Splice Correction and Reduction of Toxic *DMPK* RNA *In Vitro* and *In Vivo* Utilizing Novel Antibody Targeted Antisense Oligonucleotides

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ASGCT ANNUAL MEETING | MAY 14, 2021

Joachim, *living with DM1*

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OUR MISSION

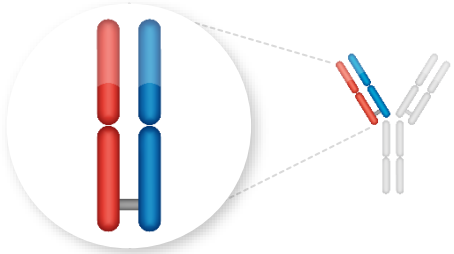
Life-transforming therapies

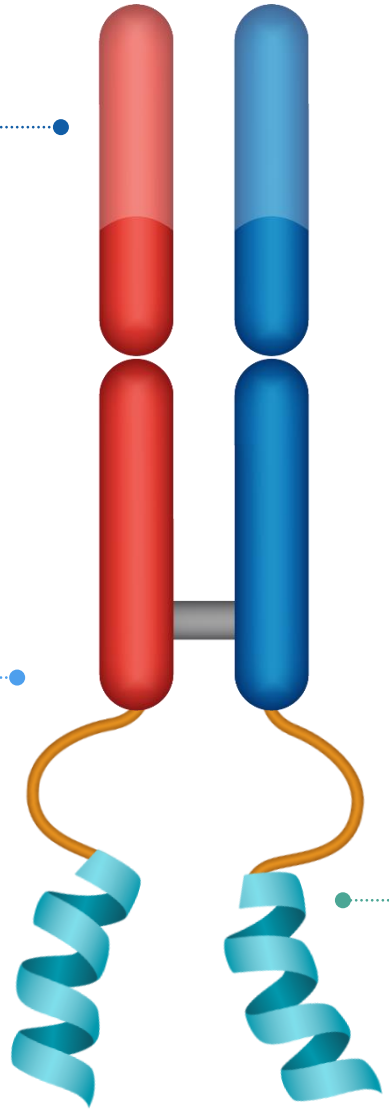
for patients with serious muscle diseases

Dyne FORCE Platform: Modern Oligo Therapeutics for Muscle Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



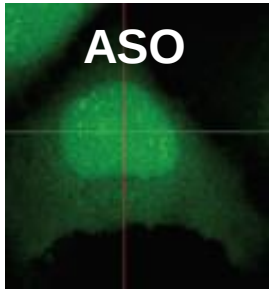


LINKER

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 et al: NAR , 2006, v.34, p.1369

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**			

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

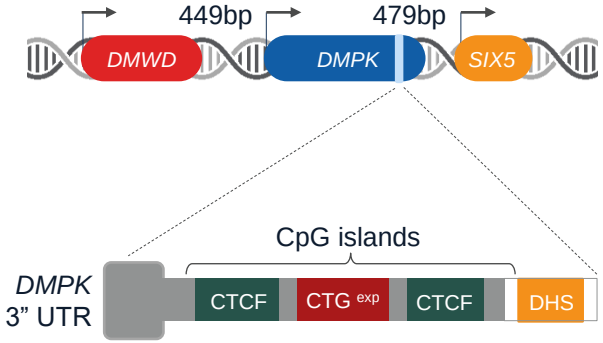
OUR APPROACH

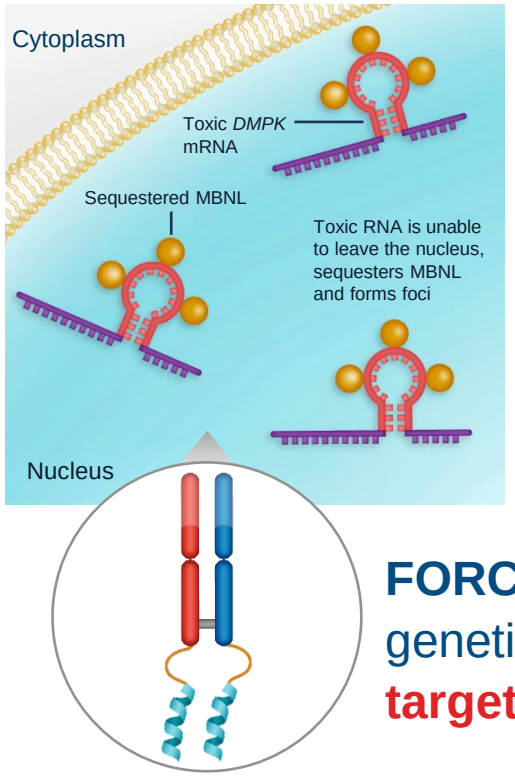
Disease-Modifying Nuclear *DMPK* Knockdown

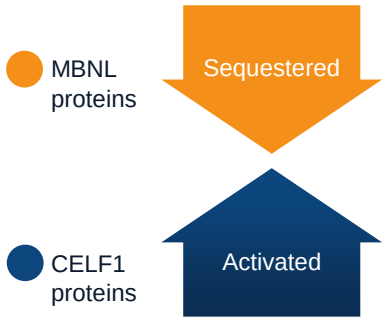
Targeting toxic gain of function *DMPK* RNA to potentially **stop or reverse** disease progression

