrophy (DM1)	DMPK						US: >40,000 Europe: >74,000
Duchenne Muscular Dystrophy (DMD)	Exon 51 Exon 53 Exon 45 Exon 44						US: ~12,000-15,000 Europe: ~25,000
Facioscapulohumeral Muscular Dystrophy (FSHD)	DUX4						US: ~16,000-38,000 Europe: ~35,000
Pipeline Expansion Opportunities							
Rare Skeletal Cardiac Metabolic							

FORCE Demonstrated Functional Benefit Across Multiple Indications and Disease Models

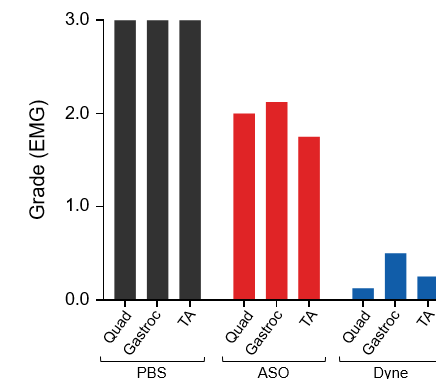
DMPK Knockdown Gastrocnemius



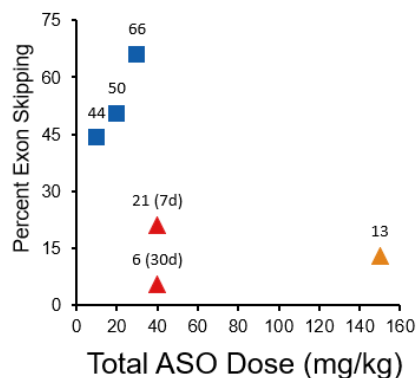
Splicing Changes Splicing



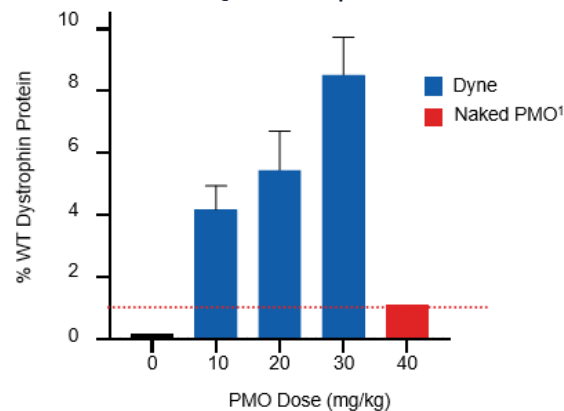
Functional Benefit Myotonia



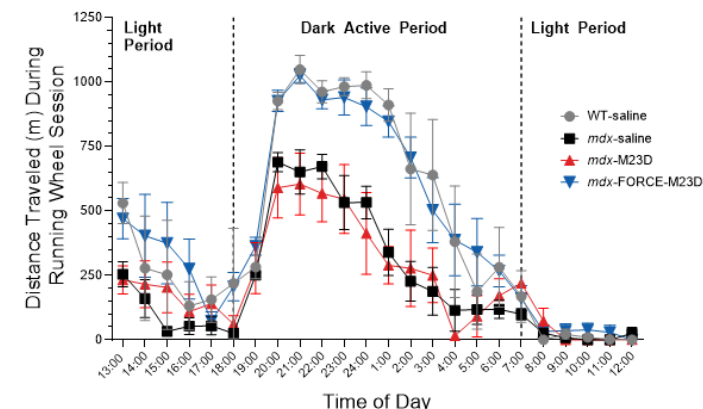
Exon Skipping Quadriceps



Dystrophin Expression Quadriceps



Functional Benefit Home Cage Running Wheel



Program



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FORCE™ platform and DM1 program
Romesh Subramanian, Ph.D., Chief Scientific Officer



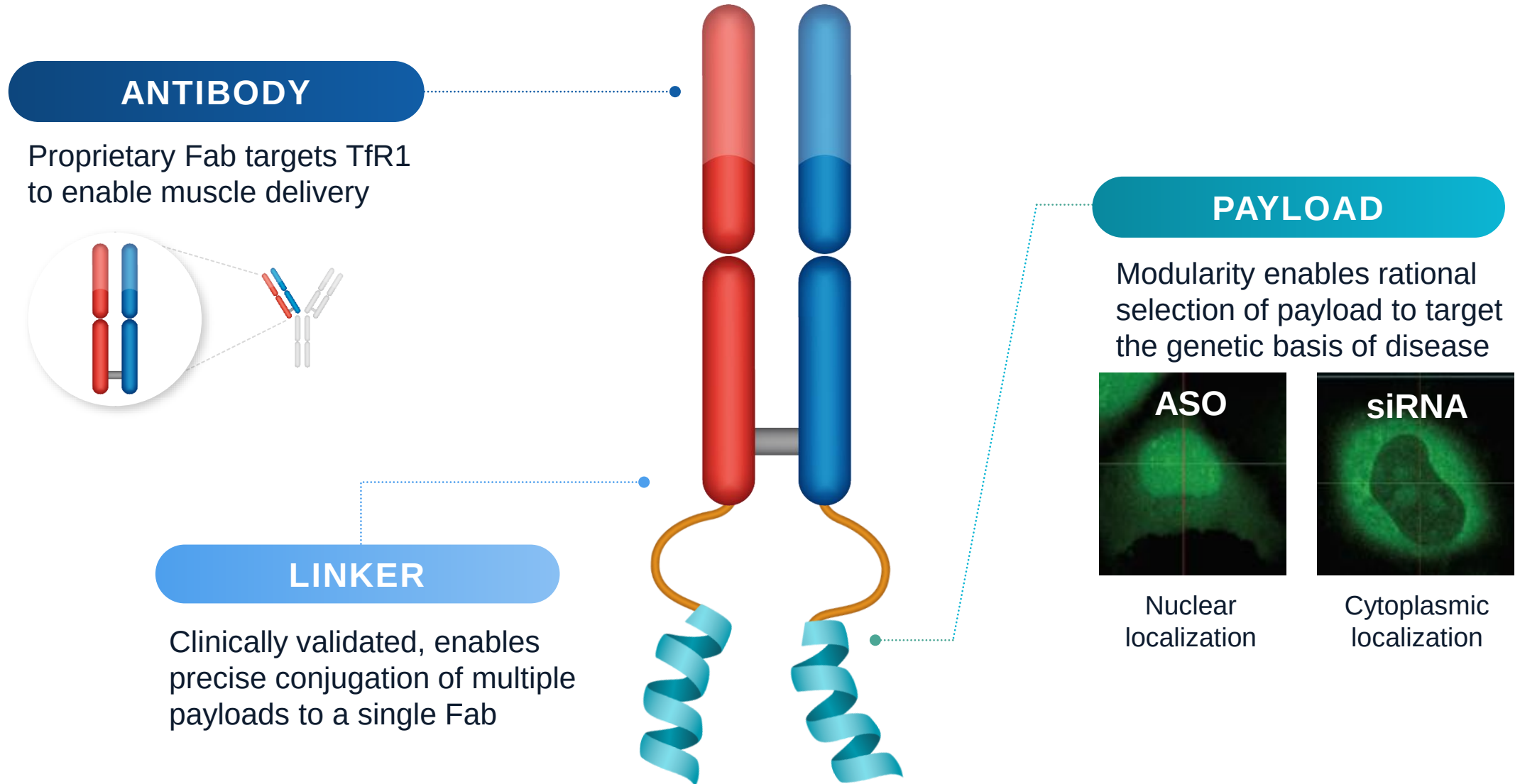
hTfR1/DMSXL Model Data
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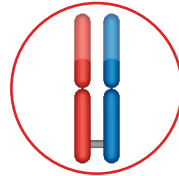
Perspectives on DM1 and targeting the genetic basis of the disease
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Discussion and Q&A

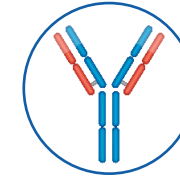
Dyne FORCE Platform: Modern Oligo Therapeutics for Muscle Diseases



Fabs Offer Multiple, Powerful Advantages Over mAbs



Fab

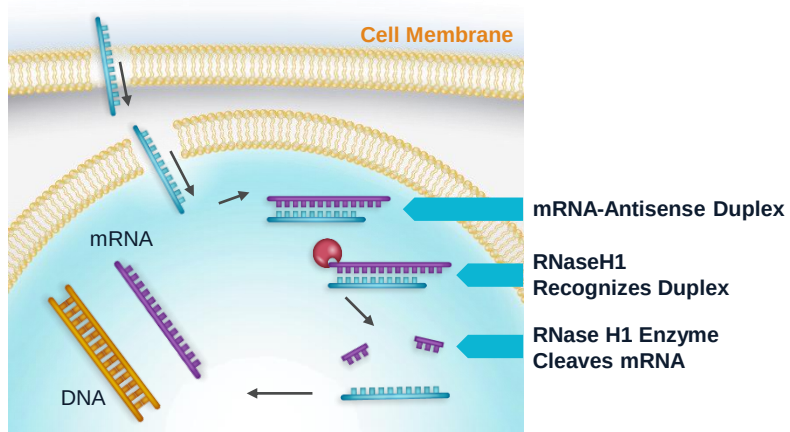


mAb

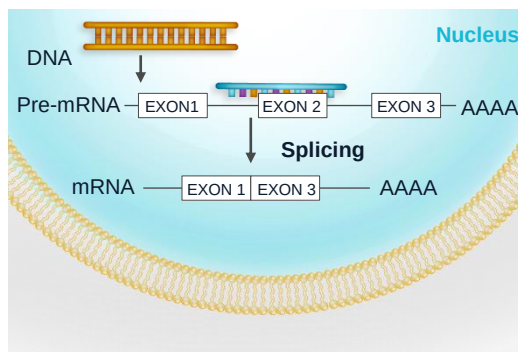
Feature		Fab		mAb
Delivery to Muscle	✓	Enhanced delivery of payloads	—	Limited delivery due to TfR1 degradation post binding
Enhanced Tissue Penetration	✓	1/3 size of mAb leads to increased tissue penetration	—	Increased size reduces tissue penetration
Tolerability	✓	Lower protein load leads to increased tolerability	—	3x larger protein load
Effector Cell Activation	✓	Lower risk due to lack of Fc domain	—	Fc domain can activate effector cells
Complement Activation	✓	Lower risk due to lack of Fc domain	—	Fc domain can activate complement system
Residence Time	✓	Greater residence time in muscle cell due to lower FcRn binding	—	Fc domain – FcRn binding recycles therapeutic out of muscle cell
Large Scale Manufacturing	✓	Yields enable large scale manufacturing	✓	Yields enable large scale manufacturing

Rationally Select Payload to Target Genetic Basis of Disease

ASO acts in the nucleus and cytoplasm

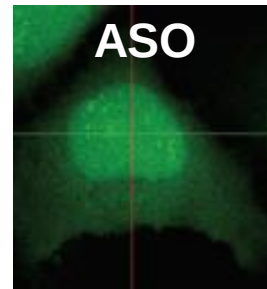


Splice-modulating ASO



Single-Stranded Antisense

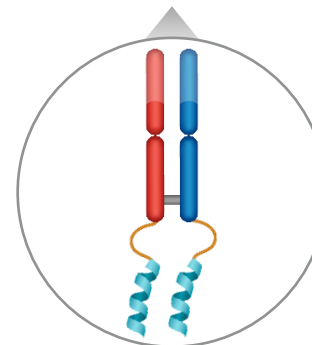
Subcellular distribution of ASO and siRNA



