Repeat dosing with DYNE-101 is well tolerated and leads to a sustained reduction of *DMPK* RNA expression in key muscles for DM1 pathology in hTfR1/DMSXL mice and NHPs

Stefano Zanotti, Ph.D.

Joachim, *living with DM1*

American Society of Gene & Cell Therapy | 16 May 2022

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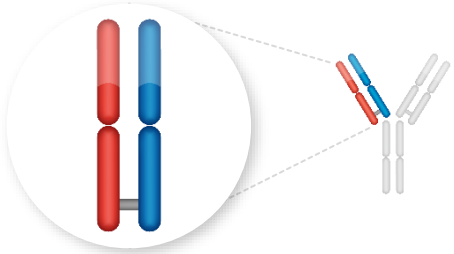
Dyne FORCE™ platform: Modern oligo therapeutics for muscle diseases

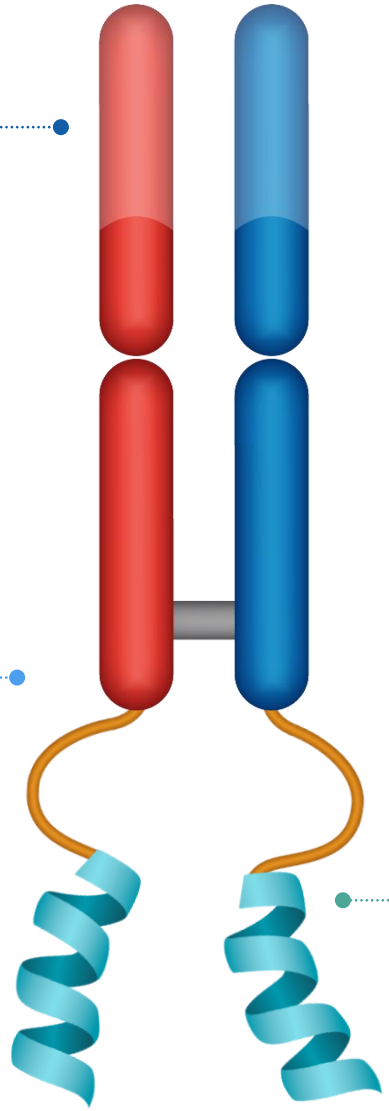
ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



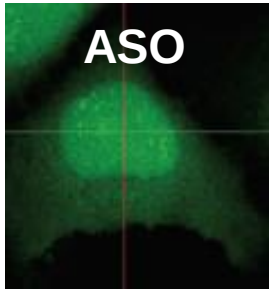
LINKER

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



PAYLOAD

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



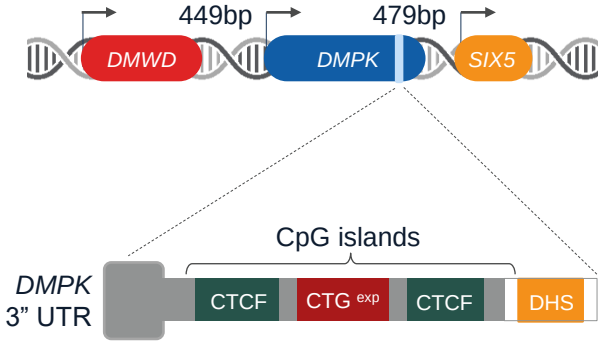
Nuclear localization

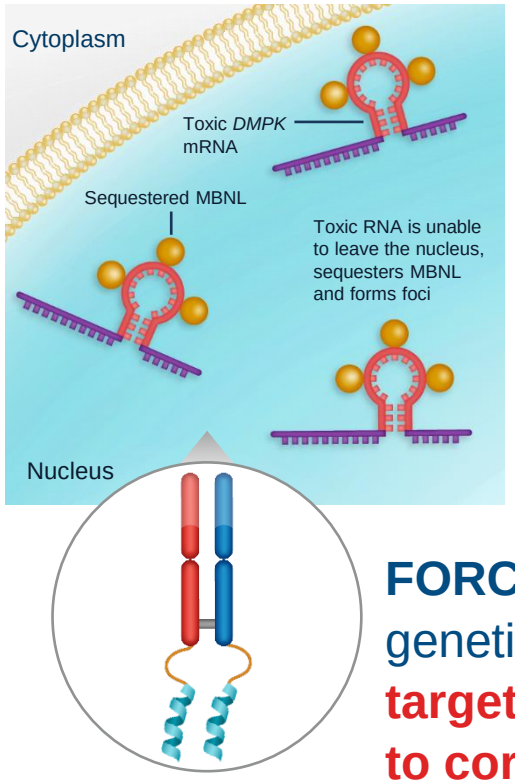
Cytoplasmic localization

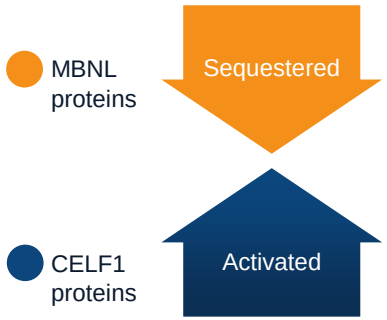
Adapted from: Ohrt et al: NAR , 2006, v.34, p.1369