FORCE Targets the Genetic Basis of DM1

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





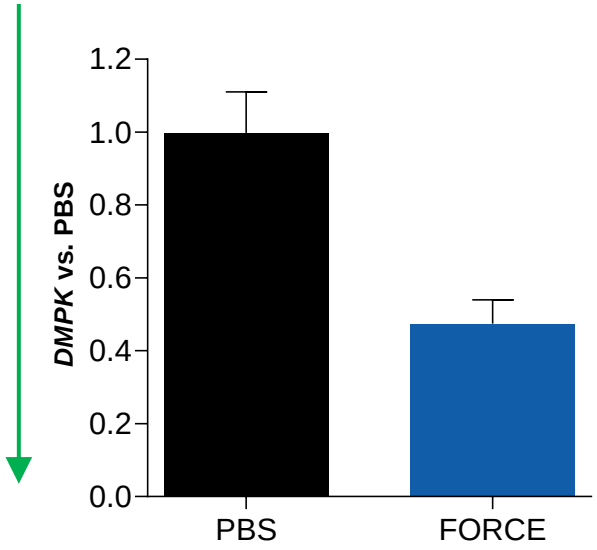


- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

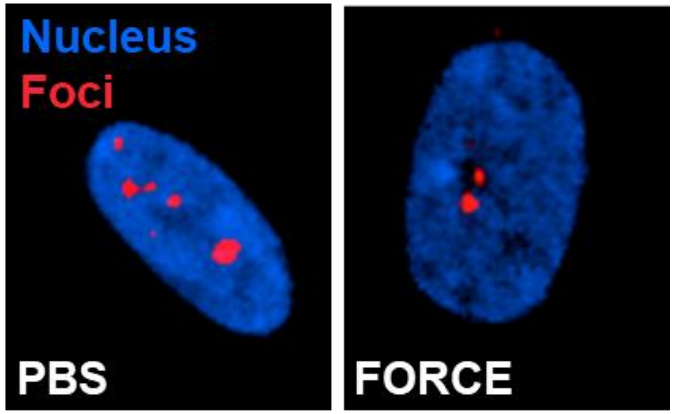
FORCE designed to address the genetic basis of disease by **targeting toxic nuclear *DMPK* RNA**

2,600 CTG Repeats DM1 Myoblasts: FORCE Demonstrated Robust *DMPK* KD, Foci Reduction, and Splice Correction

