



The FORCE™ Platform Delivers Oligonucleotides to the Brain in a DM1 Mouse Model and in NHPs

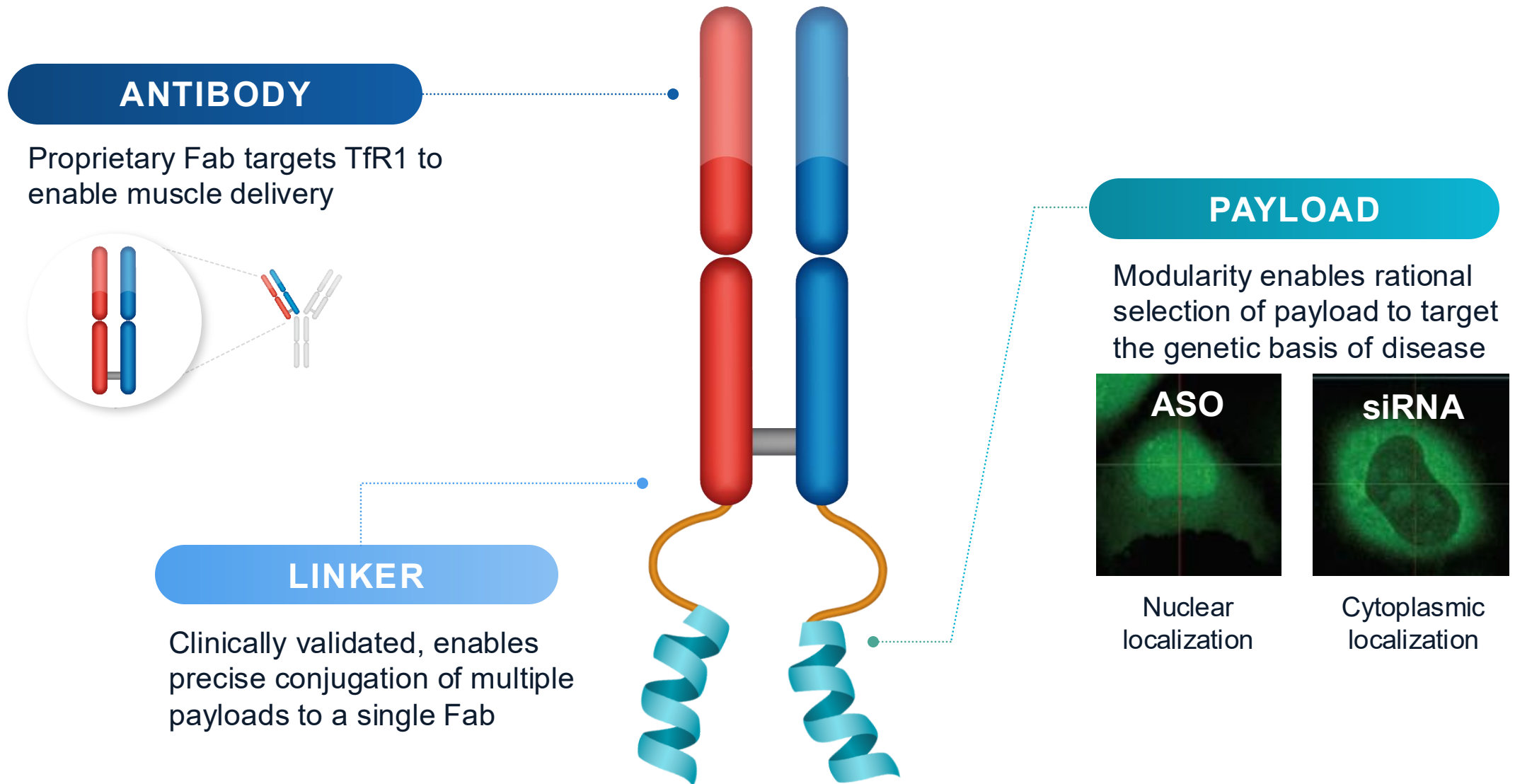
Stefano Zanotti, Ph.D.