FORCE targets the genetic basis of DM1 to correct splicing

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



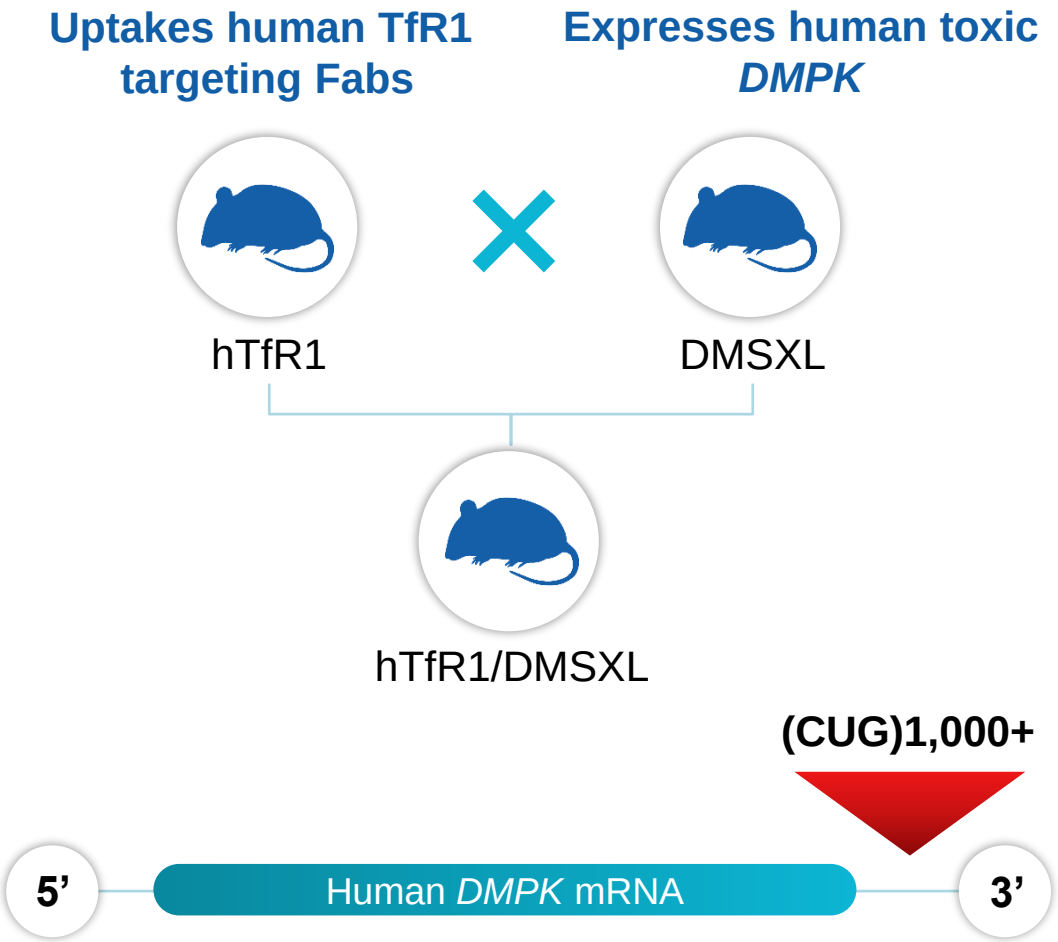


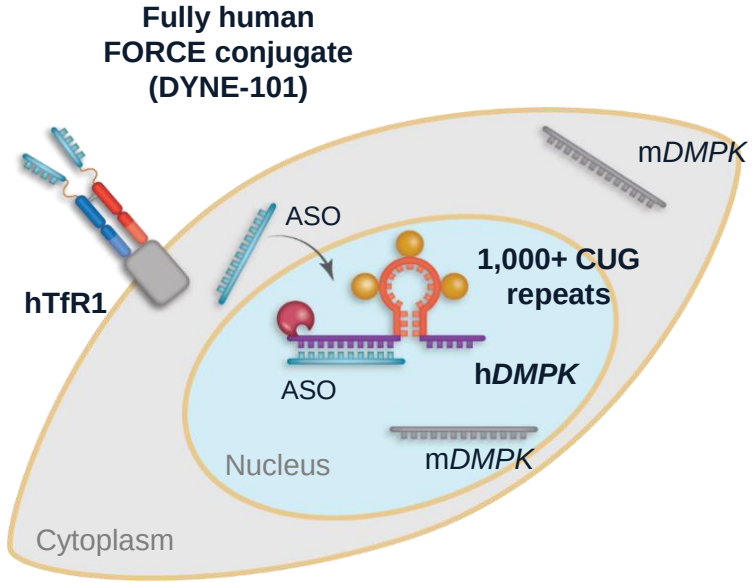


- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

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

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

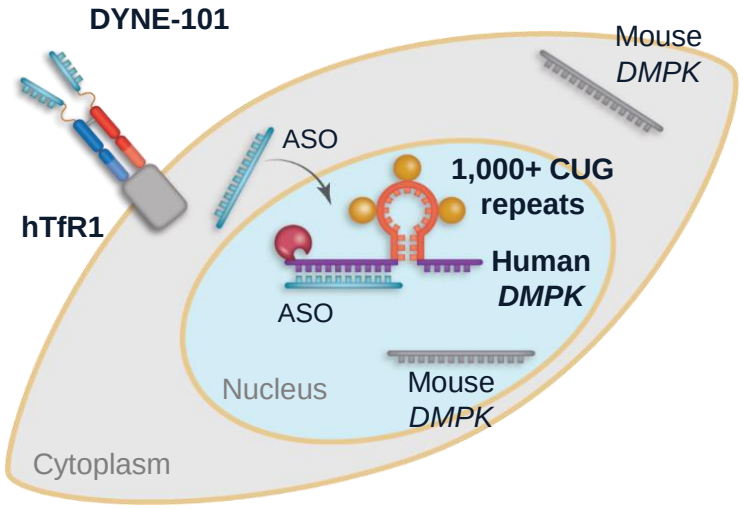




