



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

Forward-looking statements

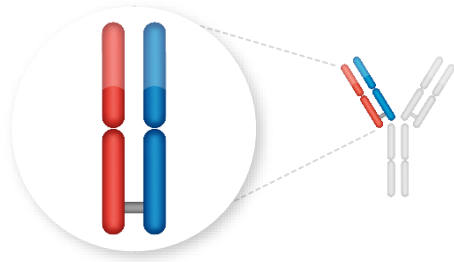
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Dyne FORCE™ platform: Modern oligo therapeutics for muscle diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery

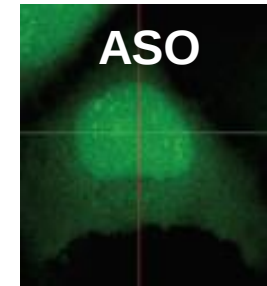


LINKER

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



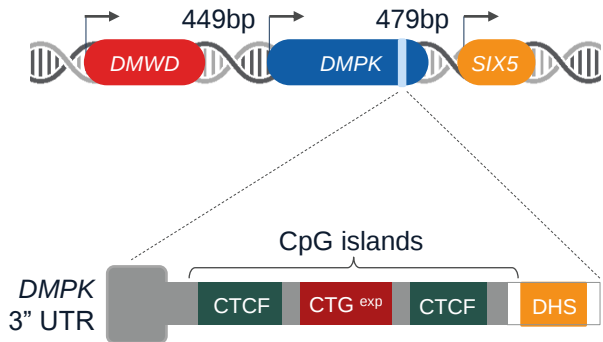
Nuclear
localization



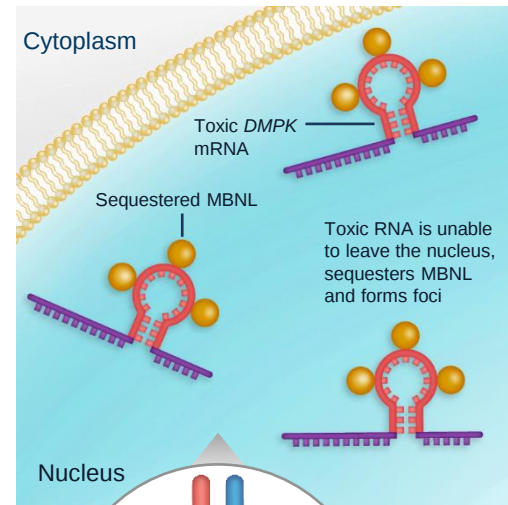
Cytoplasmic
localization

FORCE targets the genetic basis of DM1 to correct splicing

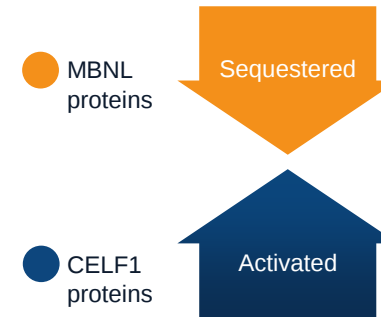
DNA Triplet Repeats



Toxic RNA Forms Foci



RNA Binds Splicing Proteins

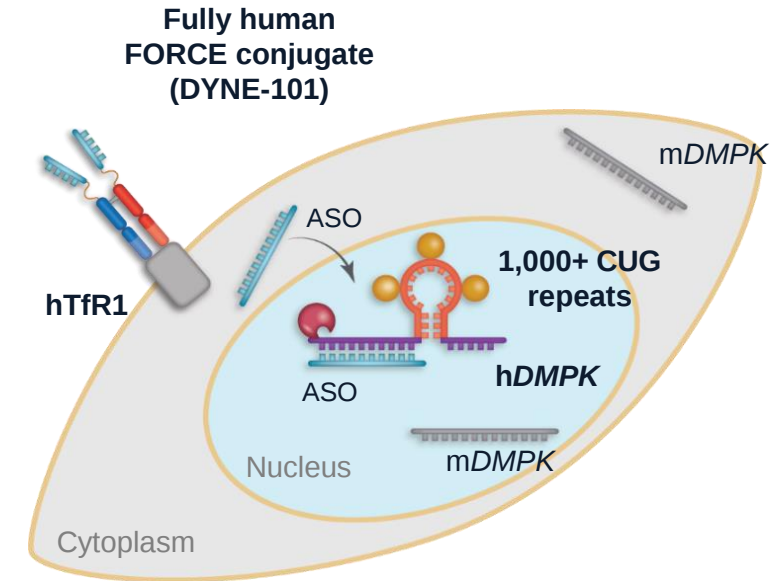
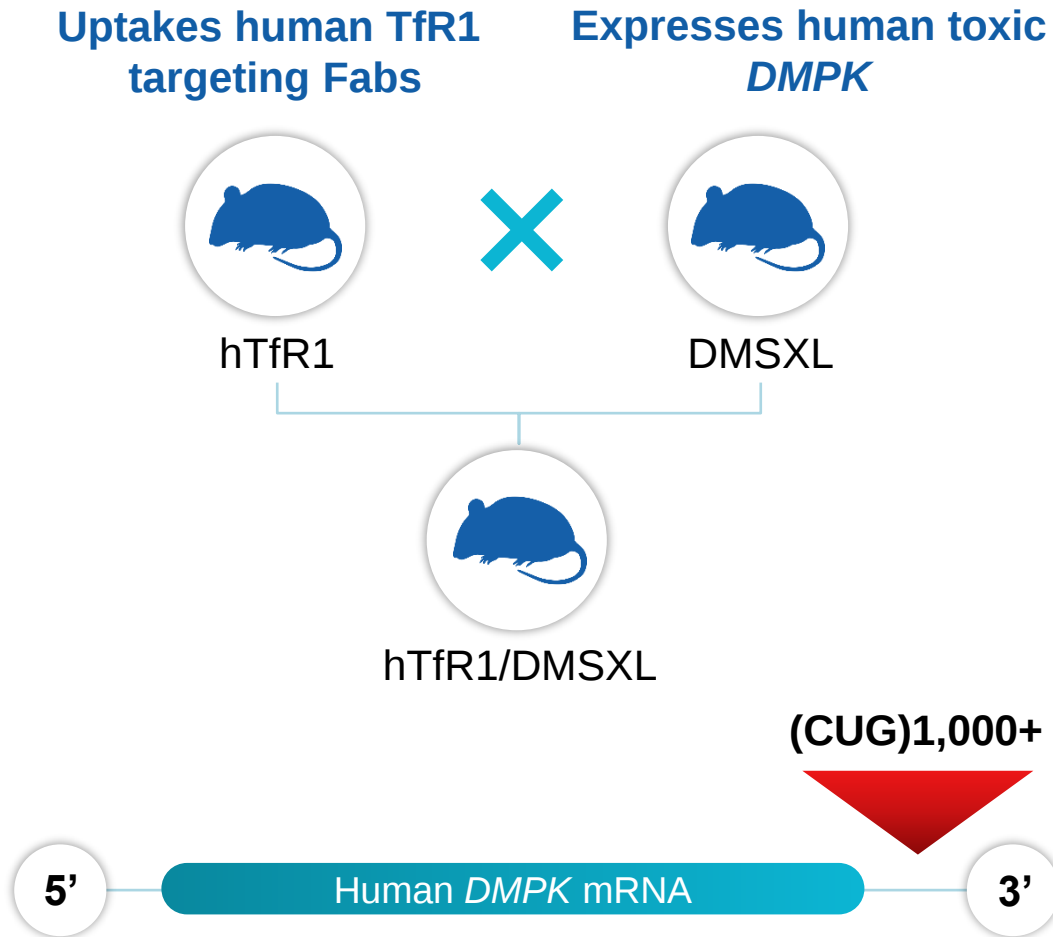


Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities

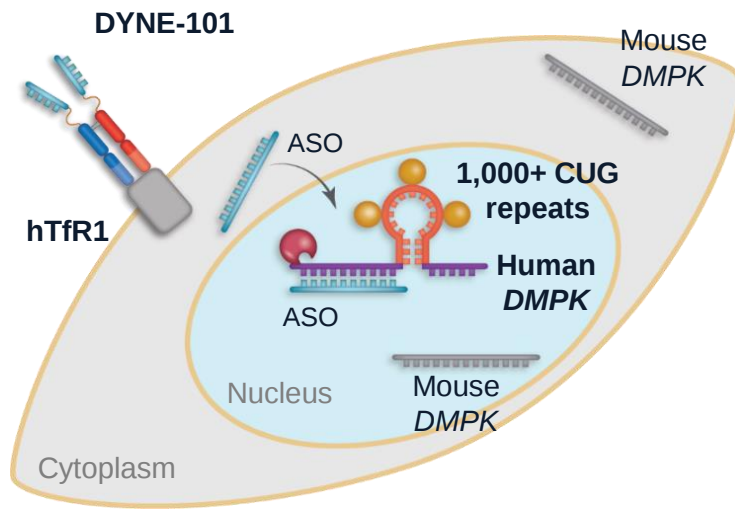
FORCE designed to address the genetic basis of disease by **targeting toxic nuclear *DMPK* RNA to correct spliceopathy**

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

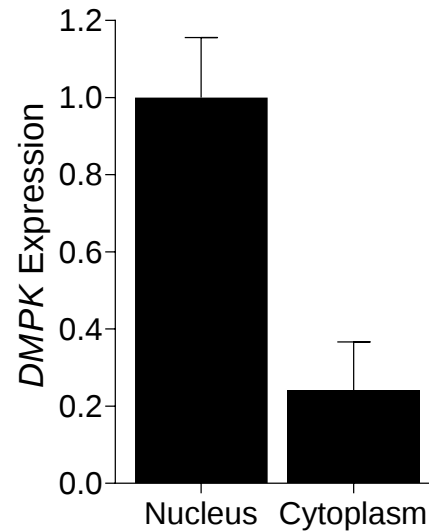


- Expresses human TfR1 receptor, enabling use of a human TfR1-targeting Fab
- Underestimates potency, expressing >10 times less human toxic *DMPK* vs. mouse *DMPK*

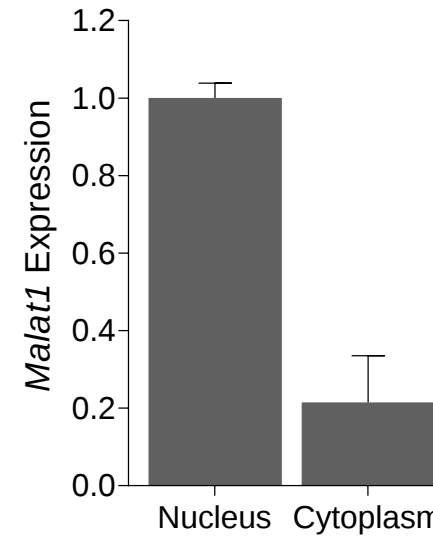
Toxic human *DMPK* is trapped in nuclei in hTfR1/DMSXL mice



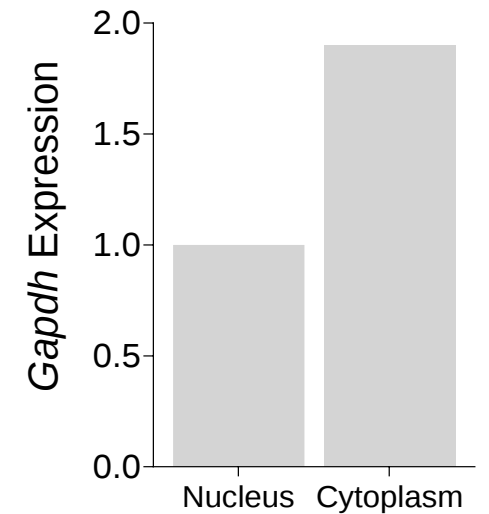
Human mutant *DMPK* enrichment in the nucleus