Joachim, living with DM1

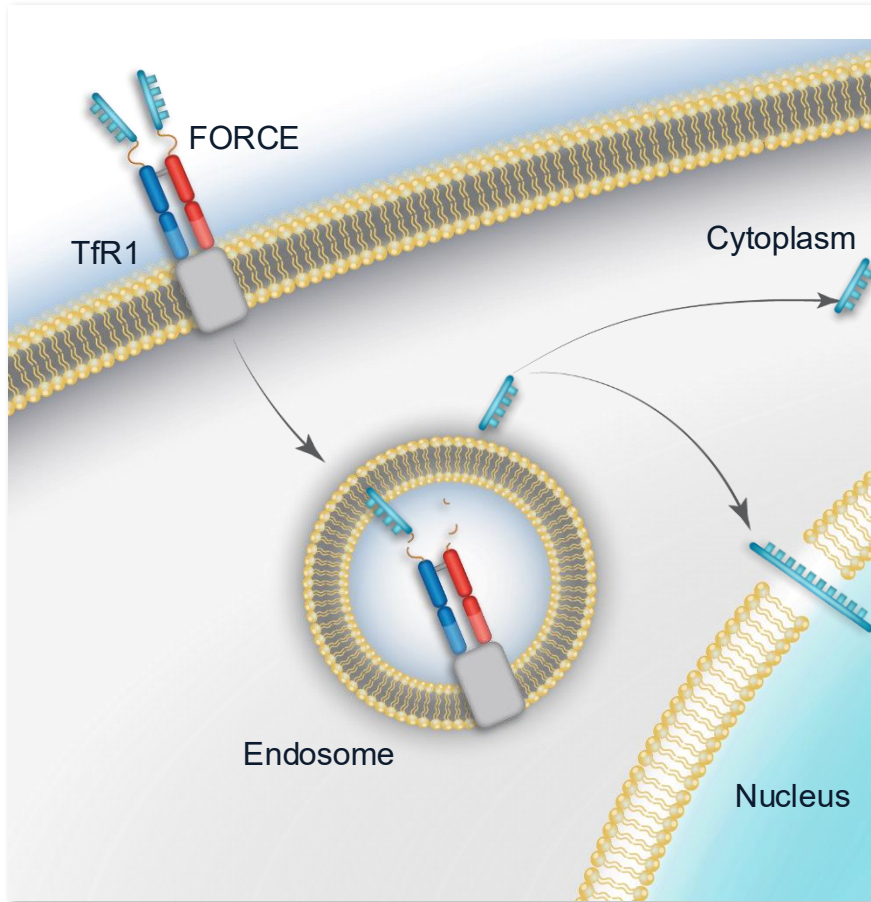
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Dyne FORCE™ Platform: Modern Oligo Therapeutics for Neuromuscular Diseases



FORCE Platform Harnesses Cell Biology to Modify Disease

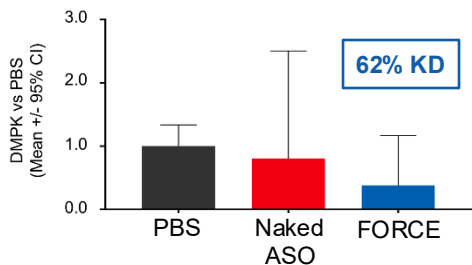


- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index
- FORCE was developed for muscle delivery
 - Binds TfR1 with high affinity

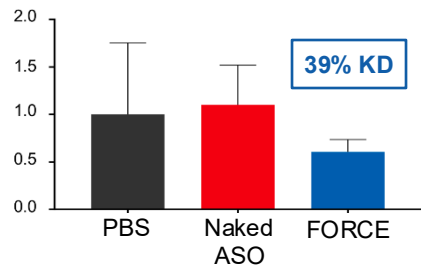
FORCE Platform Overcomes the Barriers of Oligonucleotide Delivery to Muscle



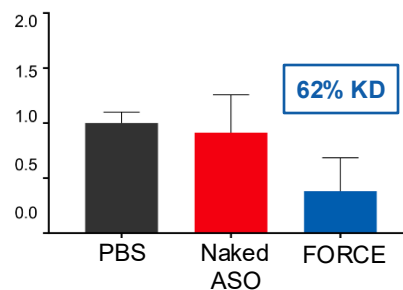
Gastrocnemius



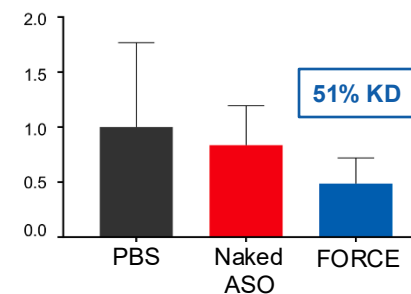
Soleus



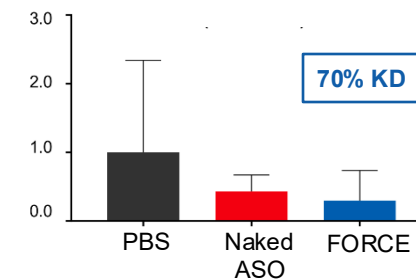
Deep Flexor



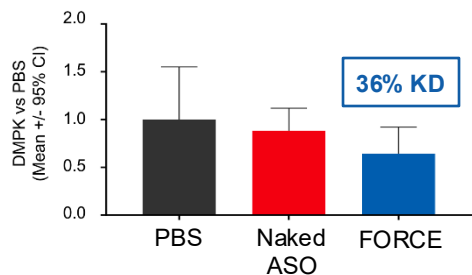
Bicep



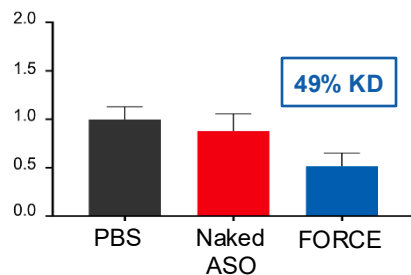
Ileum (Near Cecum)