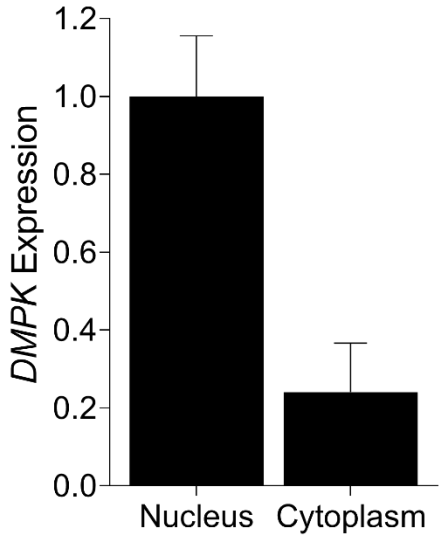
- Expresses human TfR1 receptor, enabling use of a human TfR1-targeting Fab
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

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

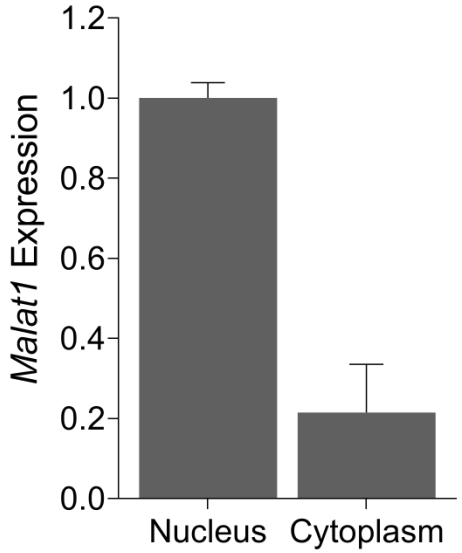
Toxic human *DMPK* is trapped in nuclei in hTfR1/DMSXL mice



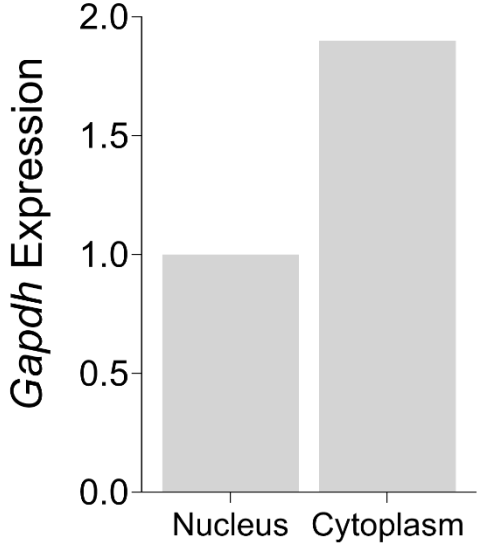
Human mutant *DMPK* enrichment in the nucleus