Nuclear localization

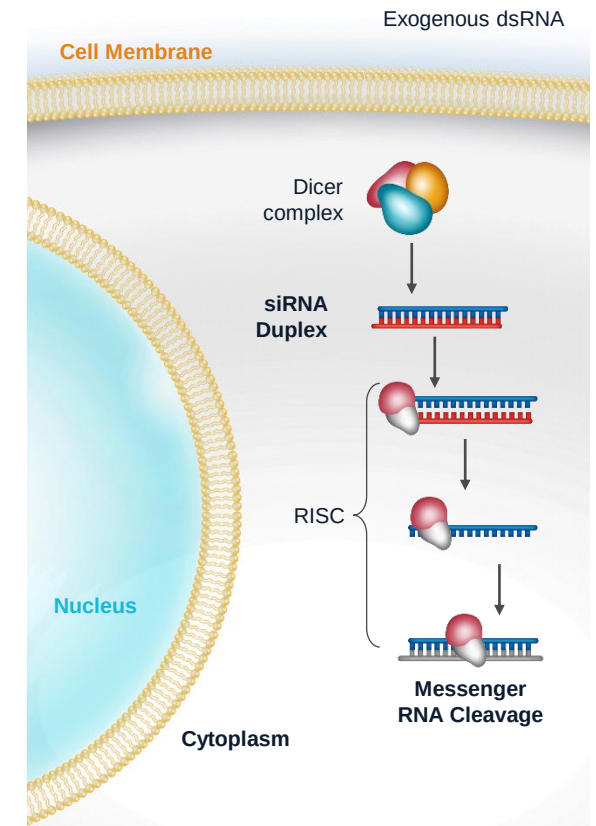


Cytoplasmic localization



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

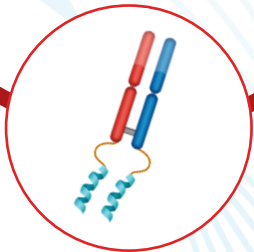
siRNA acts in the cytoplasm



Double-Stranded Antisense (siRNA)

FORCE Platform Designed to Deliver Significant Advantages

**Stop or Reverse
Disease
Progression**



Targeted Muscle Delivery

Leverages TfR1 expression
on skeletal, cardiac and smooth muscle



Targets Genetic Basis of Disease

Rationally select payloads
to match target biology



Redosable Administration

Potential for individualized patient
titration and longer-term efficacy



Enhanced Tolerability

Targeted delivery limits systemic
drug exposure



Extended Durability

Potential for prolonged disease-modifying
effects, enabling less frequent dosing



Reduced Development and Manufacturing Costs

A single Fab and linker
utilized across all programs

DM1 Program



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

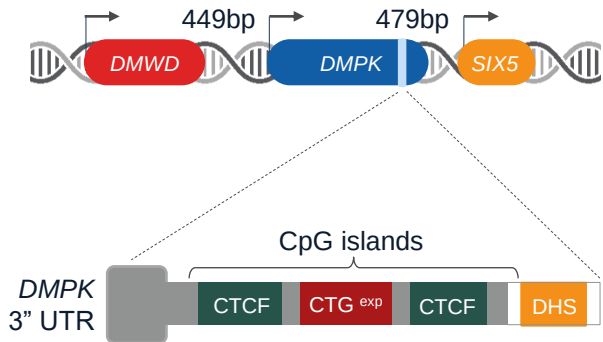
OUR APPROACH

Disease-Modifying Nuclear *DMPK* Knockdown

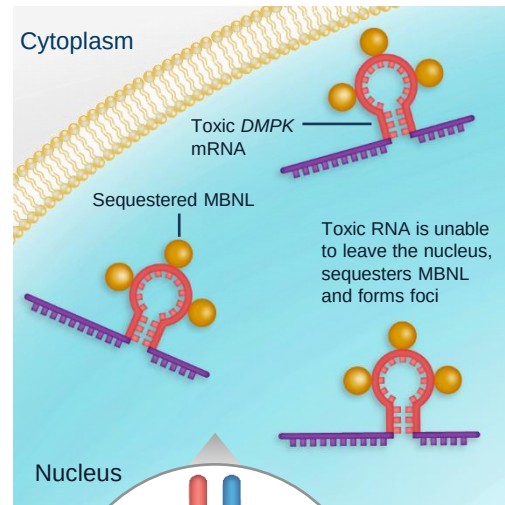
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE Targets the Genetic Basis of DM1

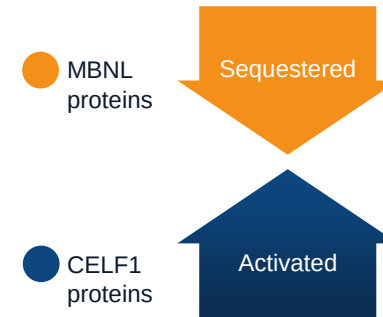
DNA Triplet Repeats



Toxic RNA Forms Foci



RNA Binds Splicing Proteins

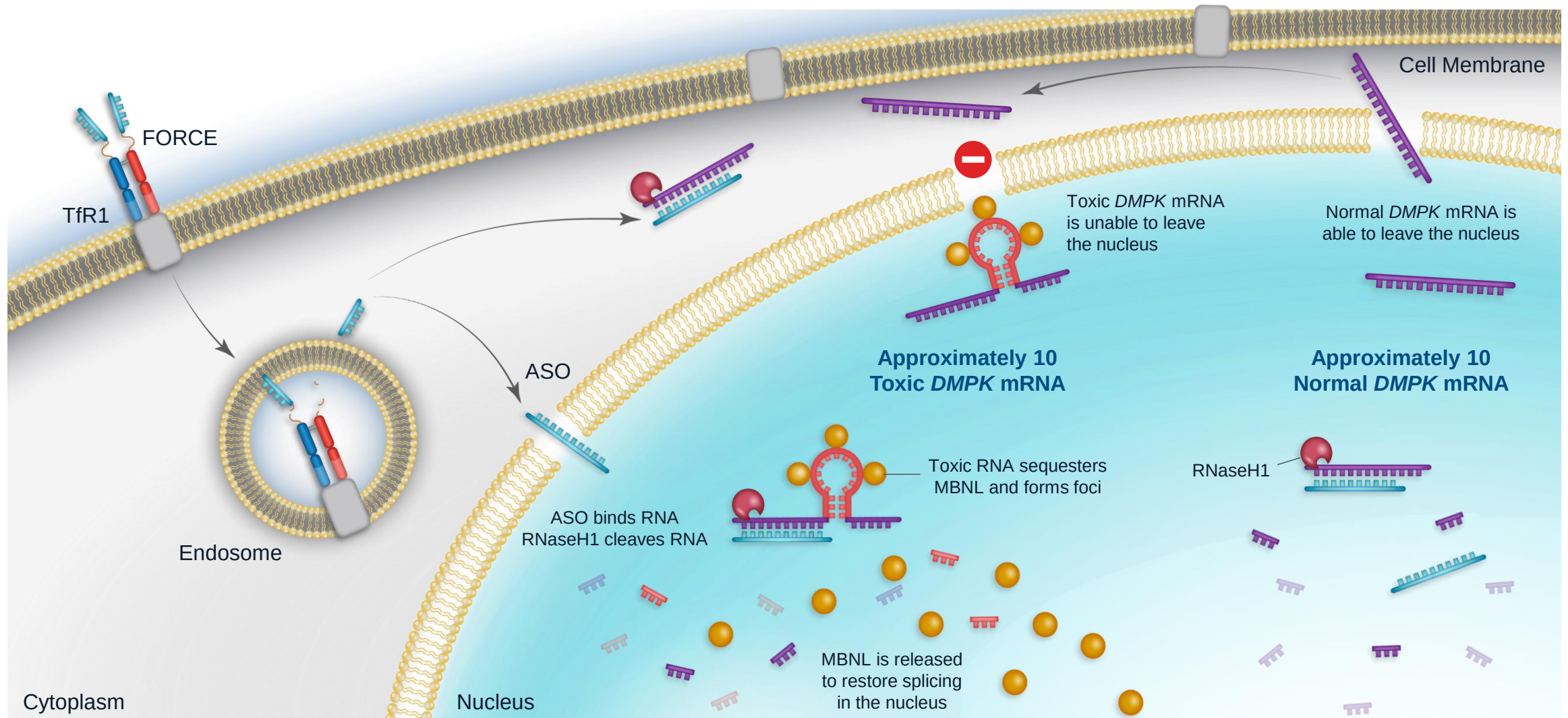


Clinical Presentation

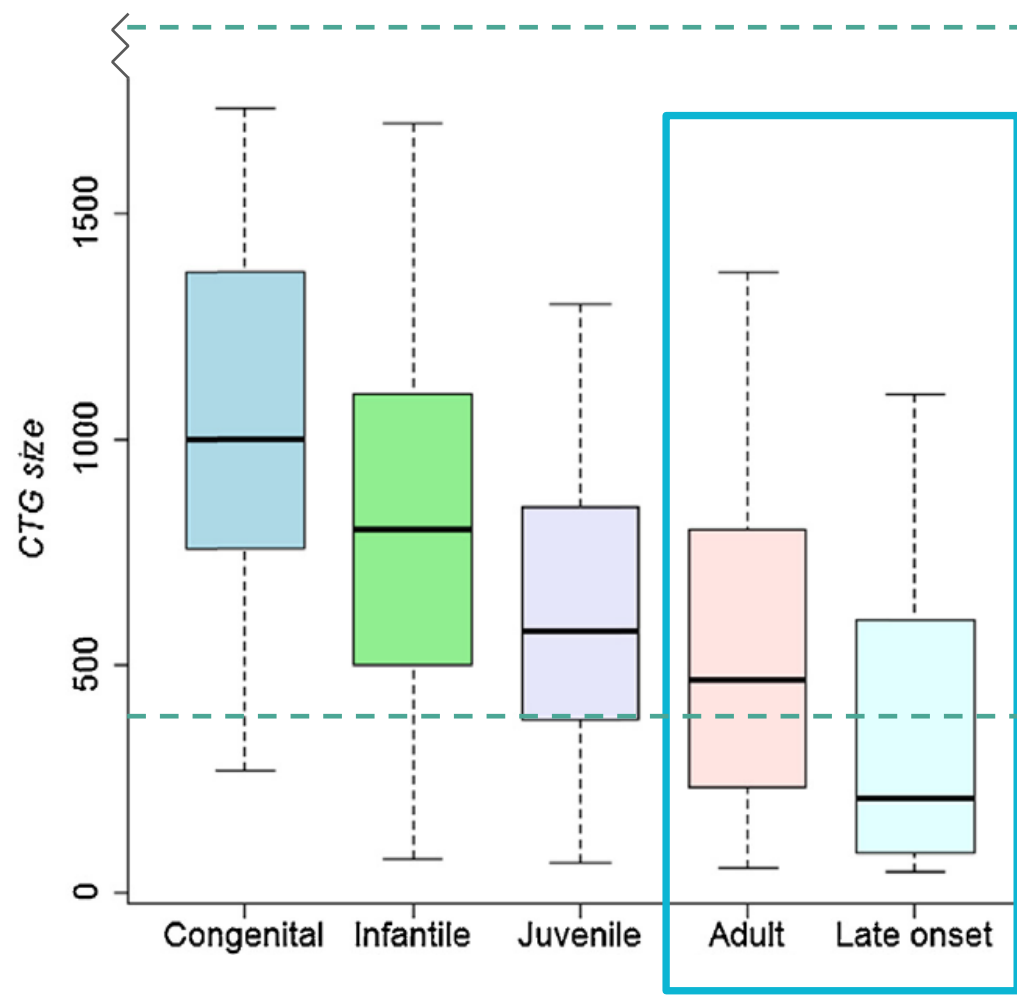
- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