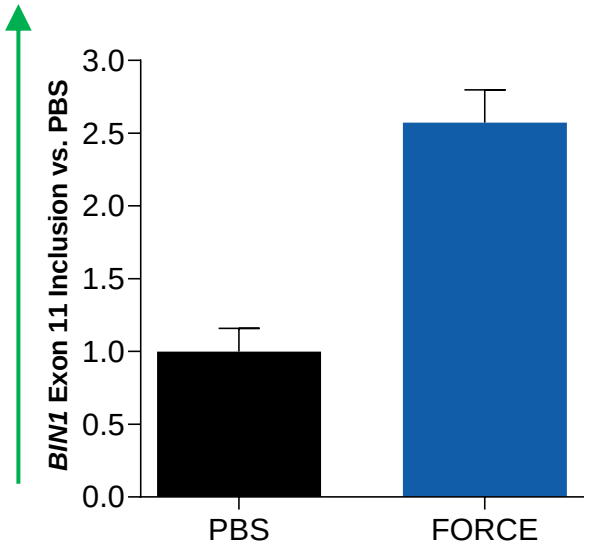
***DMPK* mRNA KD by qPCR**



DMPK foci reduction by FISH



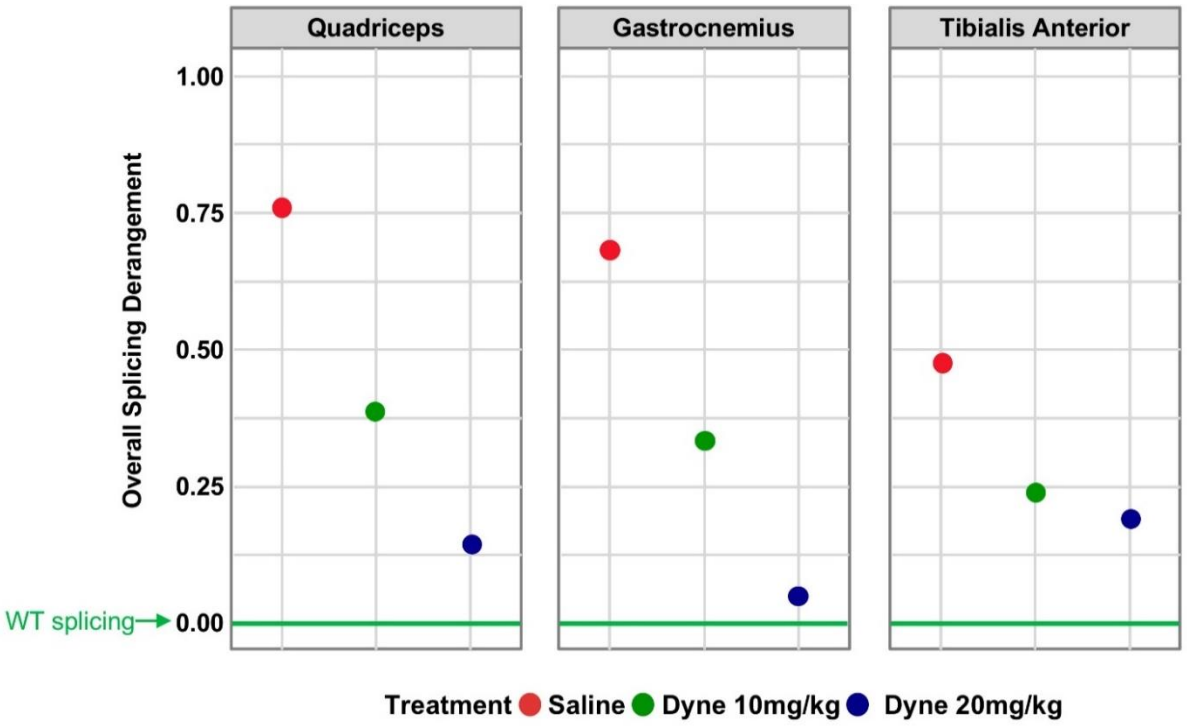
***BIN1* splice correction by qPCR**



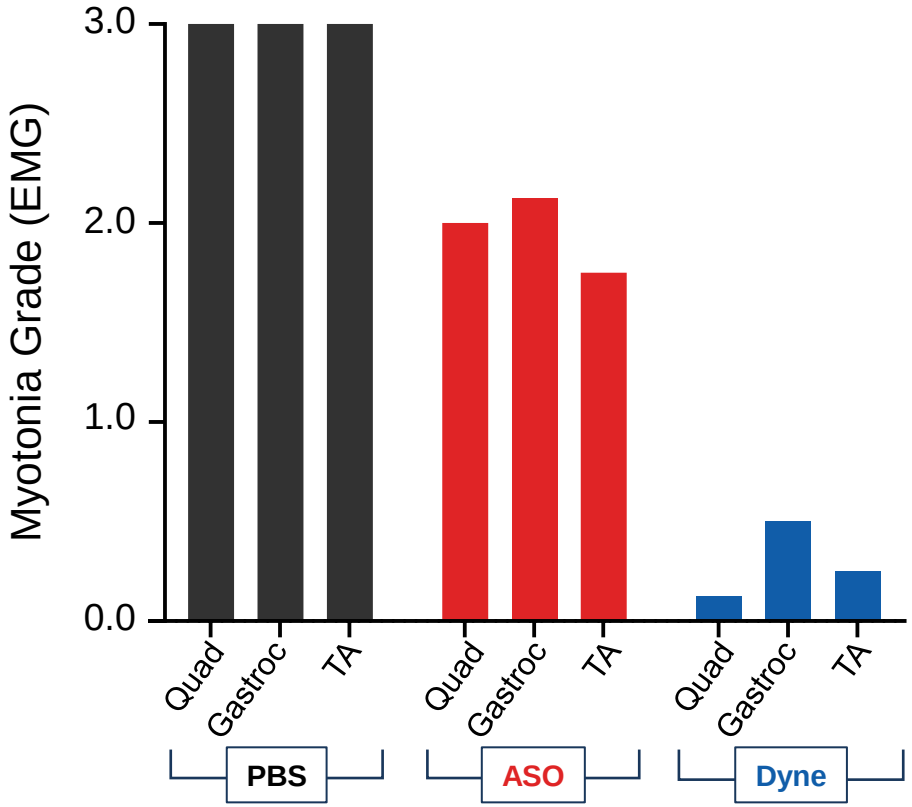
Note: Data are mean ±SD, n=4; FORCE ASO dose=500nM