Malat1 nuclear control

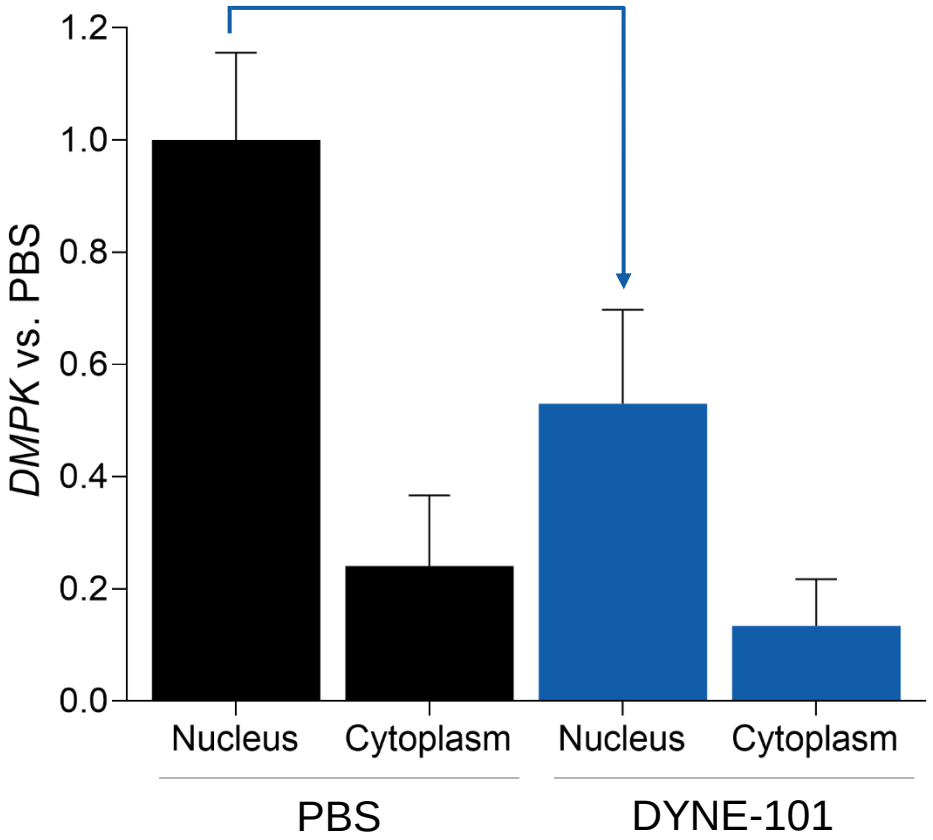


Gapdh cytoplasmic control



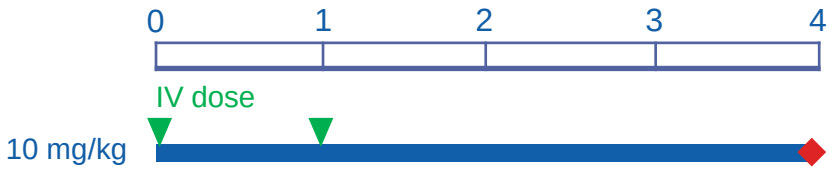
Note: fractions from gastrocnemius of vehicle-treated hTfR1/DMSXL hemizygous mice. Data are means ±SD; n = 2

DYNE-101 achieved robust toxic human *DMPK* KD in nuclei of hTfR1/DMSXL mice

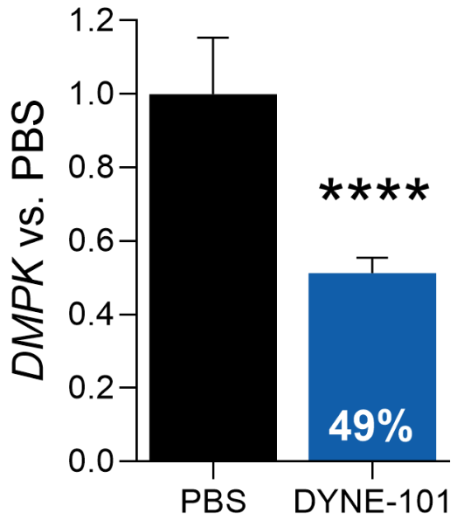


Note: hTfR1/DMSXL hemizygous mice. 10 mg/kg IV dose on d0, samples from gastrocnemius analyzed d28; Data are means ±SD; n = 2