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

FORCE Targets Toxic Nuclear *DMPK* RNA



In Vitro Models Represent DM1 Patient Population With Different Number of CTG Repeats



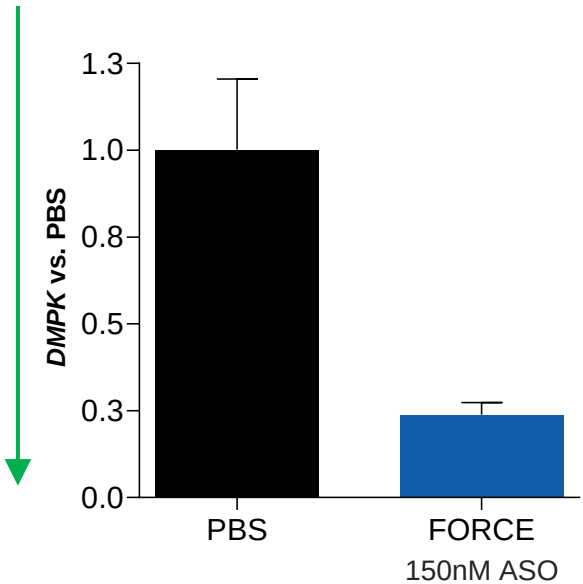
2,600 CTG Repeats DM1 Myoblasts

380 CTG Repeats DM1 Myoblasts

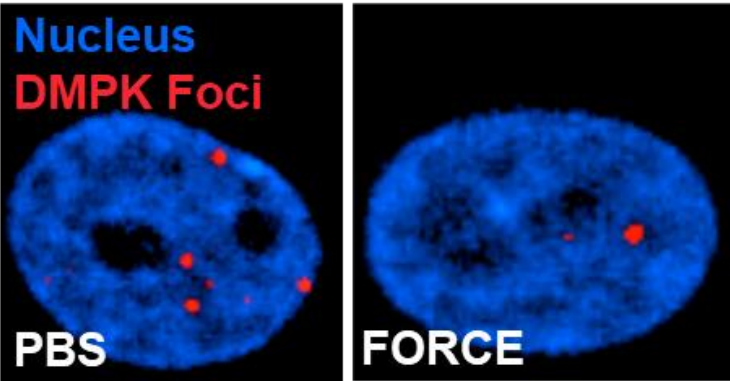
Dyne initially targeting ~75% of DM1 patients

380 CTG Repeats DM1 Myotubes: FORCE Demonstrated Robust Dose-dependent DMPK KD, Foci Reduction, and Splicing Correction

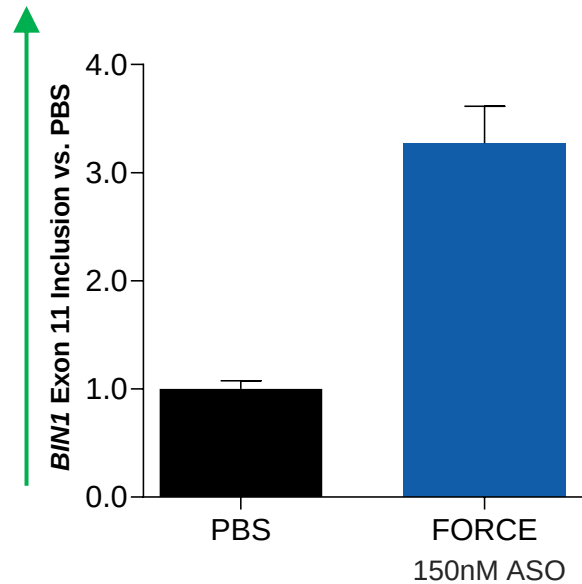
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

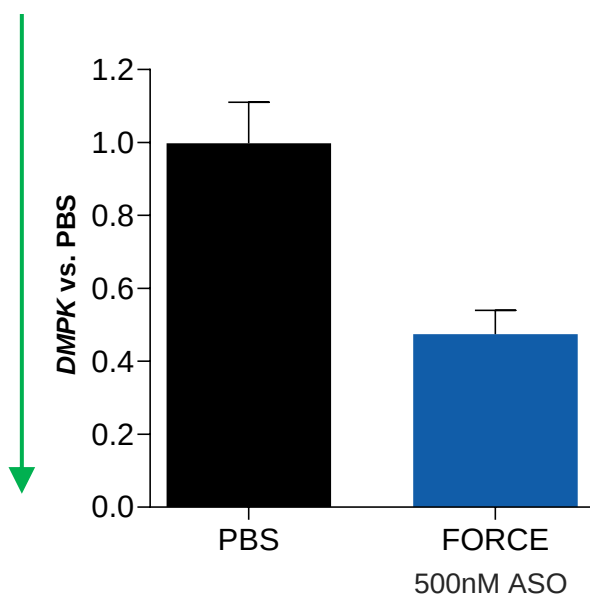


BIN1 mis-splicing correction by qPCR

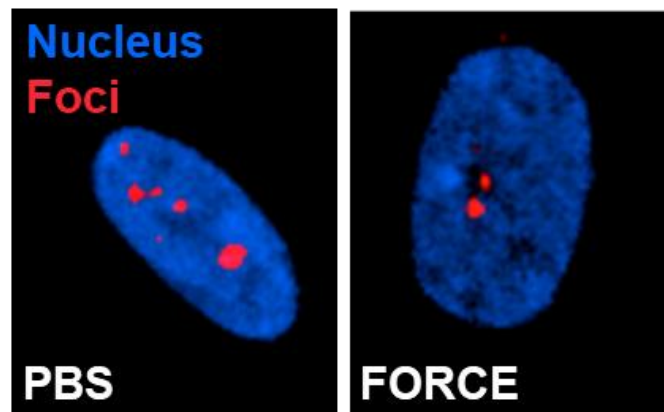


2,600 CTG Repeats DM1 Myotubes: FORCE Demonstrated Robust Dose-dependent *DMPK* KD, Foci Reduction, and Splicing Correction