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

Splicing Correction in Multiple Muscles

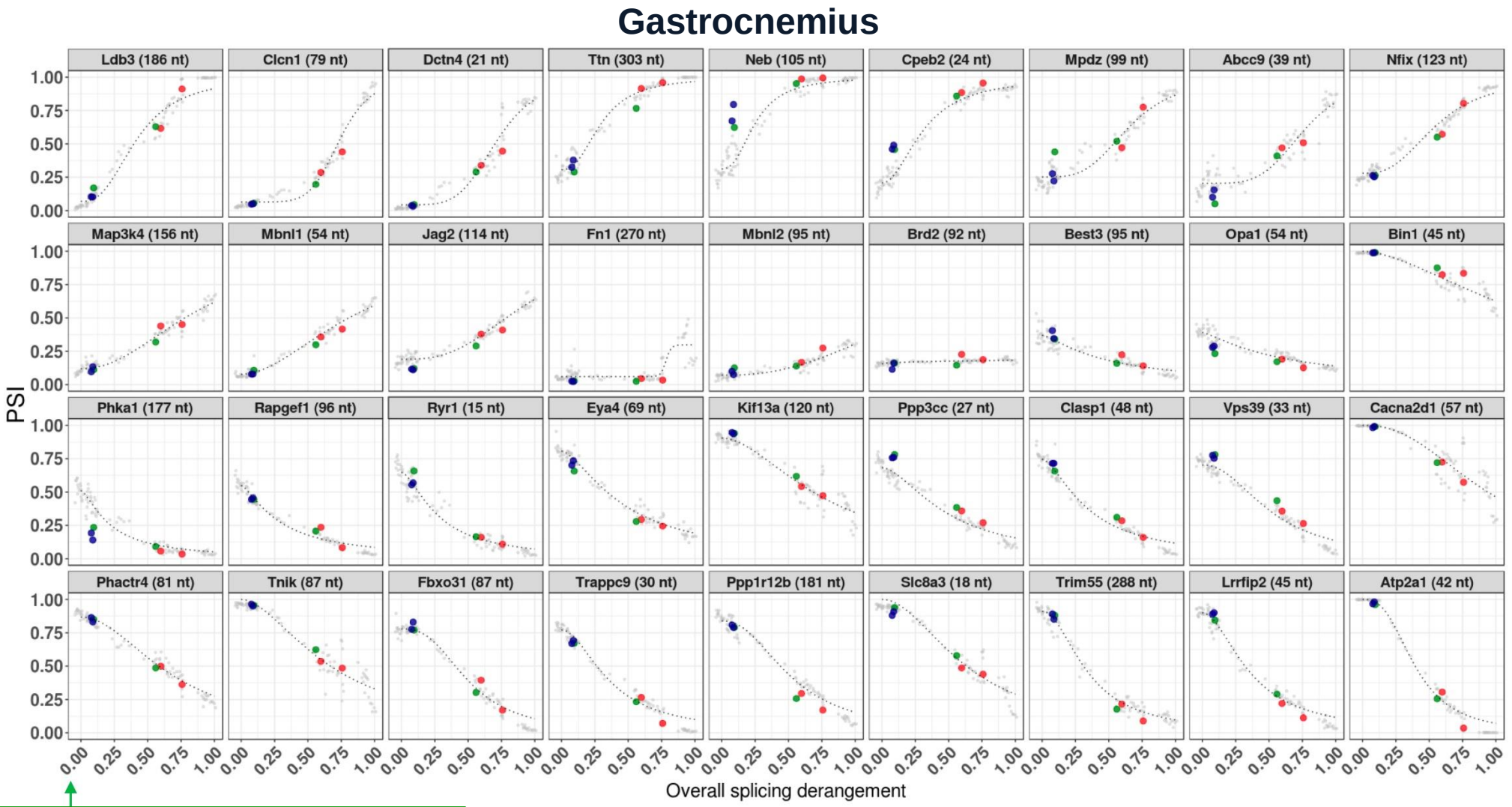


Near Complete Myotonia Reversal Within 14 Days After a Single Low Dose



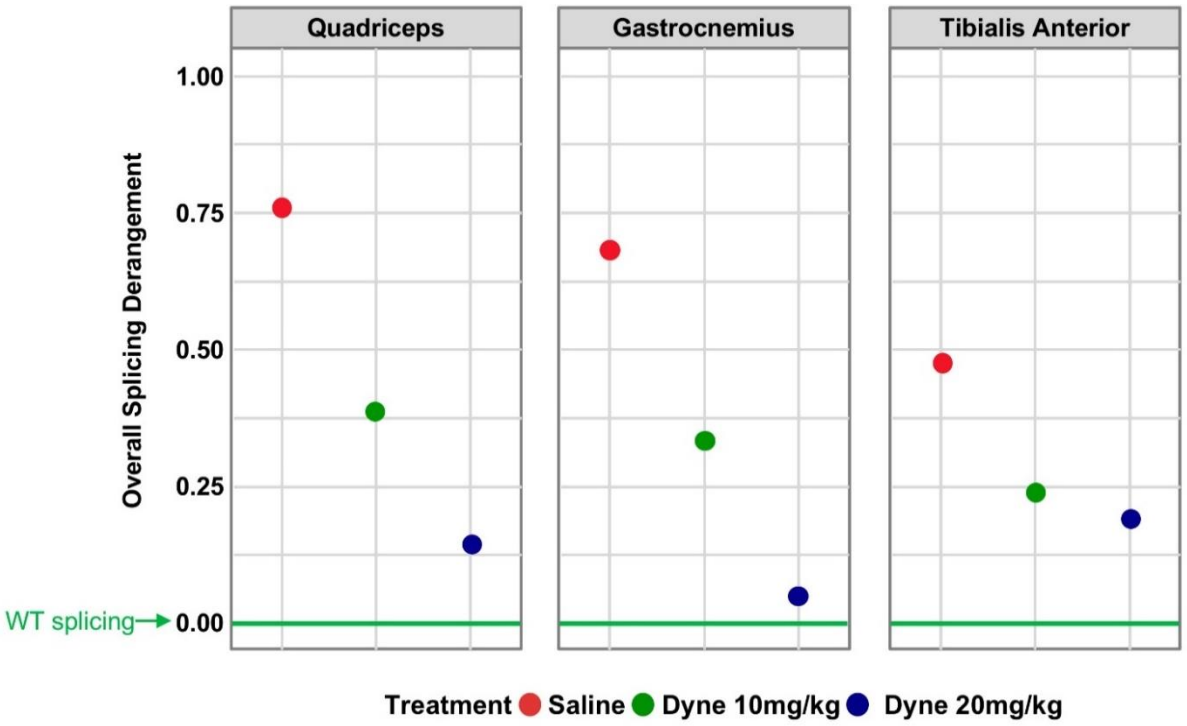
Note: HSA^{LR} mice, single dose 14-day study. Overall splicing derangement indexed to WT level of 0.00. EMG myotonic discharges were graded by a blinded examiner on a 4-point scale: 0, no myotonia; 1, occasional myotonic discharge in less than 50% of needle insertions; 2, myotonic discharge in greater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

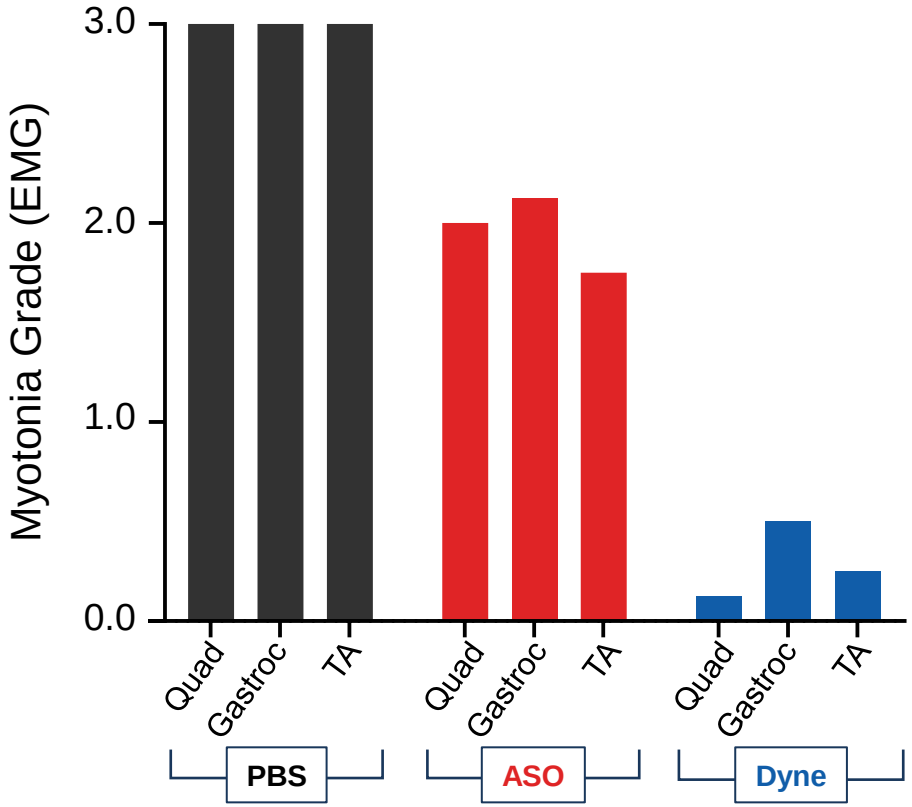


FORCE Dose-Dependently Corrected Splicing and Reversed Myotonia in the HSA^{LR} DM1 Mouse Model