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

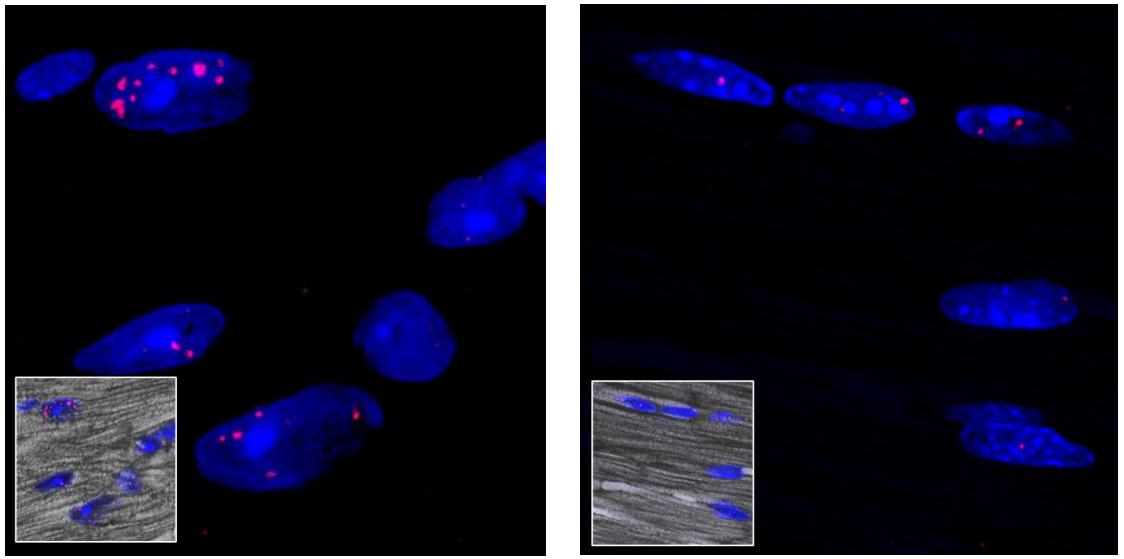


Toxic human *DMPK* expression (%KD)