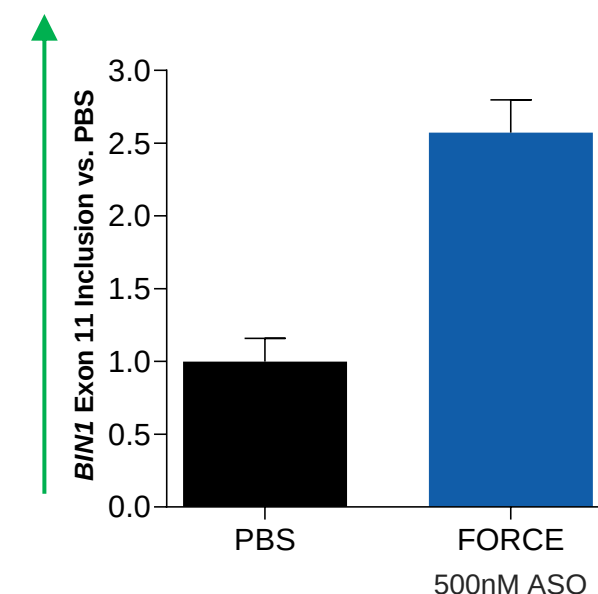
DMPK mRNA KD by qPCR



DMPK foci reduction by FISH

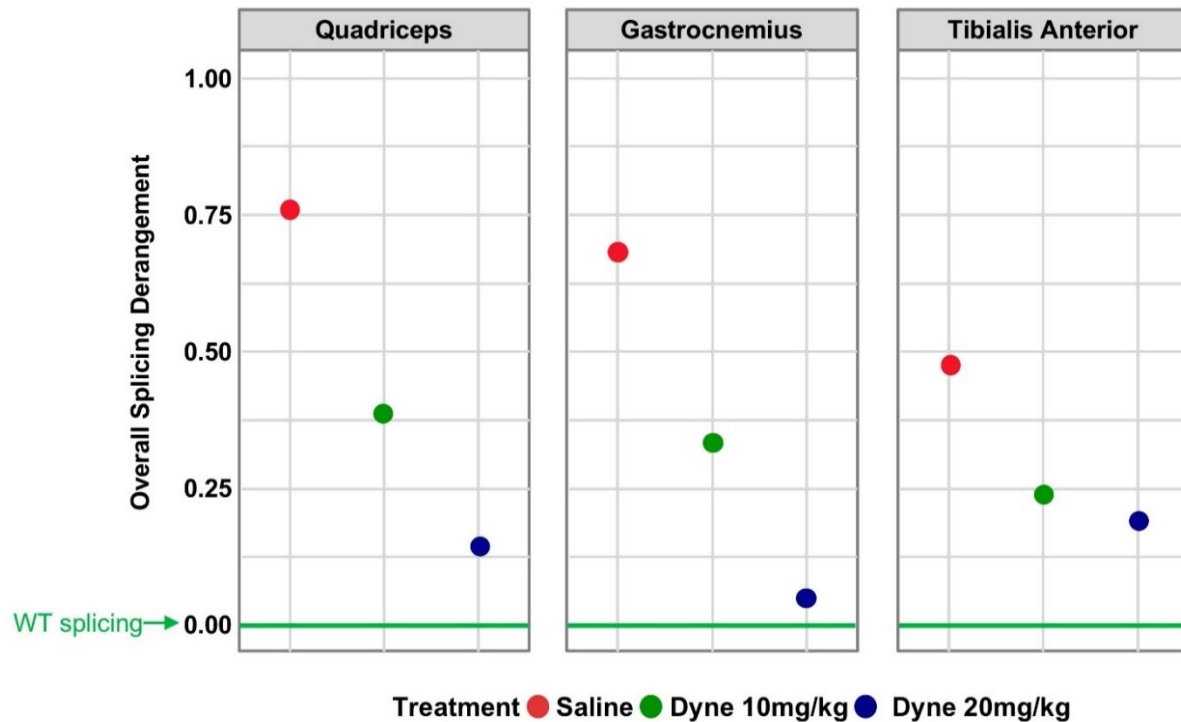


BIN1 mis-splicing correction by qPCR

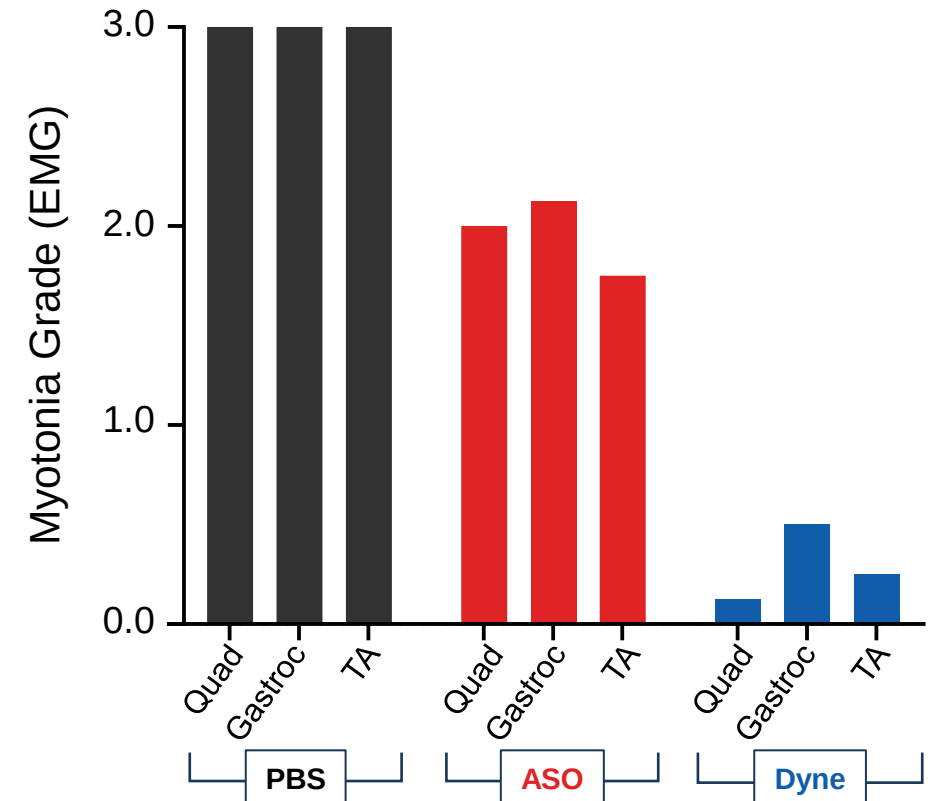


FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

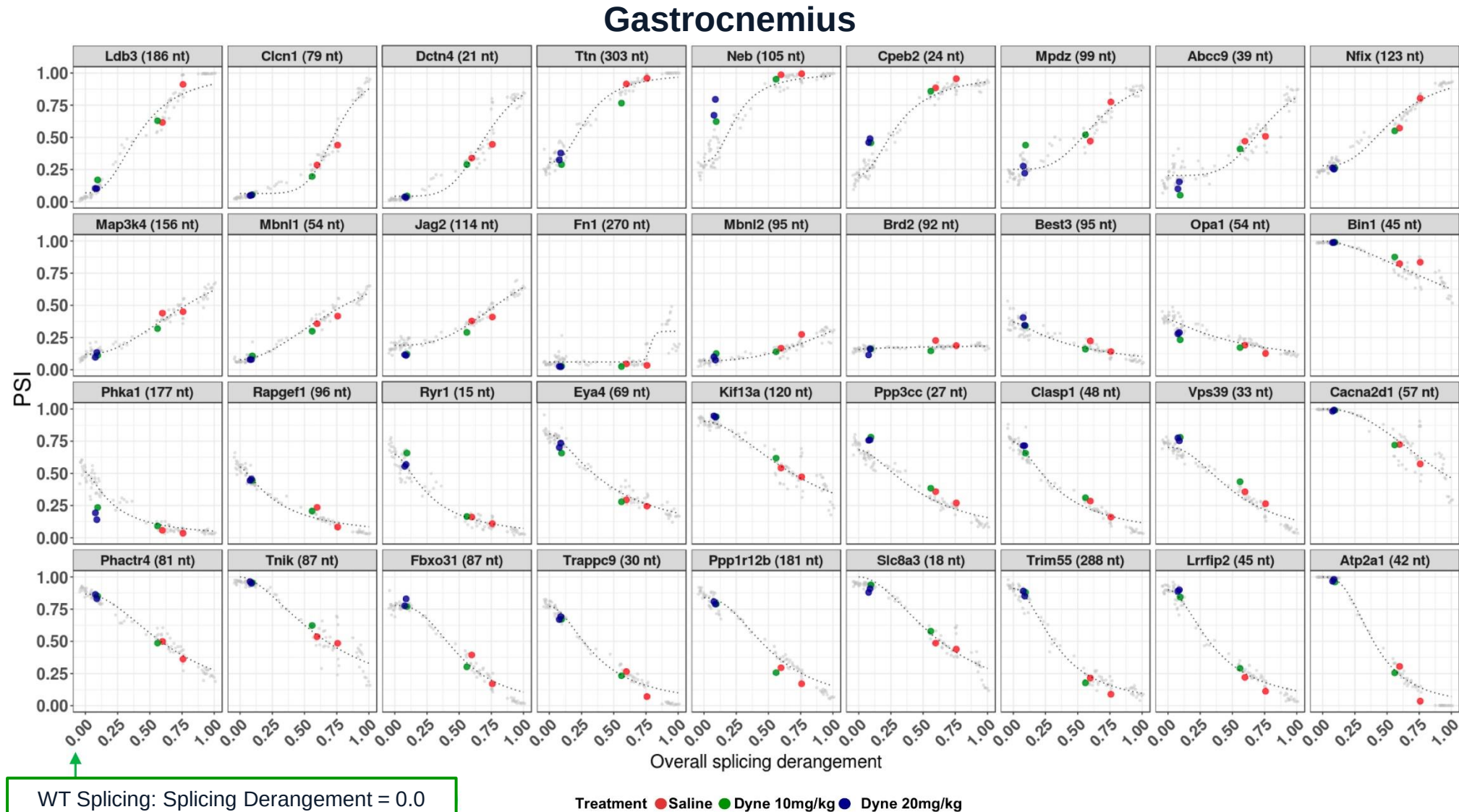
Splicing Correction in Multiple Muscles



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

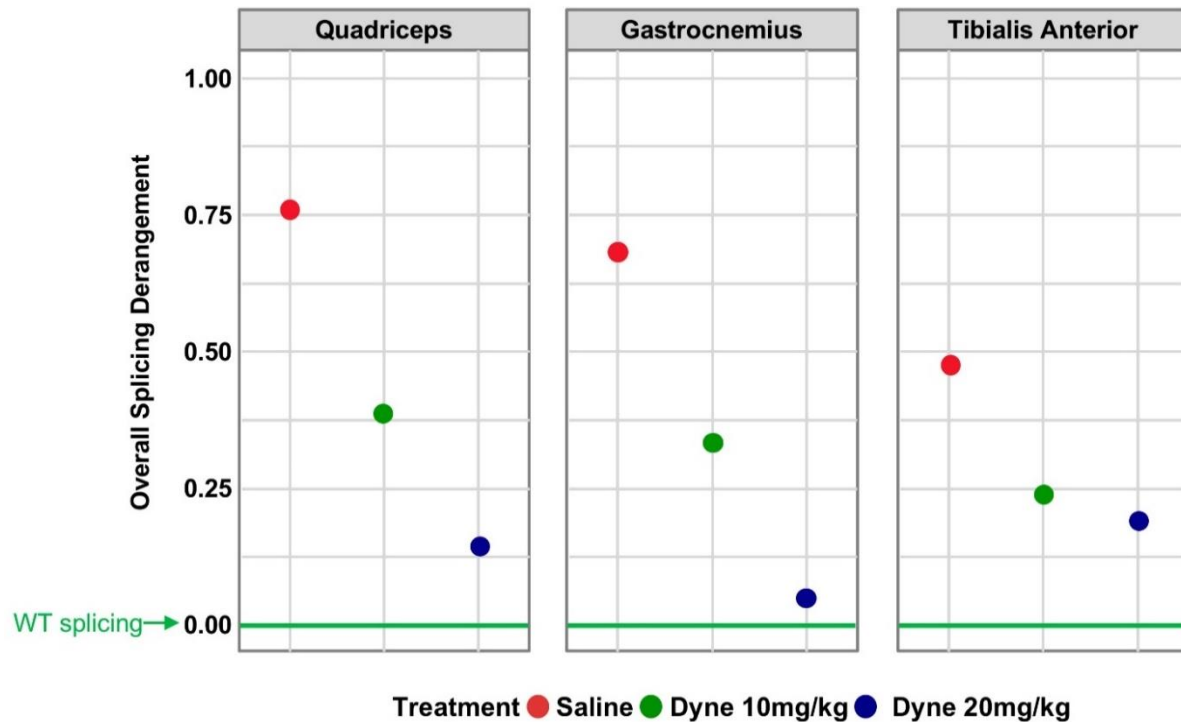


FORCE Dose-Dependently Corrected Splicing in Multiple RNAs in HSA^{LR} DM1 Mouse Model After a Single Dose