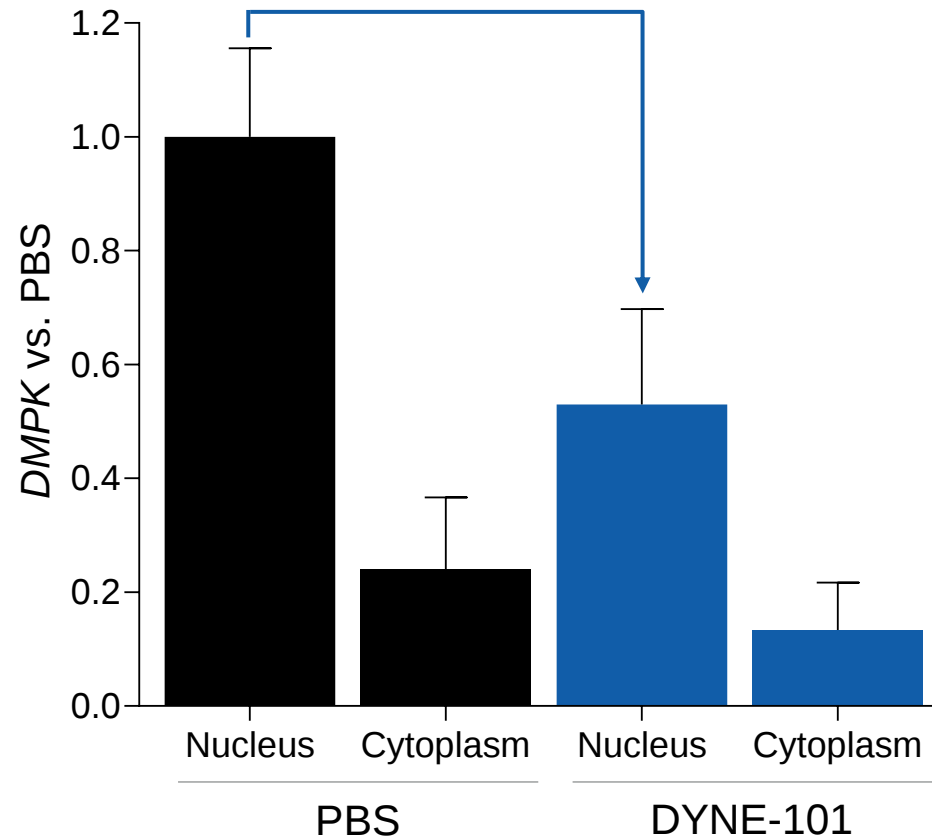
***Malat1* nuclear control**



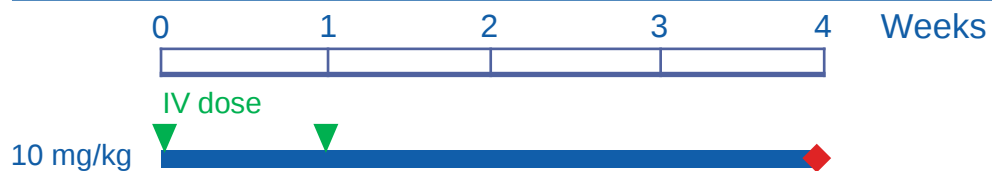
***Gapdh* cytoplasmic control**



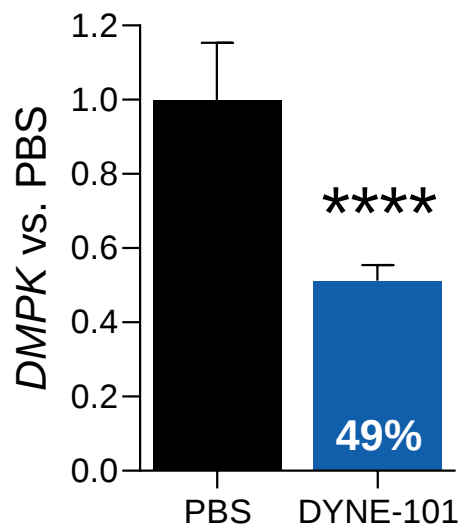
DYNE-101 achieved robust toxic human *DMPK* KD in nuclei of hTfR1/DMSXL mice