Toxic human *DMPK* foci reduction

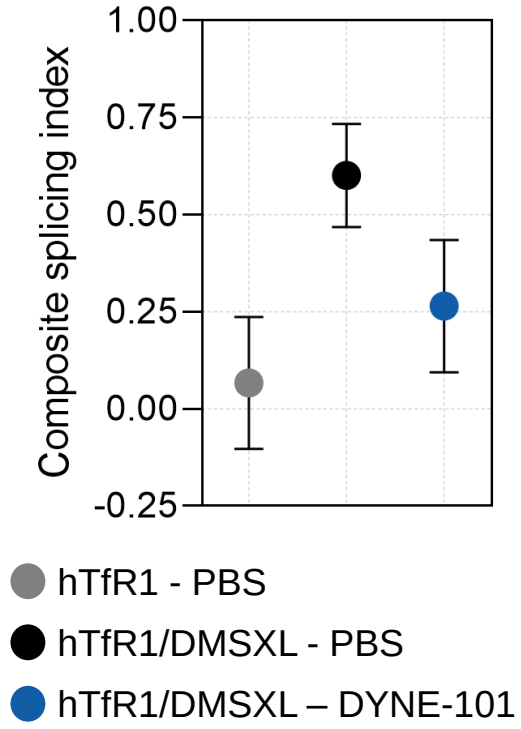
DMPK Foci Nuclei Myofibers



PBS DYNE-101

DYNE-101 reduces foci area by 49%*

Splicing correction

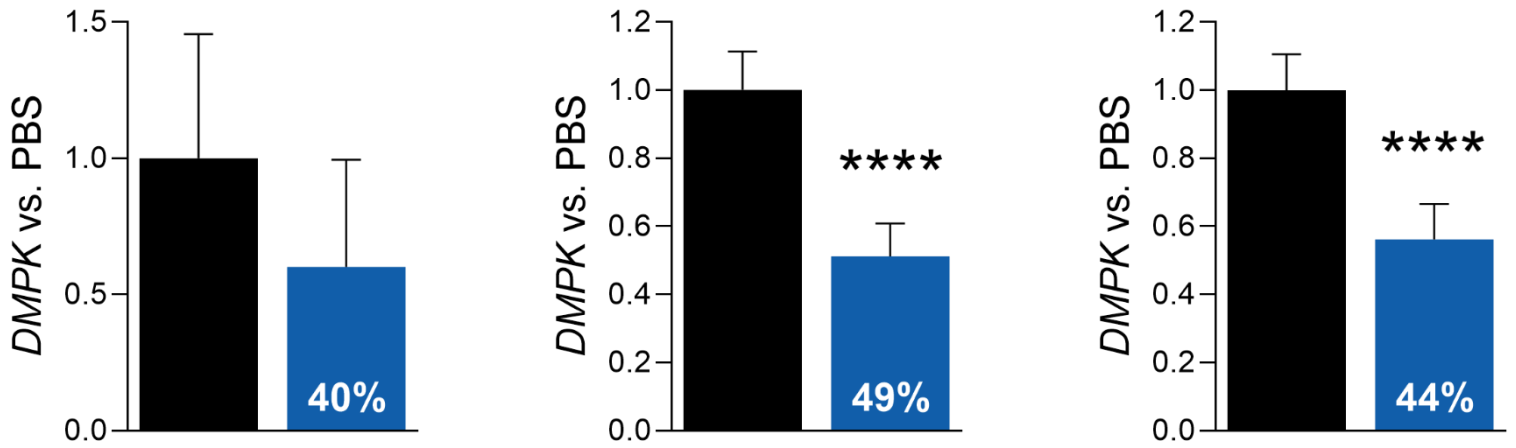


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing index includes changes in *Ldb3* exon (E) 11, *Mbnl2* E6, and *Nfix* E7. Data are means ± SD, n = 6 – 7 per arm; * p <0.05, **** p < 0.0001 significant by t-test

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

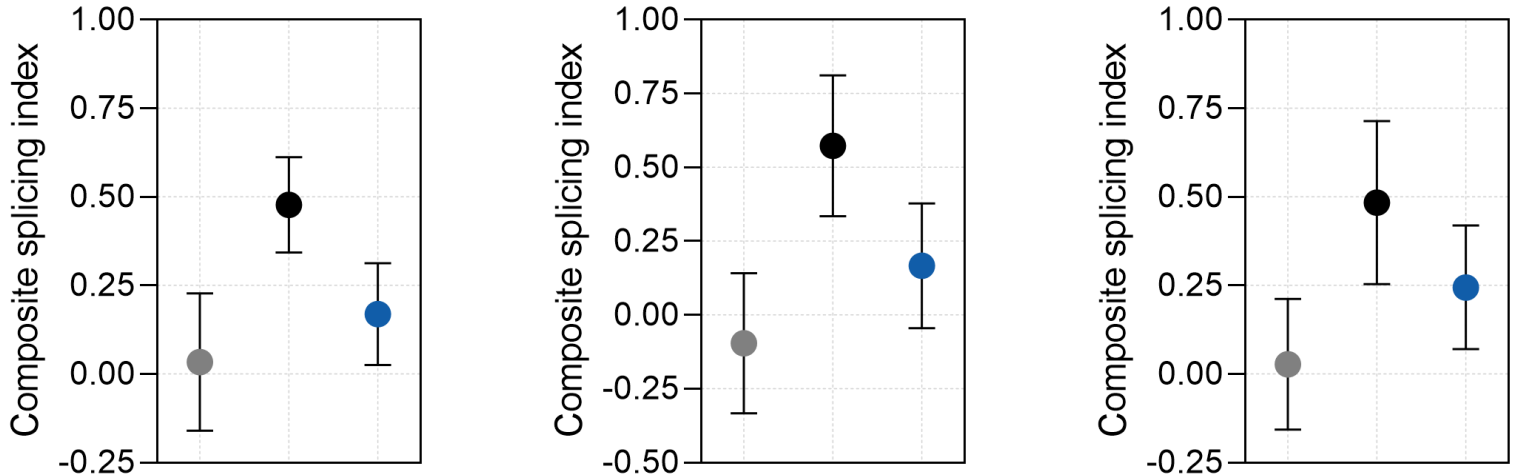
Toxic human *DMPK* expression (% KD)