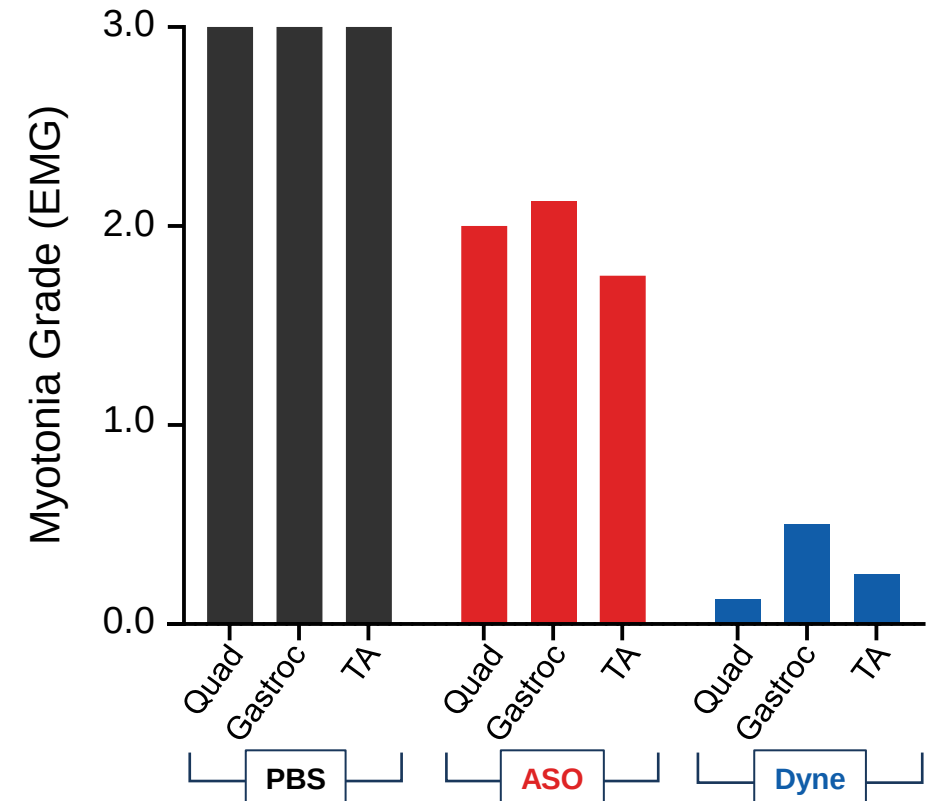


FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

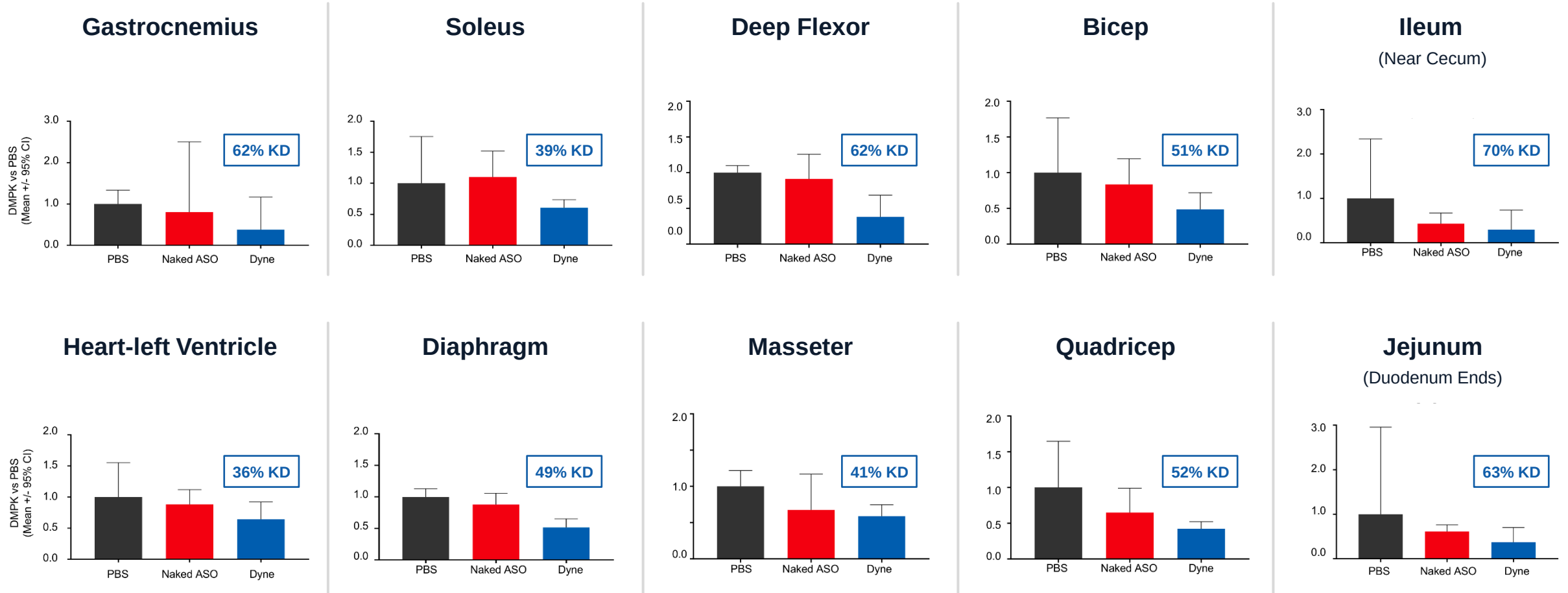
Splicing Correction in Multiple Muscles



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

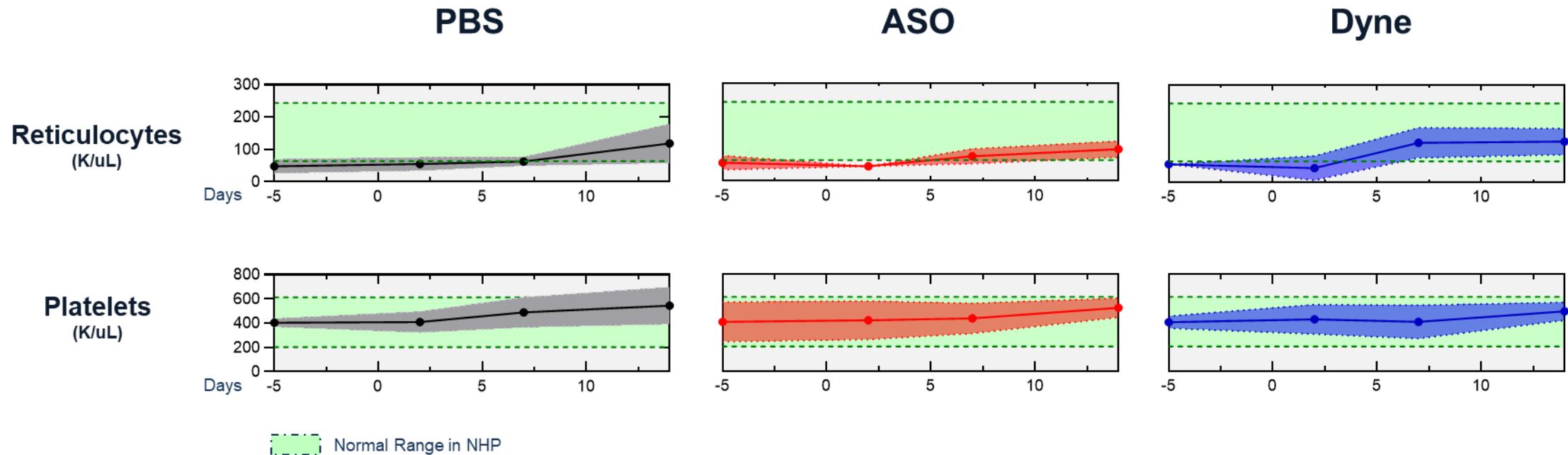


FORCE Achieved Enhanced Distribution and WT *DMPK* KD Across NHP Skeletal, Cardiac and Smooth Muscles



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

FORCE Well-Tolerated in Single Dose NHP Study



All CBC measures, including iron homeostasis and platelet counts, within normal range
Kidney and liver function, including ALT, AST, and BUN:Creatinine ratio, within normal range

Program



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hTfR1/DMSXL Model Data
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Perspectives on DM1 and targeting the genetic basis of the disease
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Discussion and Q&A

hTfR1/DMSXL Studies Focused on Pharmacokinetics and Pharmacodynamics

hTfR1/DMSXL is a PK/PD model

Uptakes human TfR1
targeting Fabs

Expresses
human toxic *DMPK*



hTfR1



DMSXL



hTfR1/DMSXL

(CUG) ~1,000



5' — Human *DMPK* mRNA — 3'