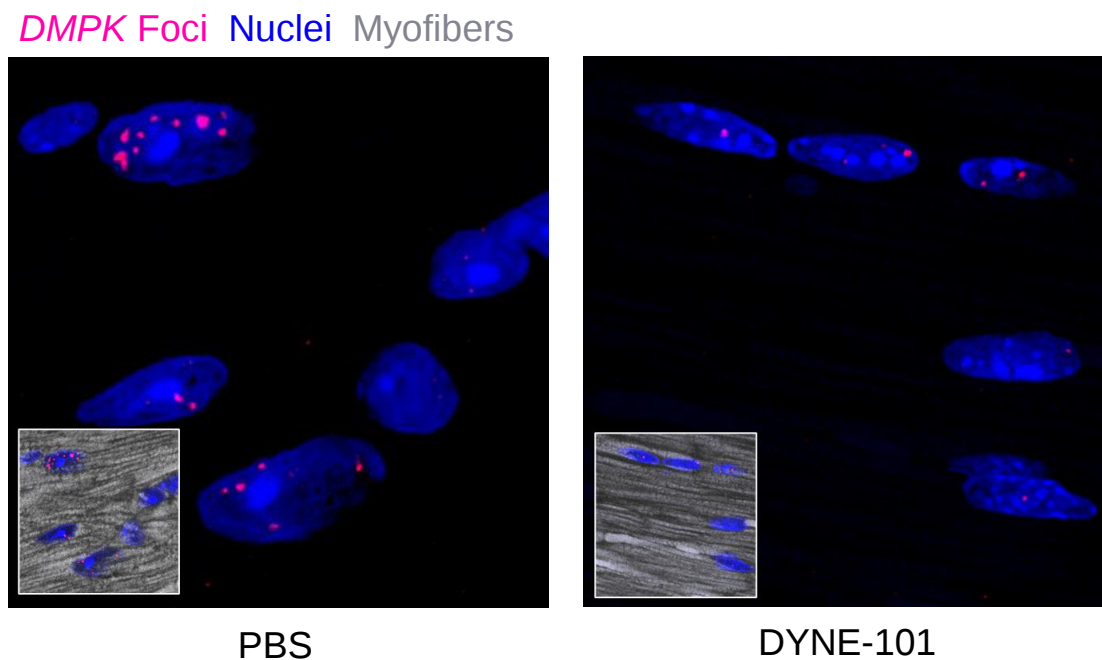
DYNE-101 demonstrated significant toxic human *DMPK* KD, foci reduction, and splicing correction in heart of hTfR1/DMSXL mice



Toxic human *DMPK* expression (%KD)

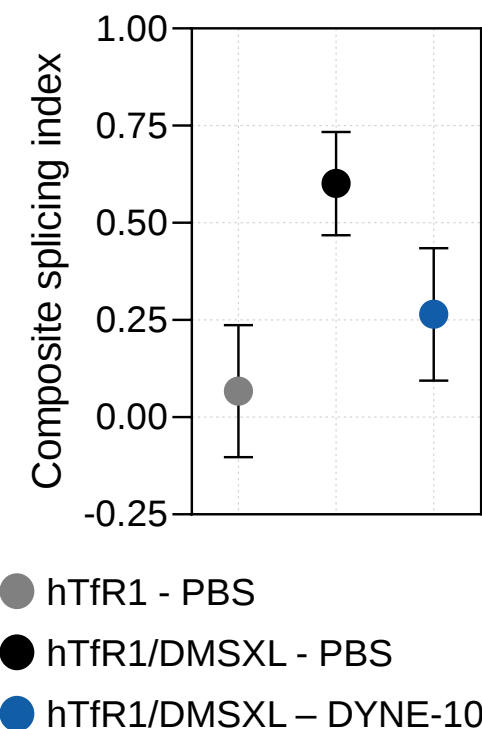


Toxic human *DMPK* foci reduction



DYNE-101 reduces foci area by 49%*

Splicing correction

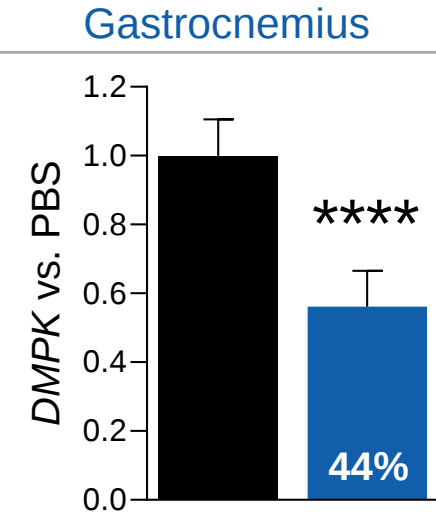
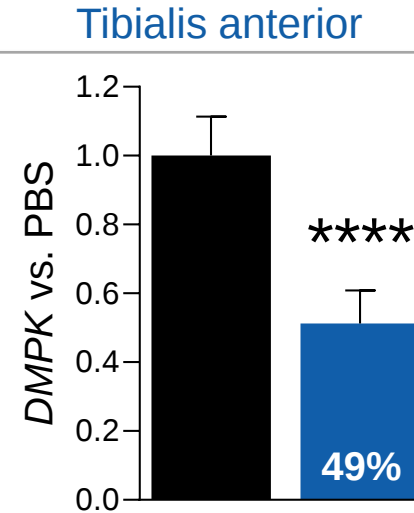
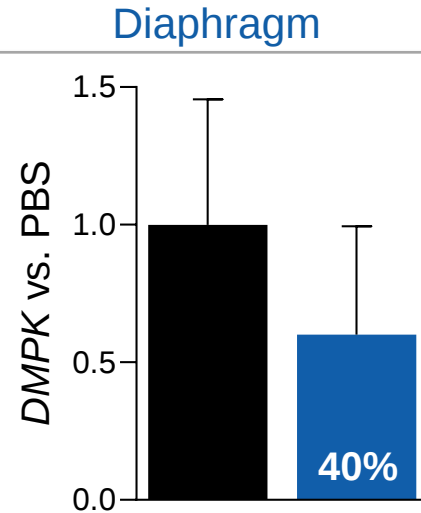