Splicing Correction in Multiple Muscles



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



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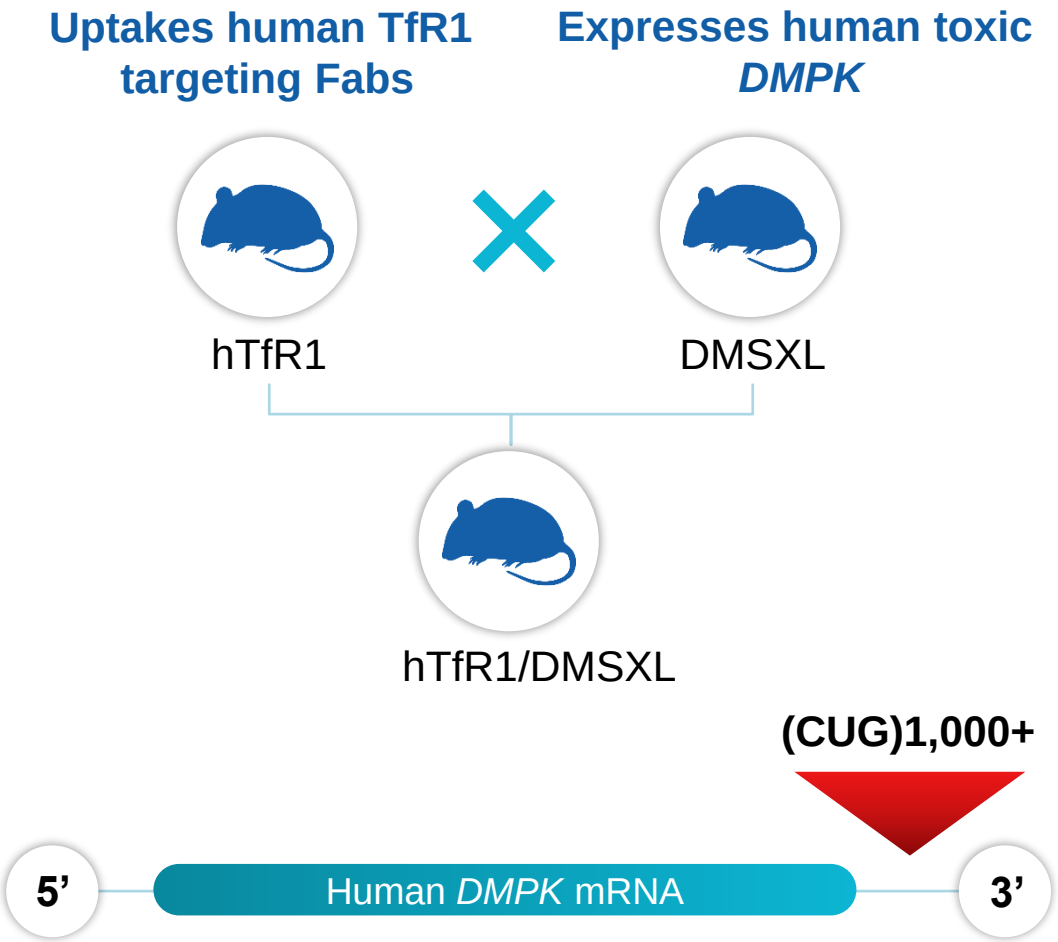
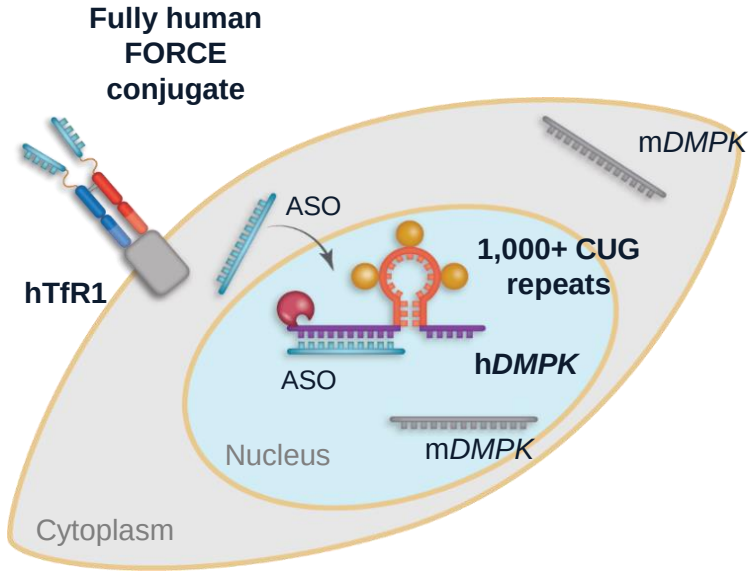
hTfR1/DMSXL: Innovative Model Developed by Dyne to Evaluate Pharmacodynamics By Measuring Toxic Human Nuclear *DMPK* KD