- Enables measurement of human toxic nuclear *DMPK* KD

NHPs are a PK and tolerability model

Cytoplasmic normal *DMPK*

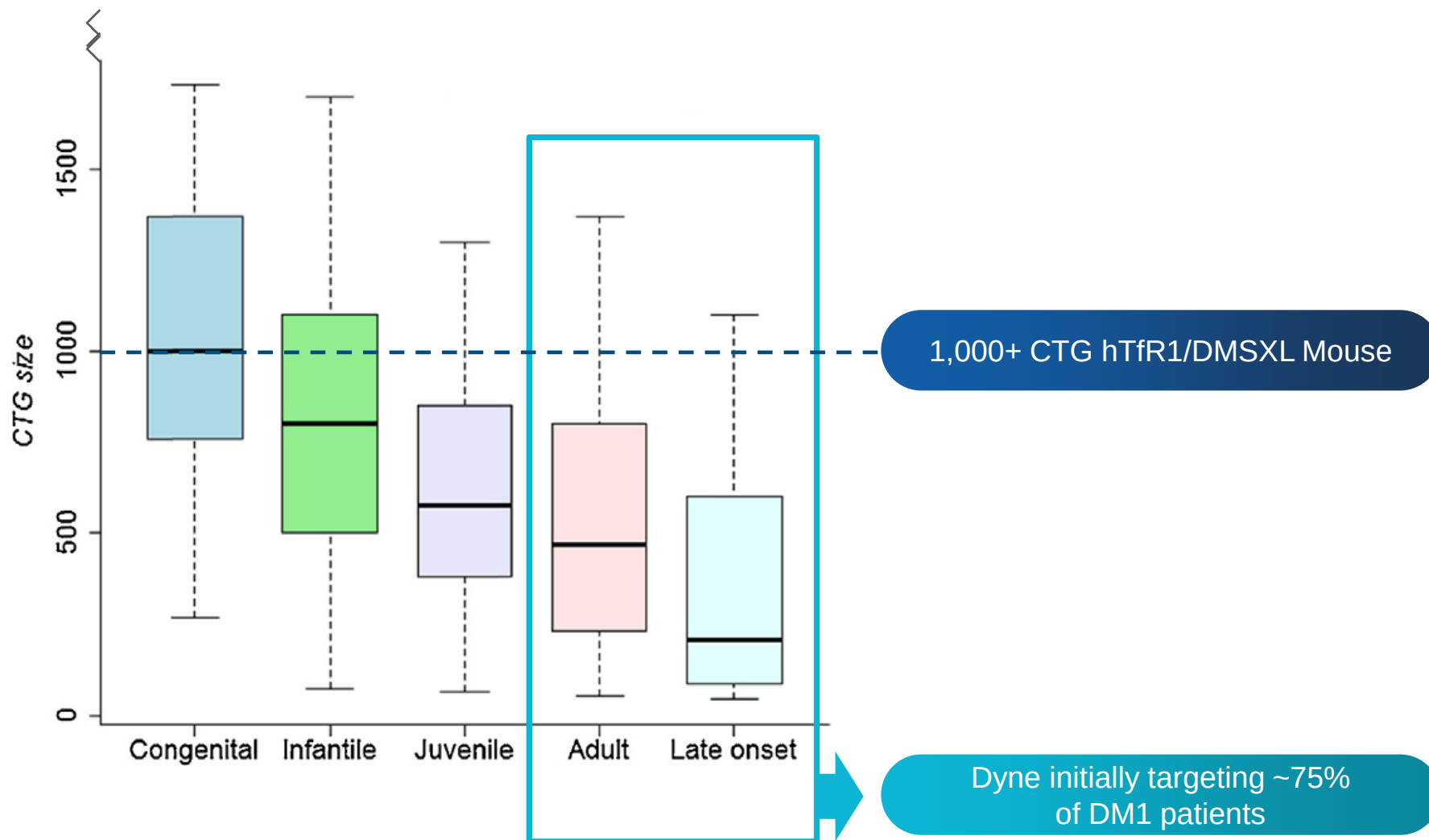


Cyno NHP

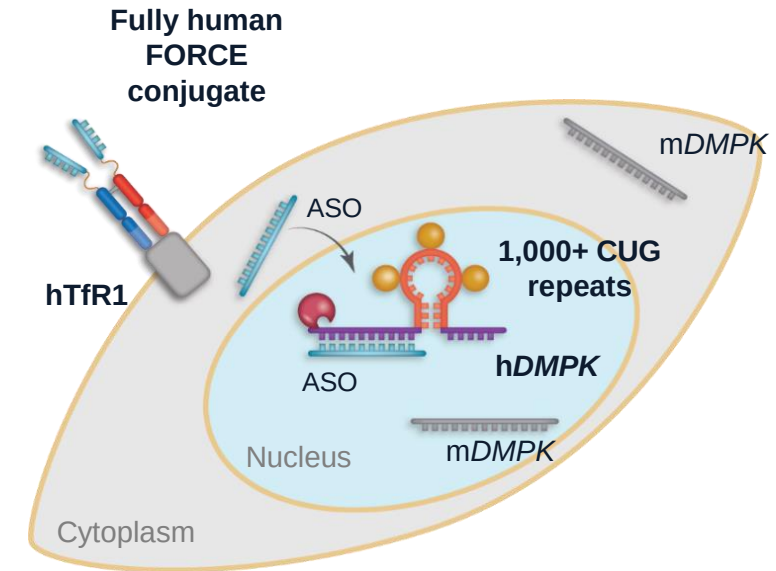
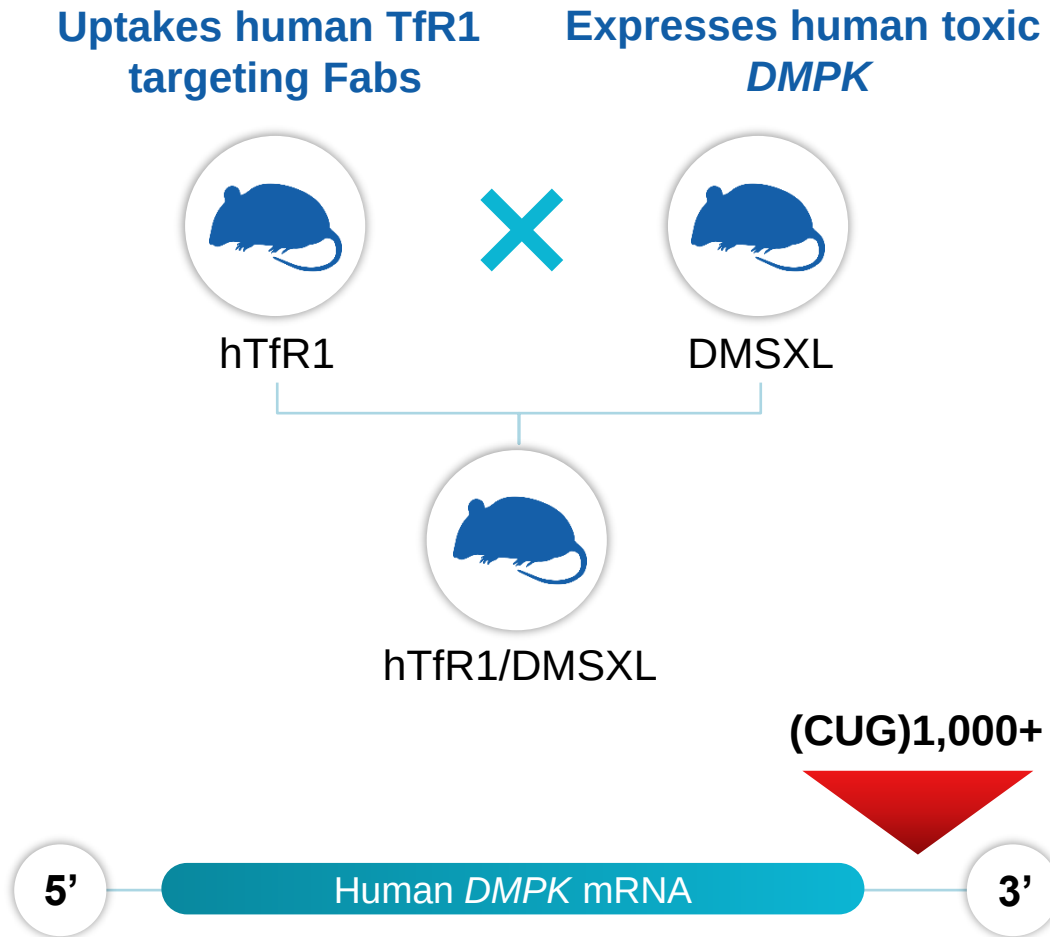
5' — Cyno *DMPK* mRNA — 3'

- Allows measurement of normal cytoplasmic *DMPK* KD

FORCE Evaluated in hTfR1/DMSXL Mouse Model with 1,000+ CTG Repeat Length Representing Severe DM1 Phenotype

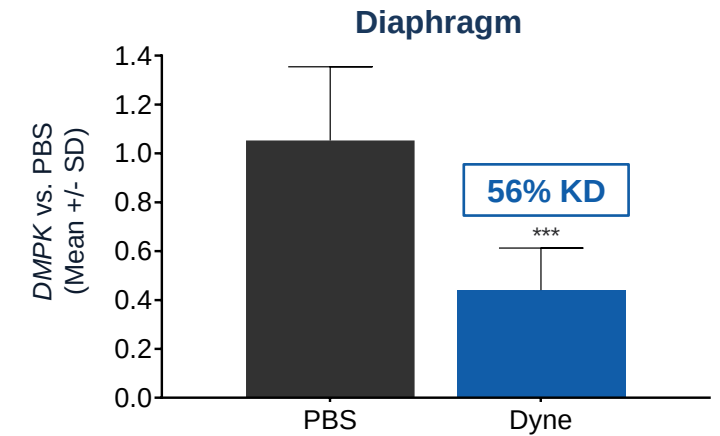
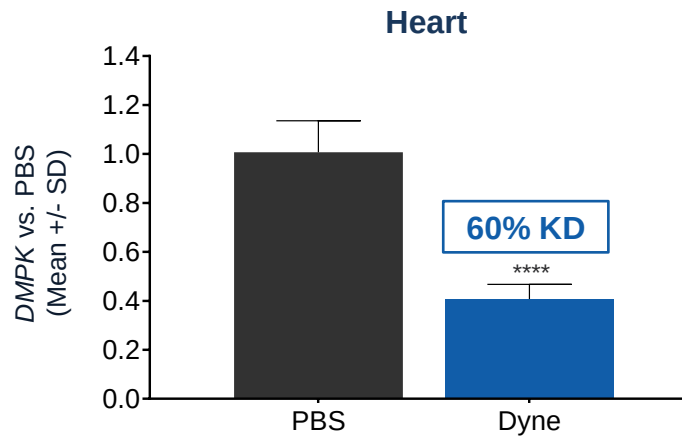
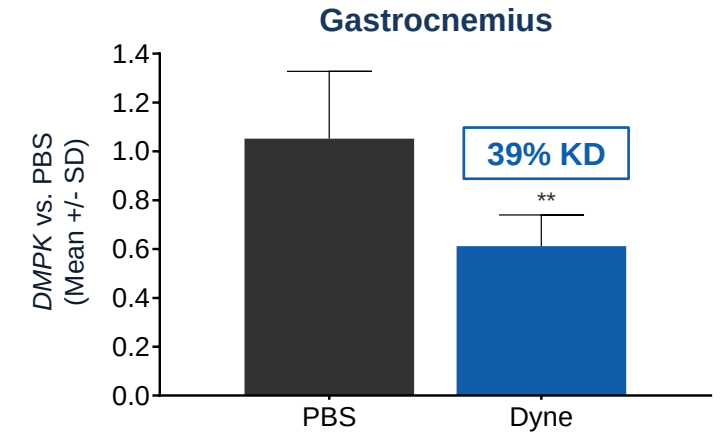
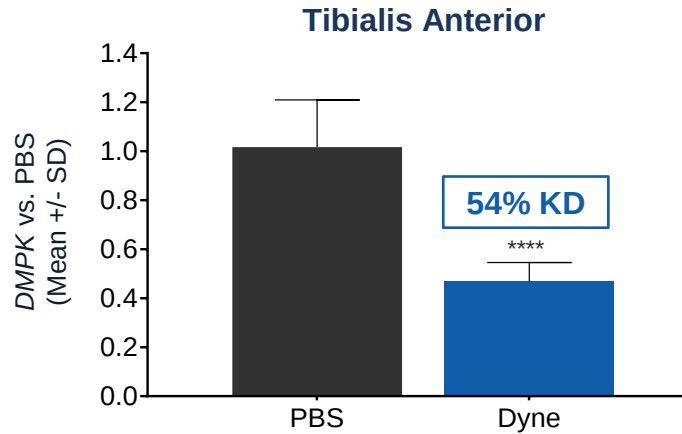
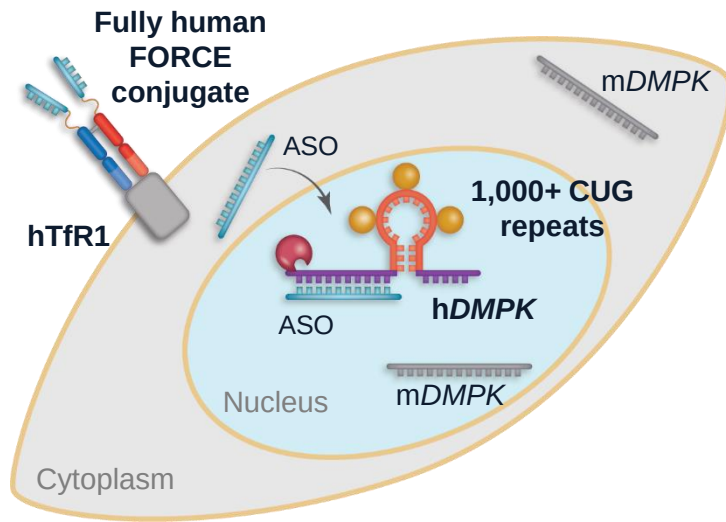


hTfR1/DMSXL: Innovative Model Developed by Dyne to Evaluate Pharmacodynamics By Measuring Toxic Human Nuclear *DMPK* KD



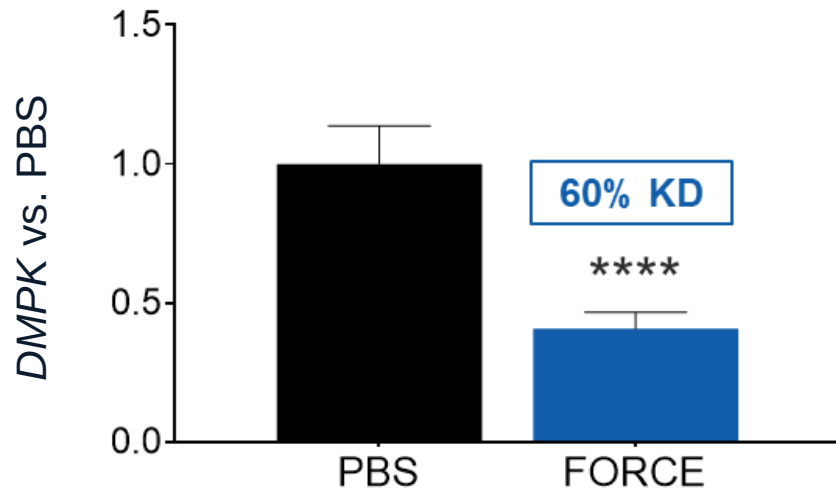
- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

Human FORCE Conjugate Demonstrated Robust Toxic Human *DMPK* KD in hTfR1/DMSXL Model

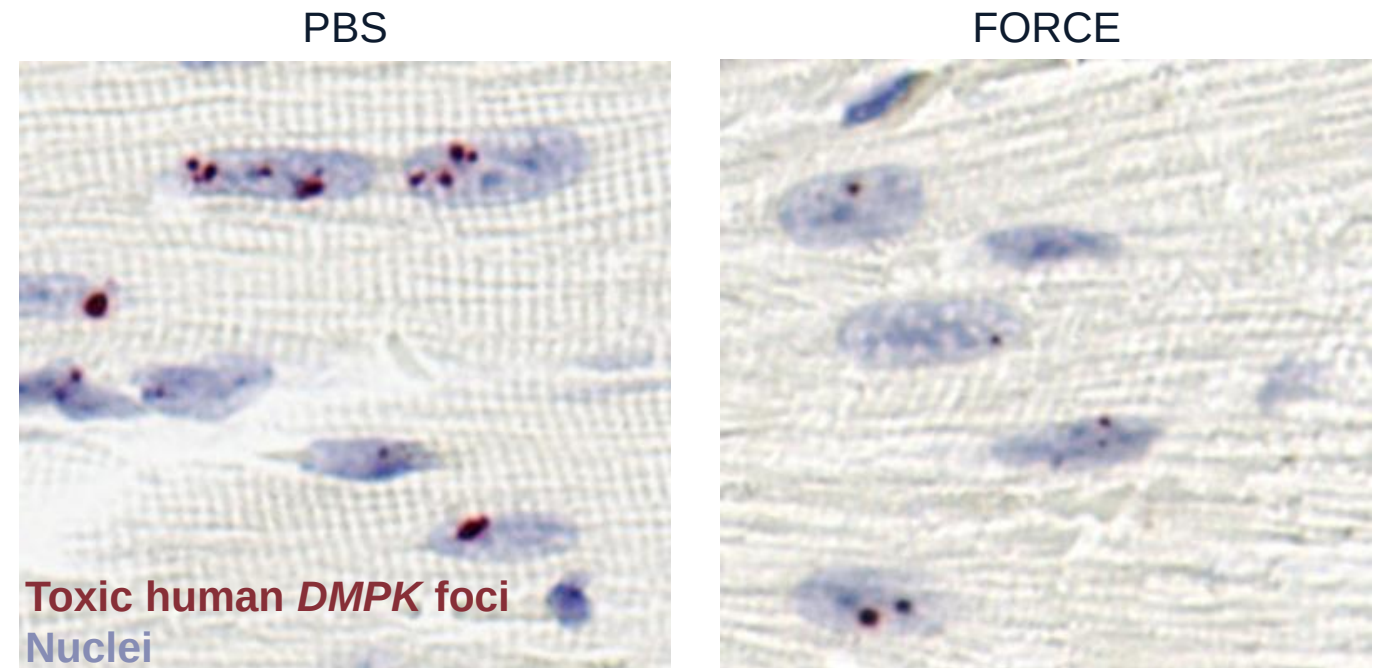


FORCE Conjugate Demonstrated Robust Toxic Human *DMPK* mRNA and Foci KD in the Heart in hTfR1/DMSXL Model