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



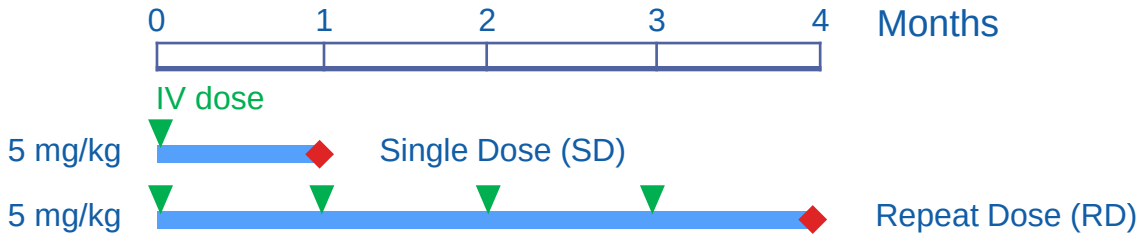
Splicing correction

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

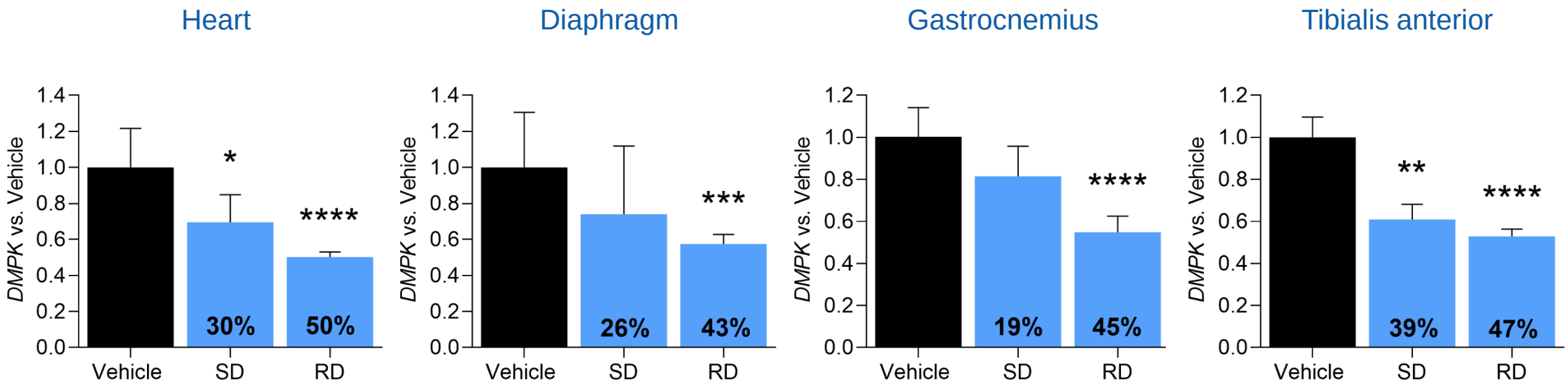


Note: hTfR1/DMSXL homozygous mice. 10 mg/kg IV doses on d0 and d7, analyzed d28
Composite splicing indices include *Bin1* E11, *Insr* E11, *Ldb3* E11, *Mbnl2* E6, *Nfix* E7, and *Ttn* E313 mis-splicing measured by qRT-PCR. Data are means ± SD; n = 4 – 7; **** $p < 0.0001$ by *t*-test

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

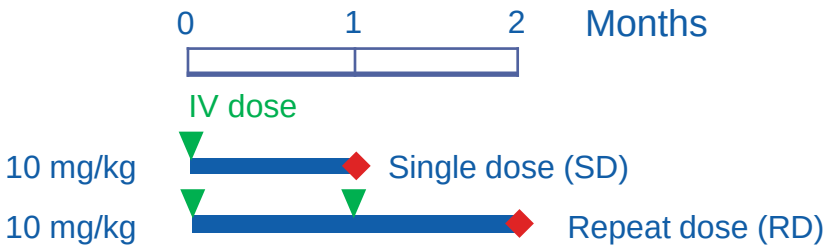


Toxic human *DMPK* expression (% KD)