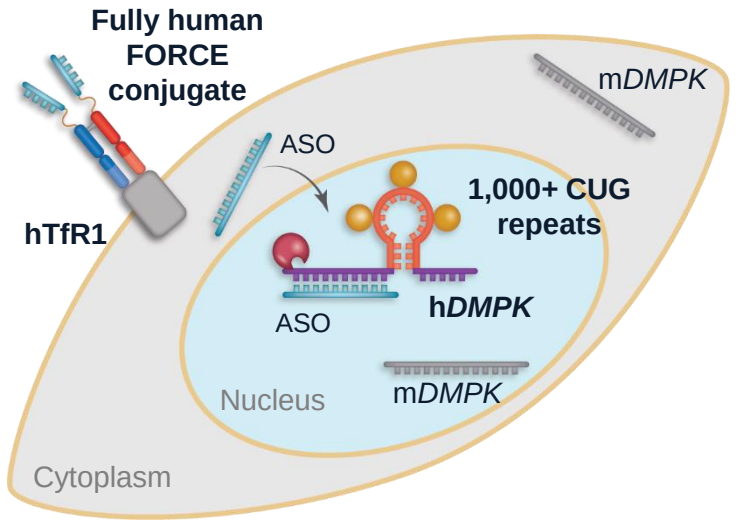


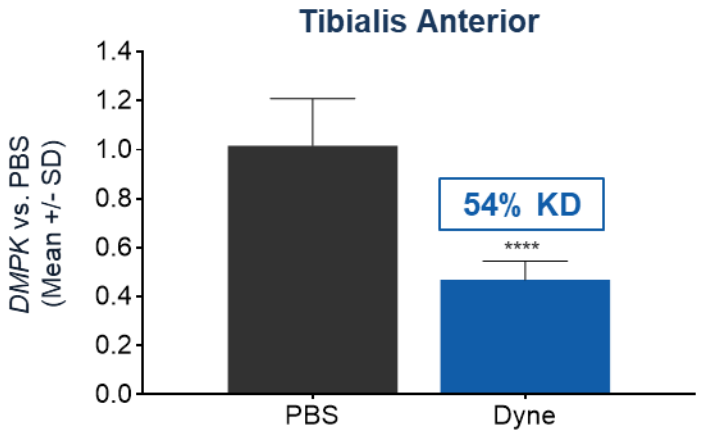


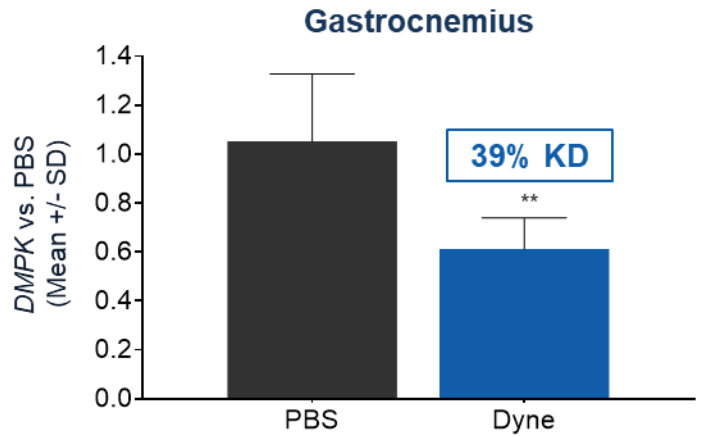
- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

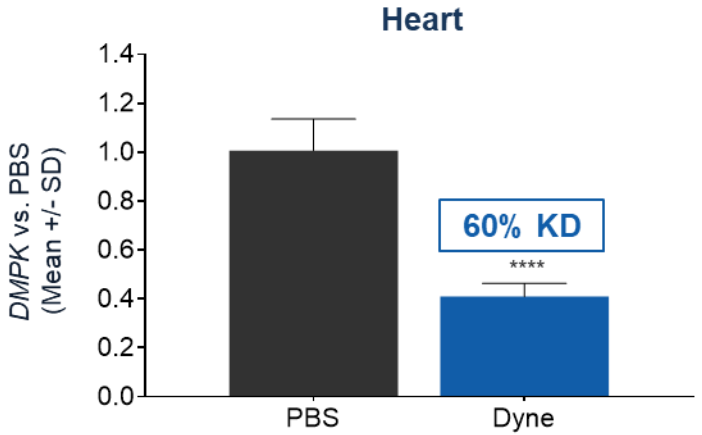
Note: DMSXL mice first described in PLOS Genetics 2012, 8(11):e1003043

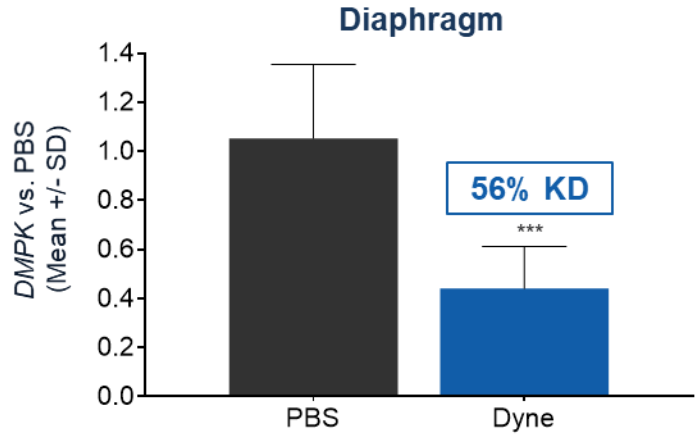
Dyne Lead Conjugate Demonstrated Robust Toxic Human *DMPK* KD in hTfR1/DMSXL Model