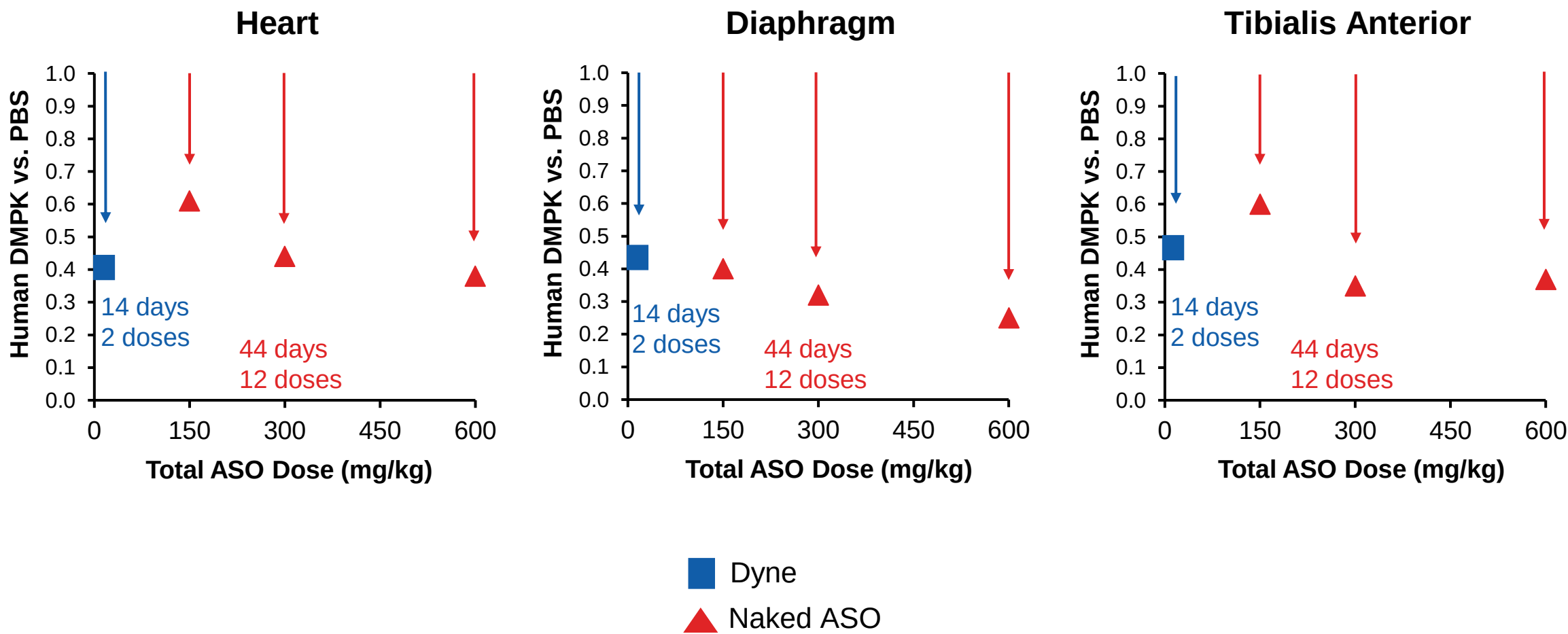
DMPK mRNA KD by qPCR



~40% Reduction in *DMPK* foci by *in situ* hybridization



Low Dose of FORCE Achieved Rapid Human Toxic *DMPK* KD While Naked ASO Required High Dose and Prolonged Exposure



Single Dose of FORCE Conjugate Achieved Sustained Human Toxic *DMPK* KD at Week 4 in hTfR1/DMSXL Model

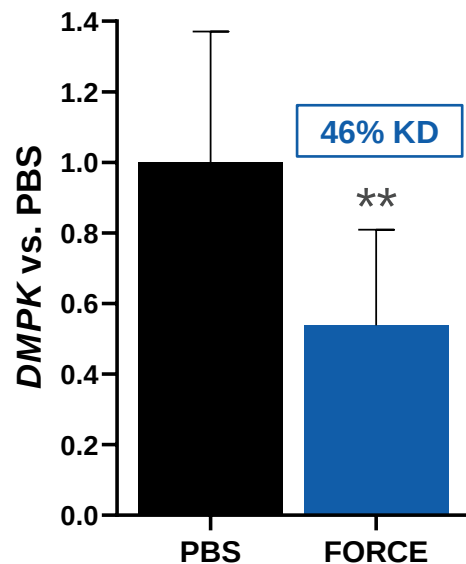


10 mg/kg

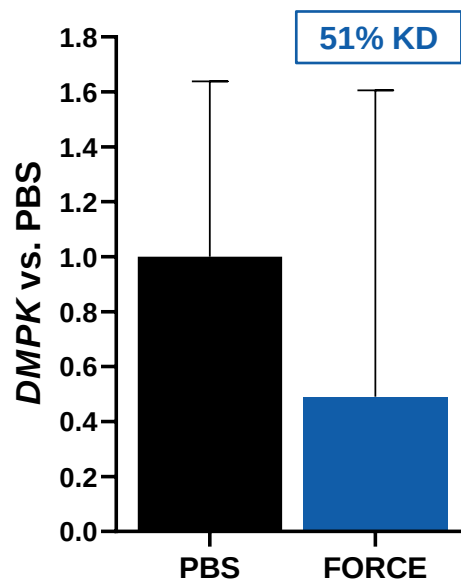
D0

Wk 4

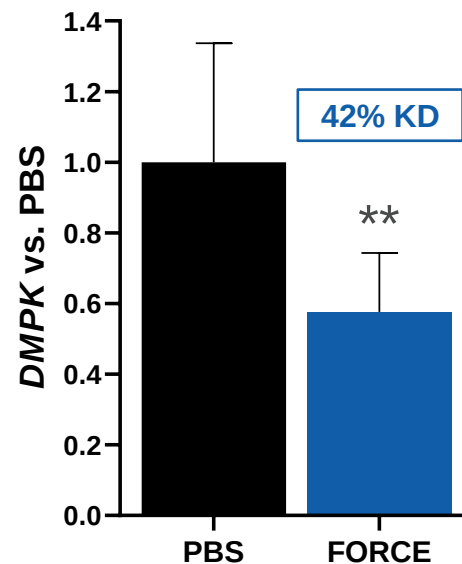
Heart



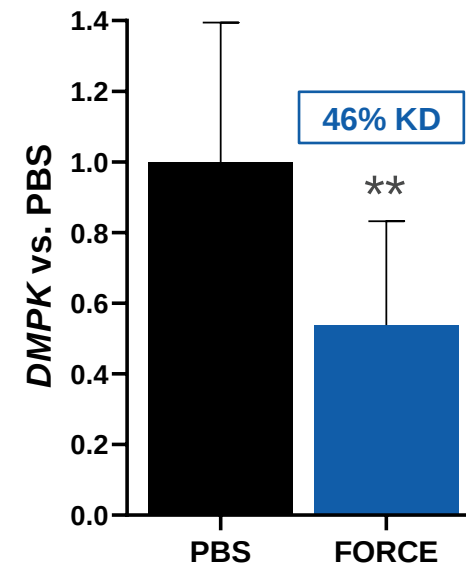
Diaphragm



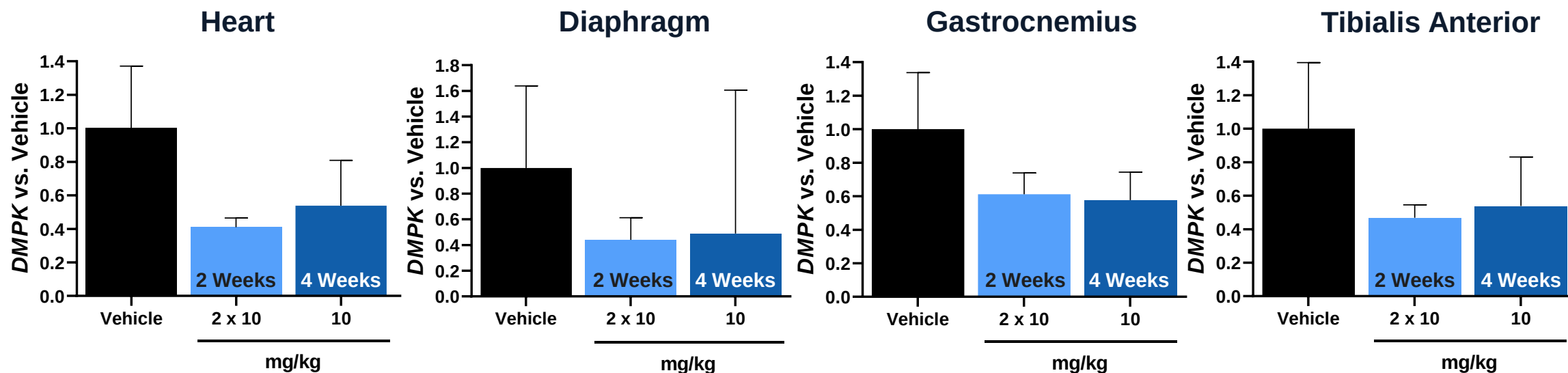
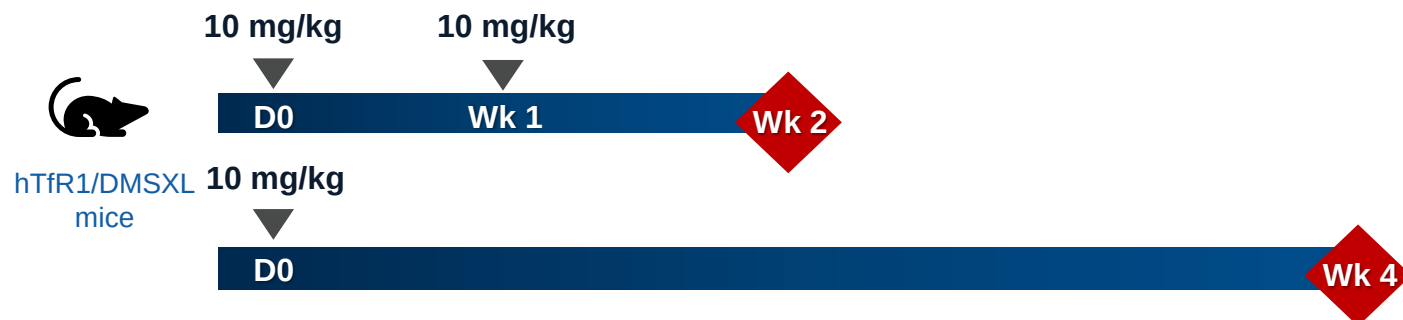
Gastrocnemius