DYNE-101 demonstrated toxic human *DMPK* KD and splicing correction in skeletal muscle of hTfR1/DMSXL mice



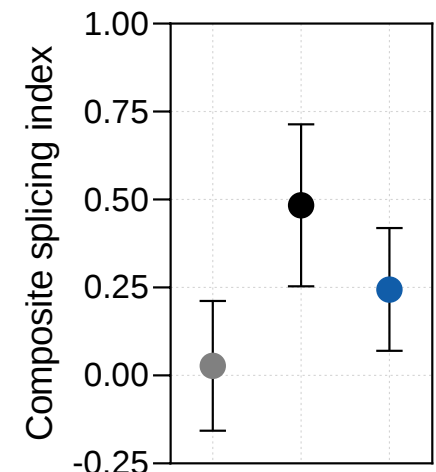
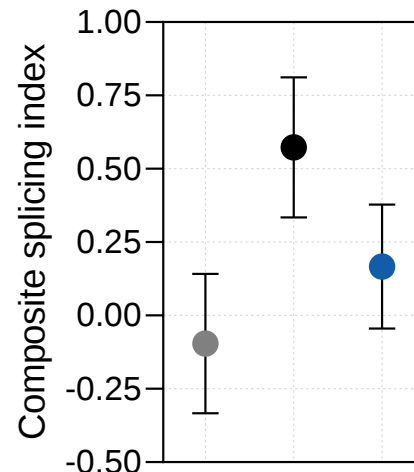
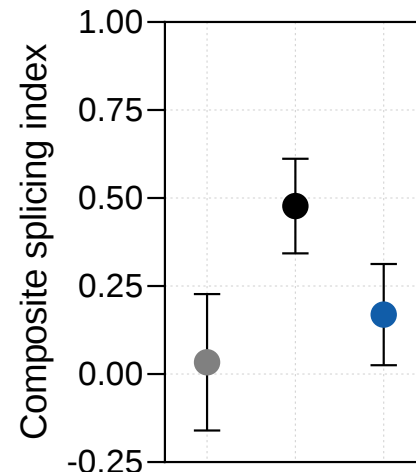
Toxic human *DMPK* expression (% KD)