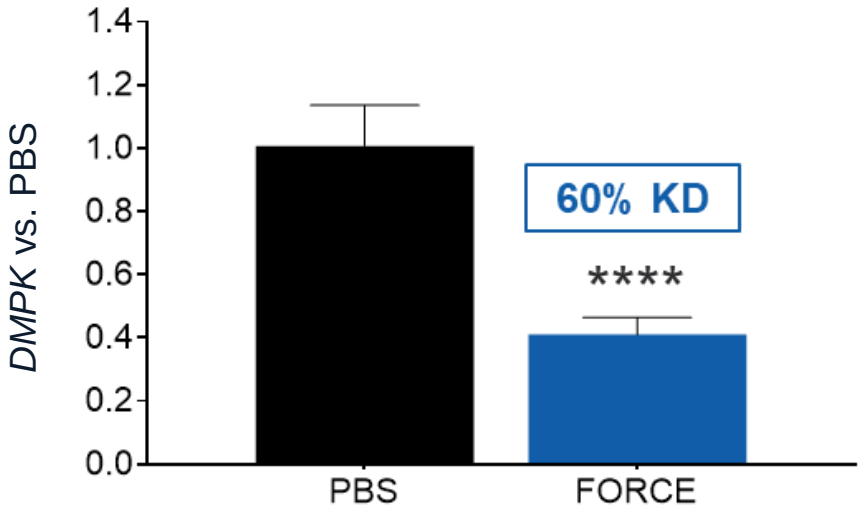




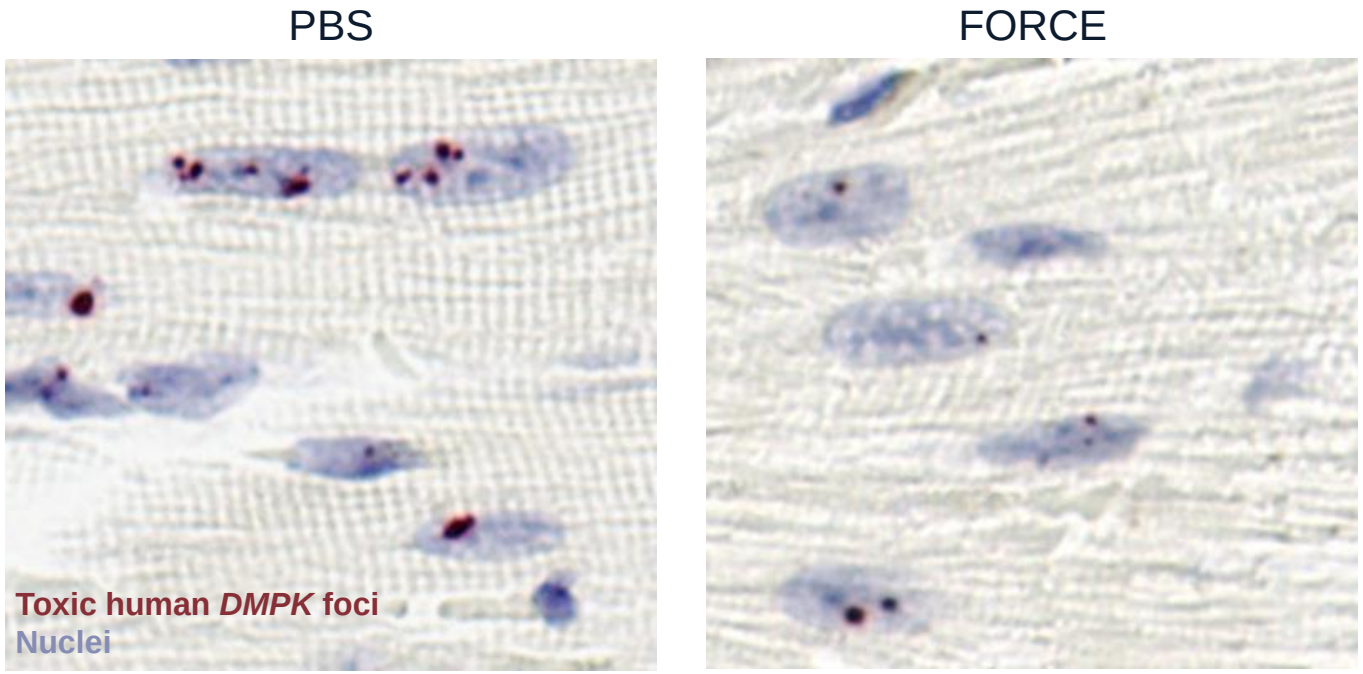
Note: 2 x 10 mg/kg, d0 and d7, analyzed d14; Data are mean ±SD; *p < 0.05, **p < 0.01,***p < 0.001, ****p < 0.0001, significant by ANOVA

FORCE Demonstrated Robust Foci Reduction in the Heart of hTfR1/DMSXL Mice

***DMPK* mRNA KD by qPCR**



***DMPK* foci reduction by *in situ* hybridization**

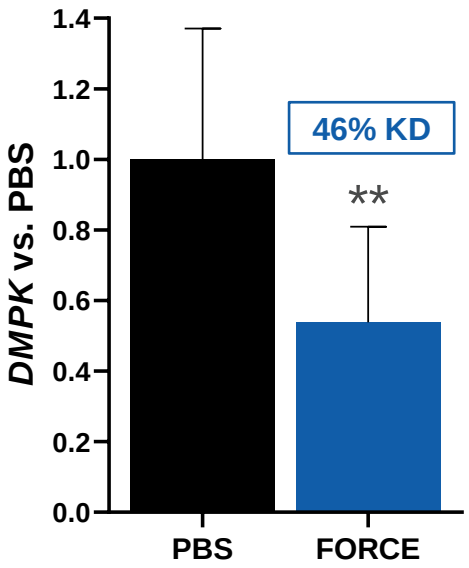


Note: 10 mg/kg ASO d0 and d7, analyzed d14; data are mean ±SD; n = 6 – 9; ****$p < 0.0001$, significant by *t*-test

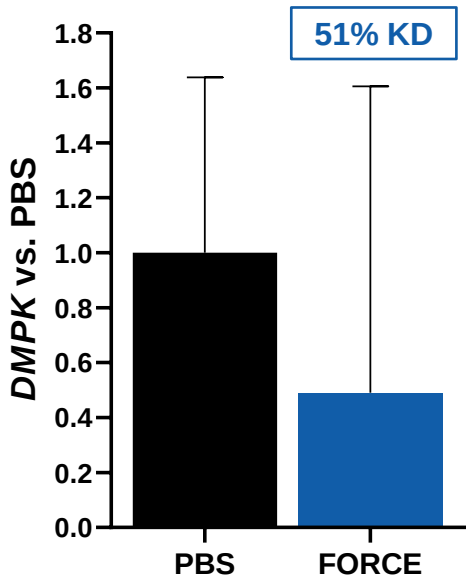
Single Dose of FORCE Conjugate Achieved Sustained Human Toxic *DMPK* KD at Week 4 in the hTfR1/DMSXL mouse