Tibialis Anterior



Force Conjugate Achieved Sustained Human Toxic *DMPK* KD in hTfR1/DMSXL Model for Twice Duration with Half the Dose



DM1 Program Summary

Preclinical 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
- ✓ **Reversed** myotonia after a single dose
- ✓ **Delivered** *DMPK* targeting ASO to mouse and NHP muscle tissues
- ✓ **Enhanced** muscle distribution
- ✓ **Durable** *DMPK* RNA reductions up to 12 weeks

Potential Advantages

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

**One of three INDs planned
between Q4 2021 - Q4 2022**

Program



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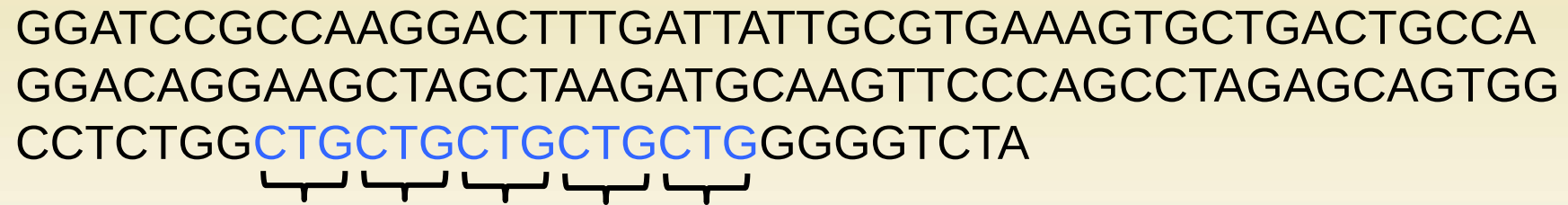
Discussion and Q&A

Impact of myotonic dystrophy

1. Dystrophy, myotonia
 2. Heart rhythm
 3. Central nervous system
 4. Other: gastrointestinal, cataract
- Progression is slow
 - Walking, use of hands, breathing, speech, swallowing
 - Historically, few drug development programs
 - Current treatment options are limited

Genetic code from section of myotonic dystrophy gene

GGATCCGCCAAGGACTTTGATTATTGCGTGAAAGTGCTGACTGCCA
GGACAGGAAGCTAGCTAAGATGCAAGTTCCCAGCCTAGAGCAGTGG
CCTCTGGCTGCTGCTGCTGCTGGGGGTCTA

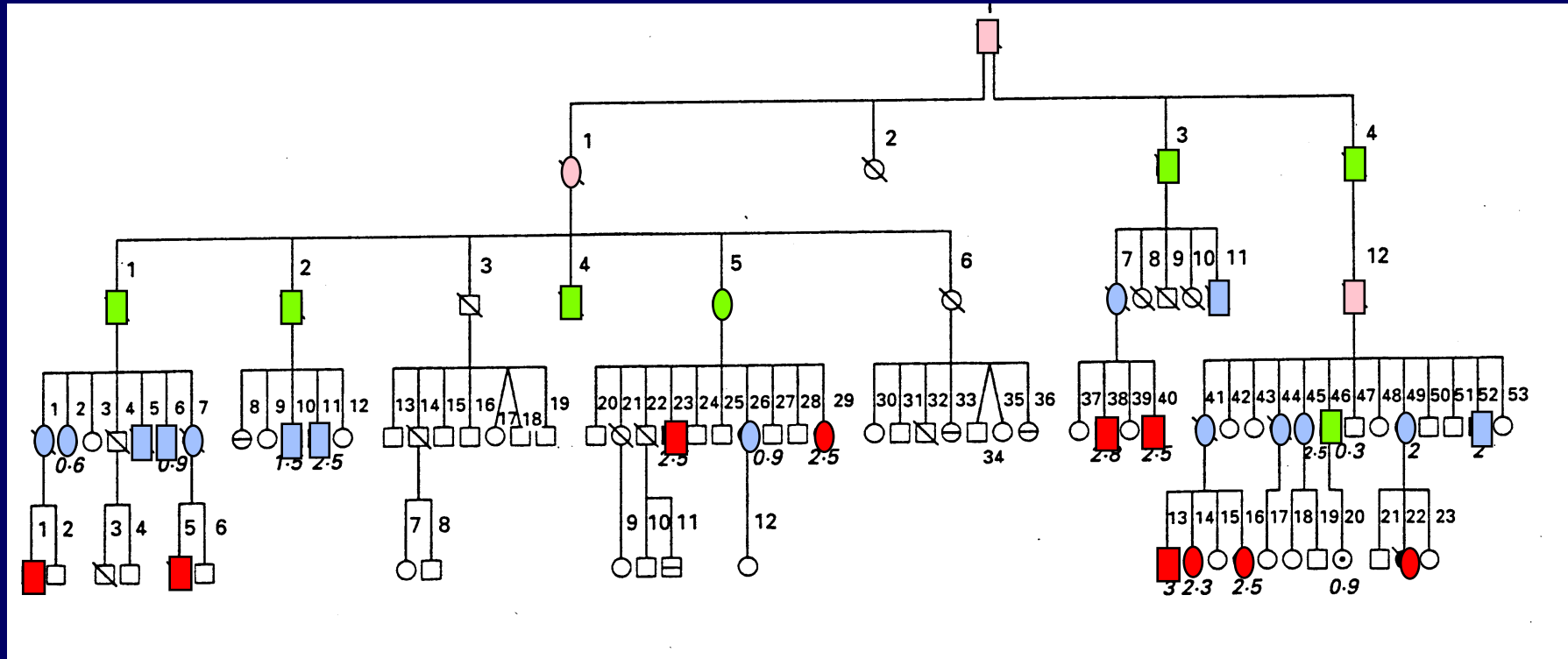


5 CTG repeats (normal)

[illegible]

200 CTG repeats

Impact on families



(Die-Smulders et al, 1994)

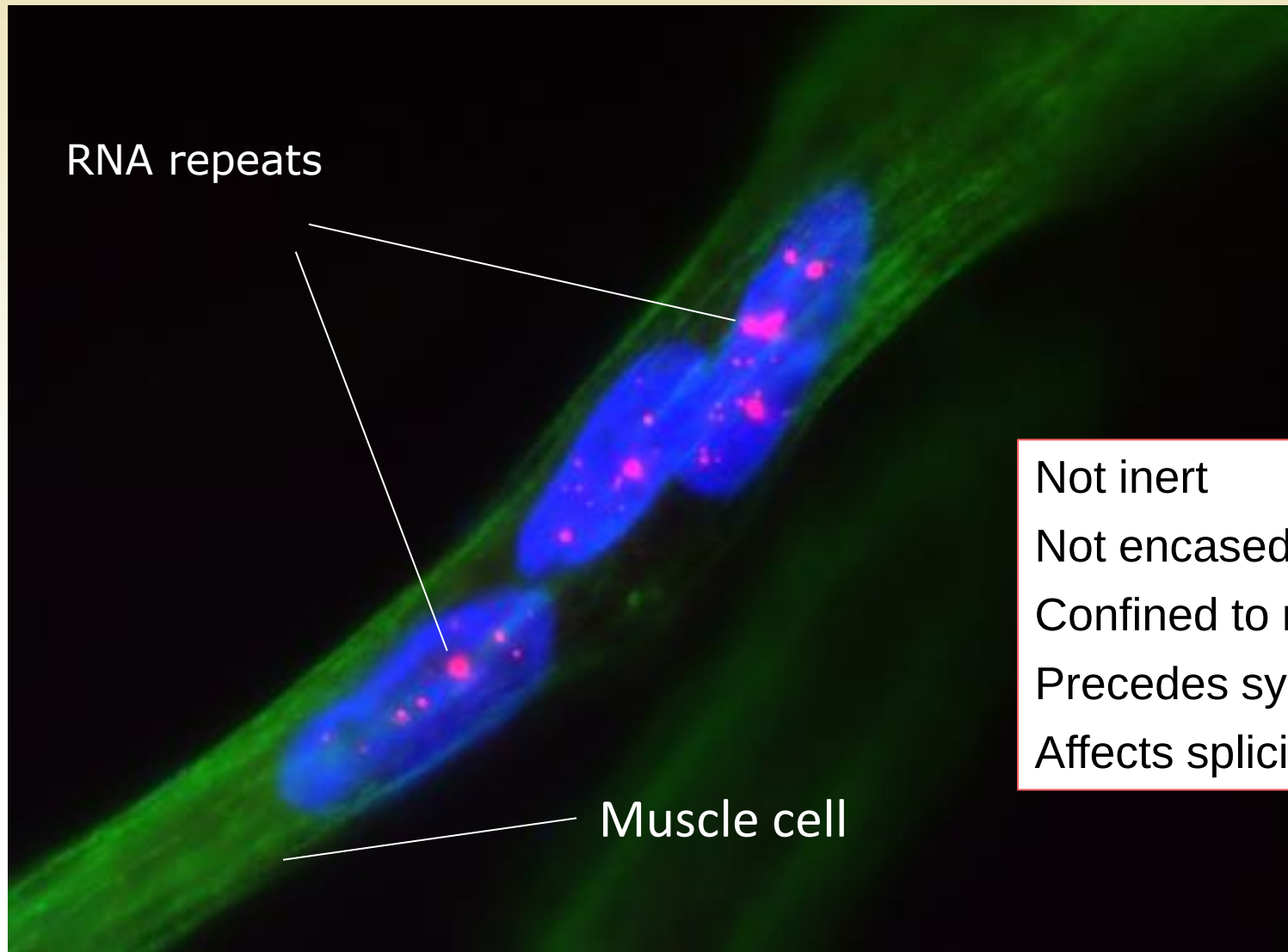
Scientific revelations #1 and #2

- Instability of repeats drives these remarkable differences in how people are affected
- RNA toxicity is the root cause

DNA repeats

RNA repeats

“RNA toxicity”



Not inert
Not encased
Confined to nucleus
Precedes symptoms
Affects splicing

A hopeful moment

- For the first time, a proven molecular target for treatment
- RNA toxicity: ideal scenario for oligonucleotide therapeutics
- In animal models, can achieve powerful effects
- Can the delivery hurdle be overcome in people?
- How will the disease respond?
- Extraordinary opportunity to carry out trials that answer questions
- Patient and research community is energized

Program



Opening remarks
Joshua Brumm, President & CEO



FORCE™ platform and DM1 program
Romesh Subramanian, Ph.D., Chief Scientific Officer



hTfR1/DMSXL Model Data
Oxana Beskrovnaya, Ph.D., SVP, Head of Research



Perspectives on DM1 and targeting the genetic basis of the disease
Charles Thornton, M.D., Saunders Distinguished Professor of
Neuromuscular Research at the University of Rochester

Discussion and Q&A



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