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

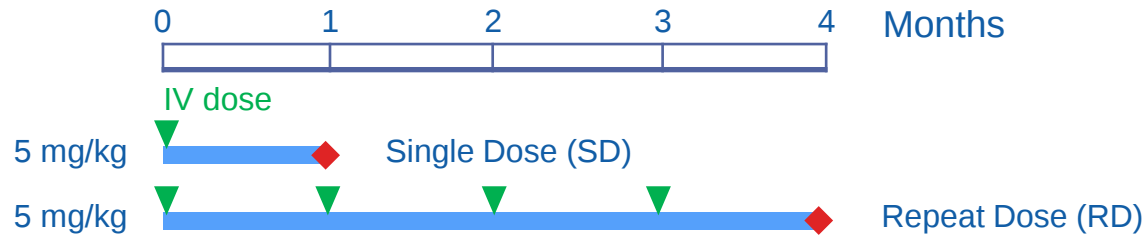


Splicing correction

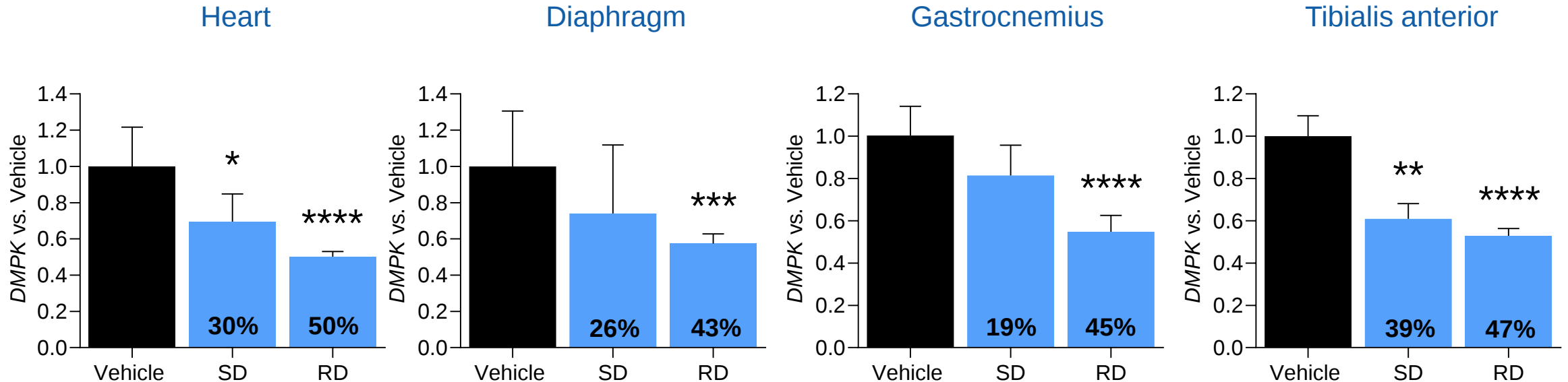
- hTfR1 - PBS
- hTfR1/DMSXL - PBS
- hTfR1/DMSXL – DYNE-101



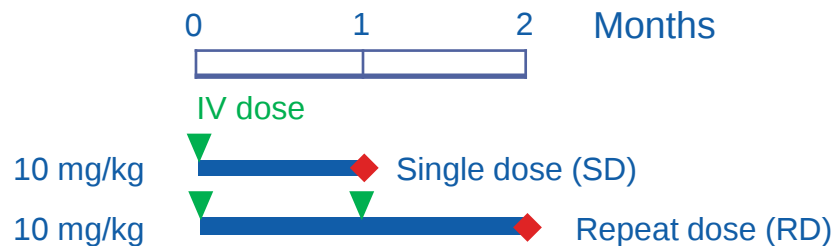
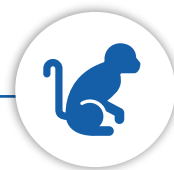
Low monthly dosing of DYNE-101 in hTfR1/DMSXL mice enhanced toxic human *DMPK* KD in cardiac and skeletal muscle