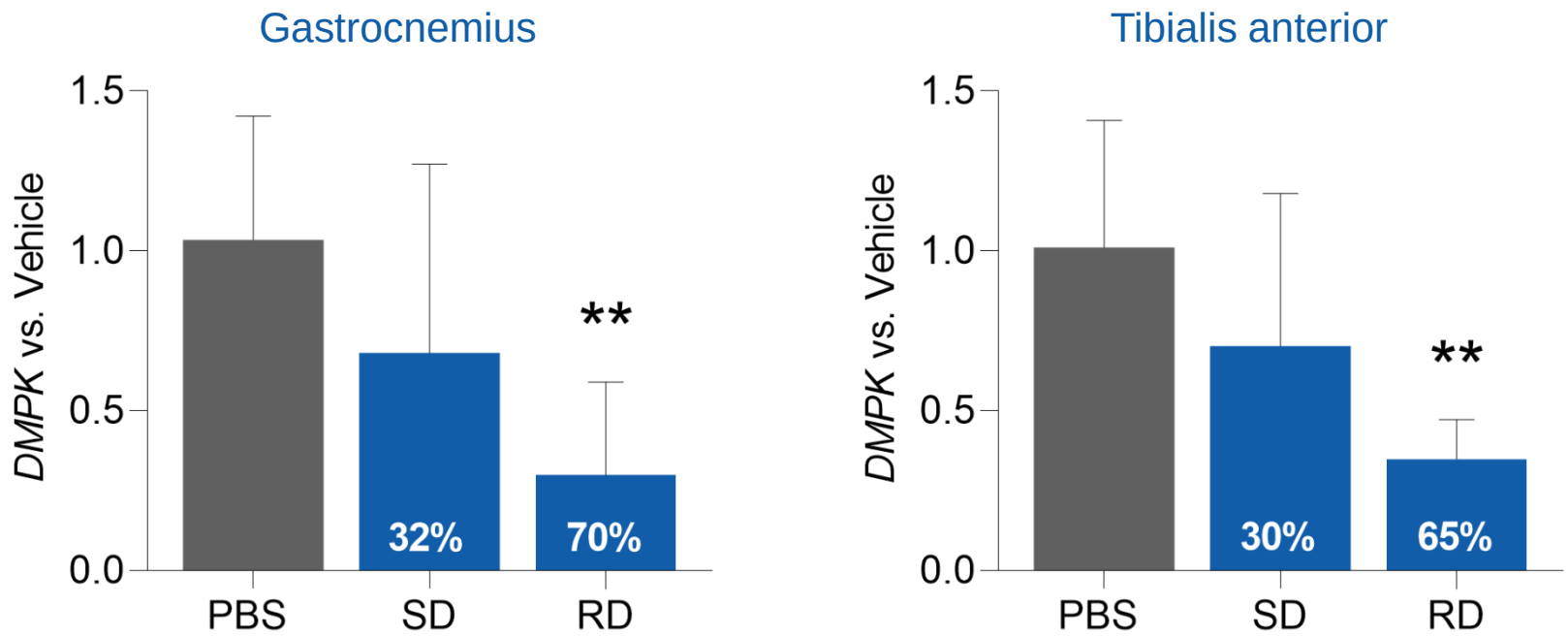


Note: hTfR1/DMSXL hemizygous mice. Data are means ± SD; n = 4 - 6 per arm; *p< 0.05, **p< 0.01, ***p< 0.001, ****p< 0.0001 significant by One-way ANOVA

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

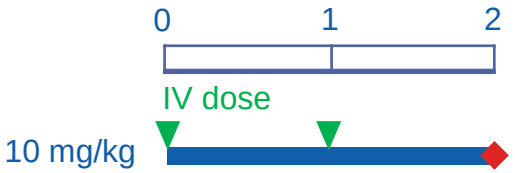


WT *DMPK* expression (% KD)

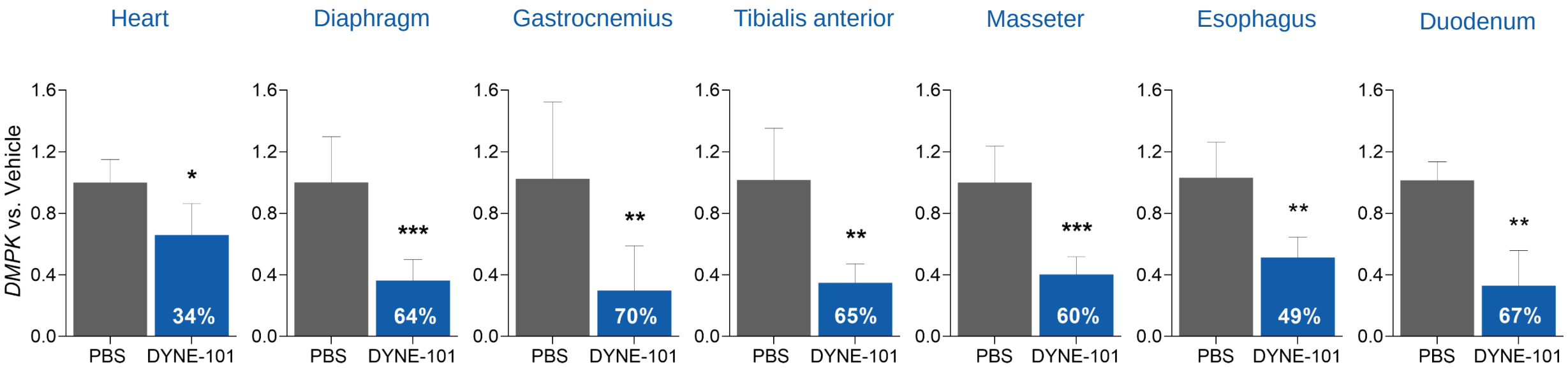


Note: Male cynomolgus monkeys. Data are means ± SD; n = 3 - 4 per arm; ***p*< 0.01 significant by One-way ANOVA

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



WT *DMPK* expression (% KD)



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

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

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

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

Conclusions

- DYNE-101 demonstrated ability to target toxic human *DMPK* RNA in the nucleus, reduce *DMPK* foci, and correct splicing in the hTfR1/DMSXL mouse model of DM1
- DYNE-101 monthly dosing in hTfR1/DMSXL mice and NHPs achieved significant *DMPK* RNA KD in different muscle types affected by DM1 pathology
- DYNE-101 was well-tolerated in a 13-week GLP toxicology study in NHPs

Data support advancement of DYNE-101 into the clinic for the treatment of DM1

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