hTfR1/DMSXL mice

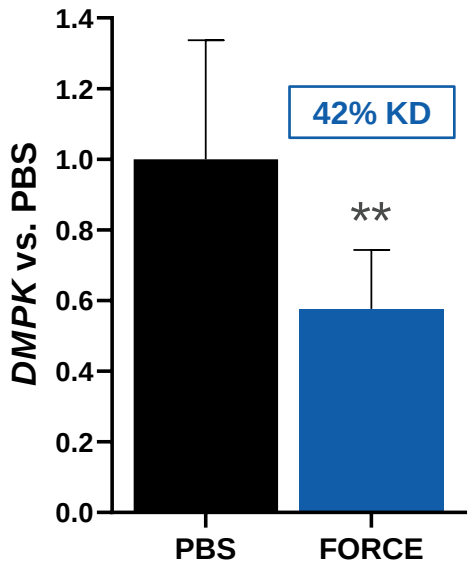
Heart



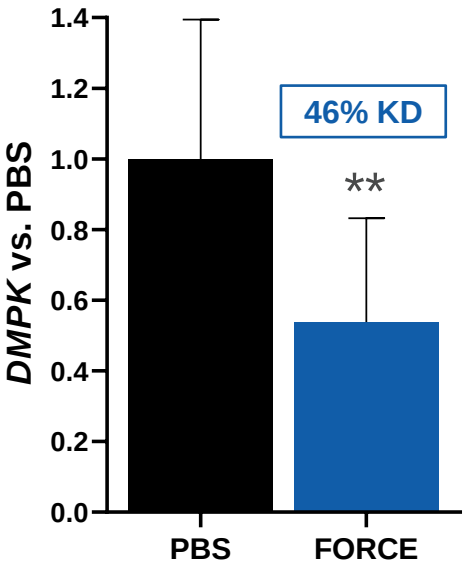
Diaphragm



Gastrocnemius

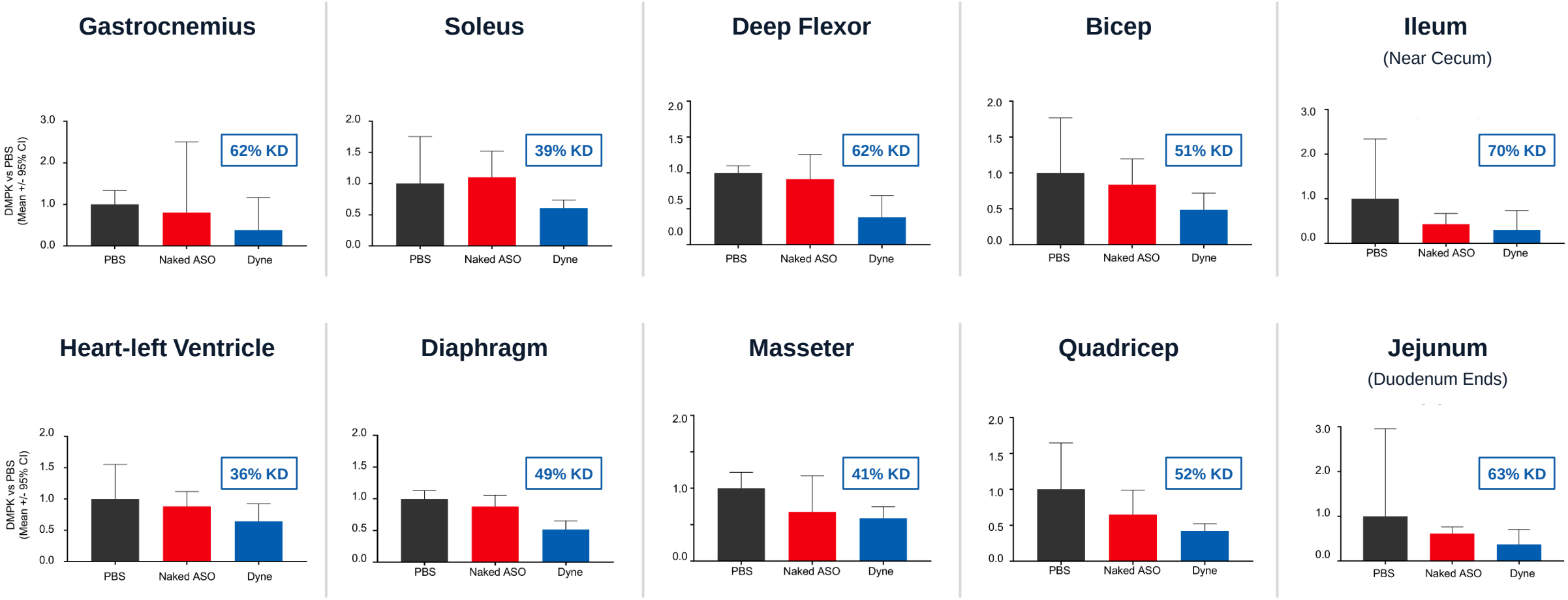


Tibialis Anterior



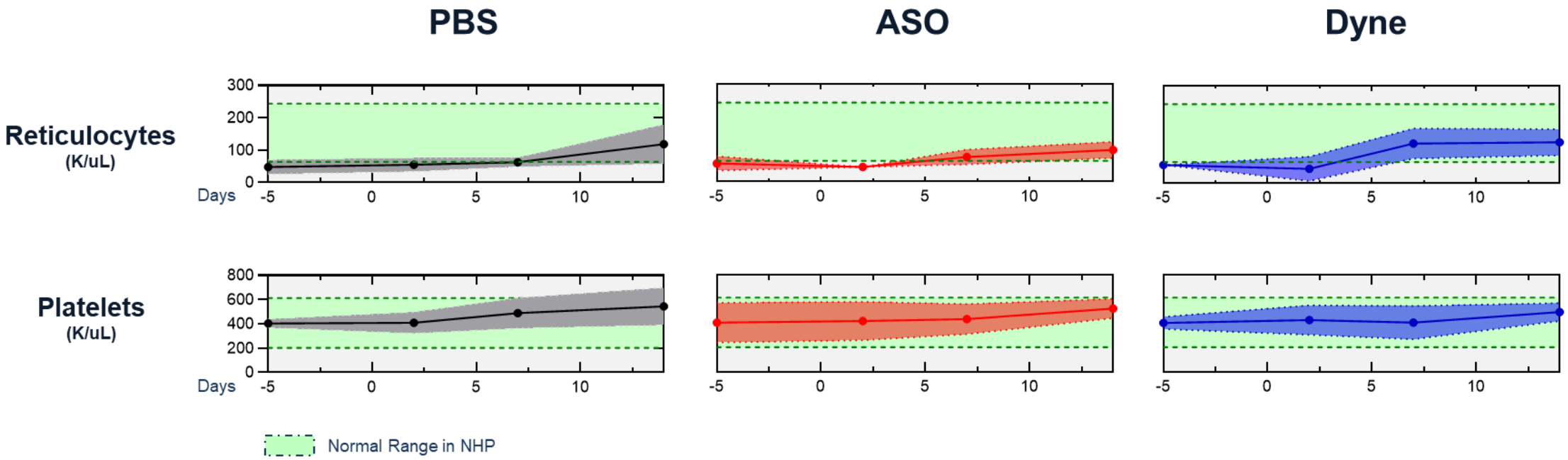
Note: 10 mg/kg ASO d0, analyzed d28; data are means ± S.D; n = 6; ***p* < 0.01, significant by *t*-test

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

Note: ALT: alanine transaminase, AST: aspartate transaminase, BUN: blood urea nitrogen

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

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