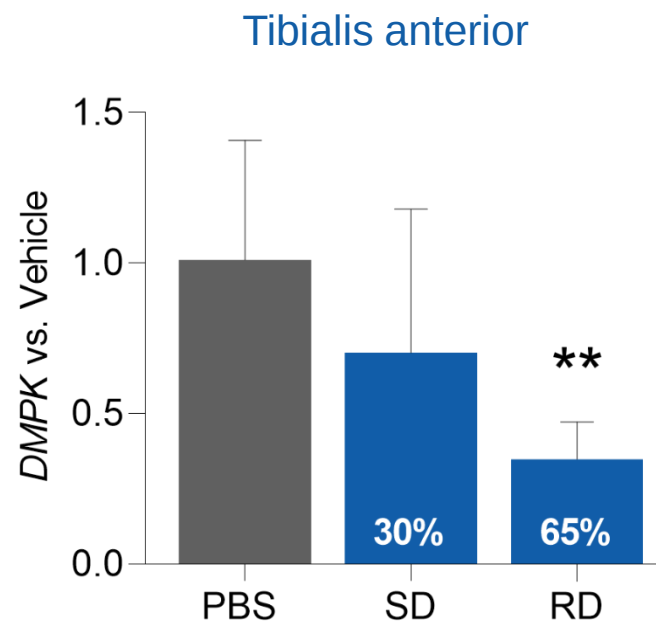
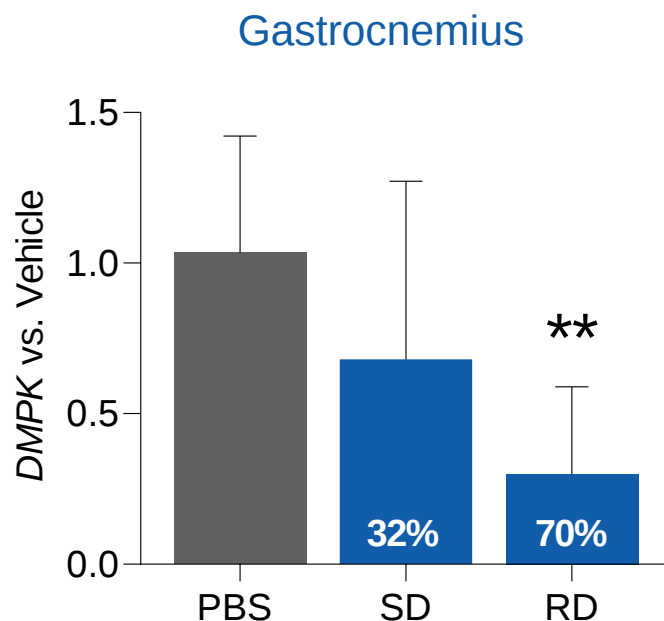
Toxic human *DMPK* expression (% KD)



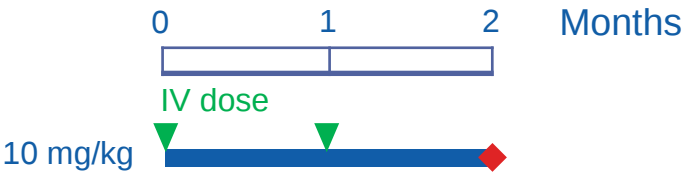
DYNE-101 repeat monthly dosing in NHPs enhanced *DMPK* KD in skeletal muscle



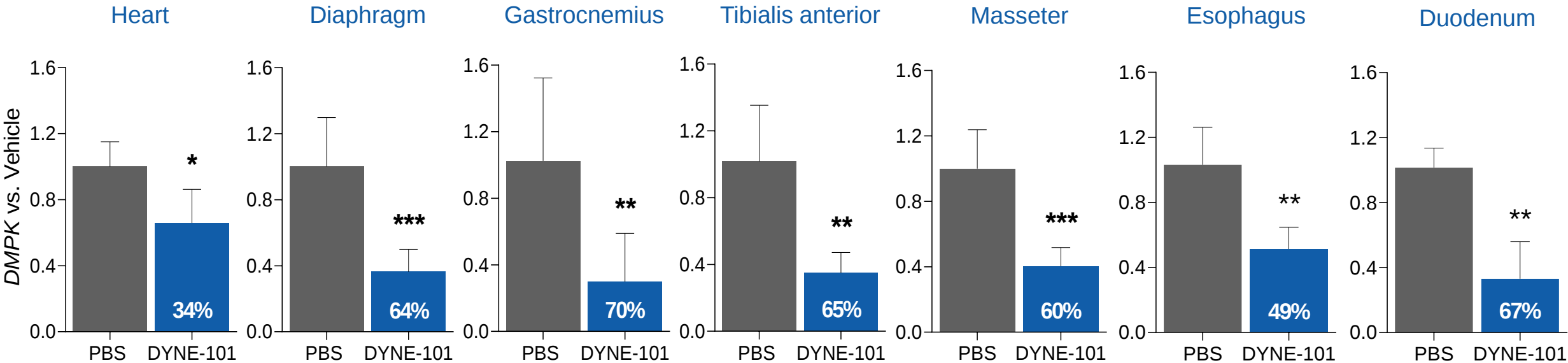
WT *DMPK* expression (% KD)



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



WT *DMPK* expression (% KD)



DYNE-101 was well-tolerated in an NHP 13-week GLP toxicology study¹



- No dose limiting toxicity observed up to a maximally feasible dose²
- 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

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 NHP achieved significant *DMPK* RNA KD in different muscle types affected by DM1 pathology
- Low monthly dosing achieves comparable *DMPK* KD to a higher dose administered weekly

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

Acknowledgements

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