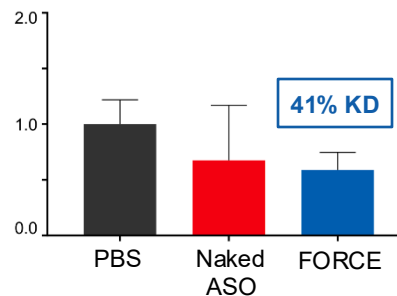
Heart-left Ventricle



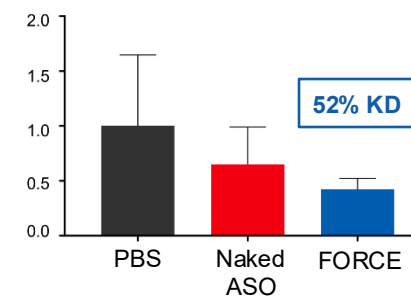
Diaphragm



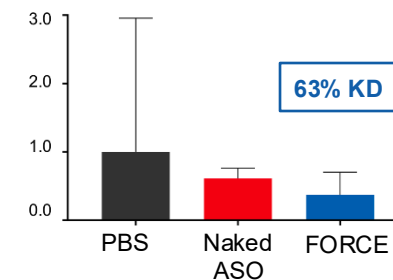
Masseter



Quadricep

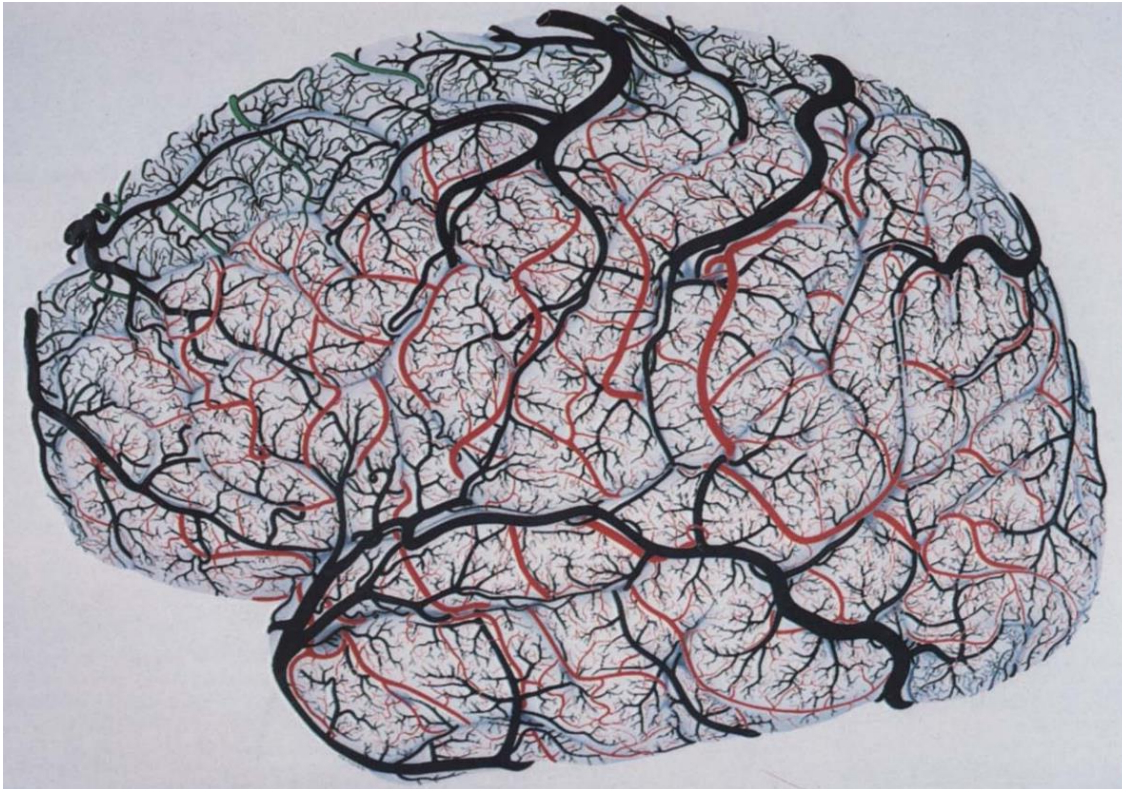


Jejunum (Duodenum Ends)

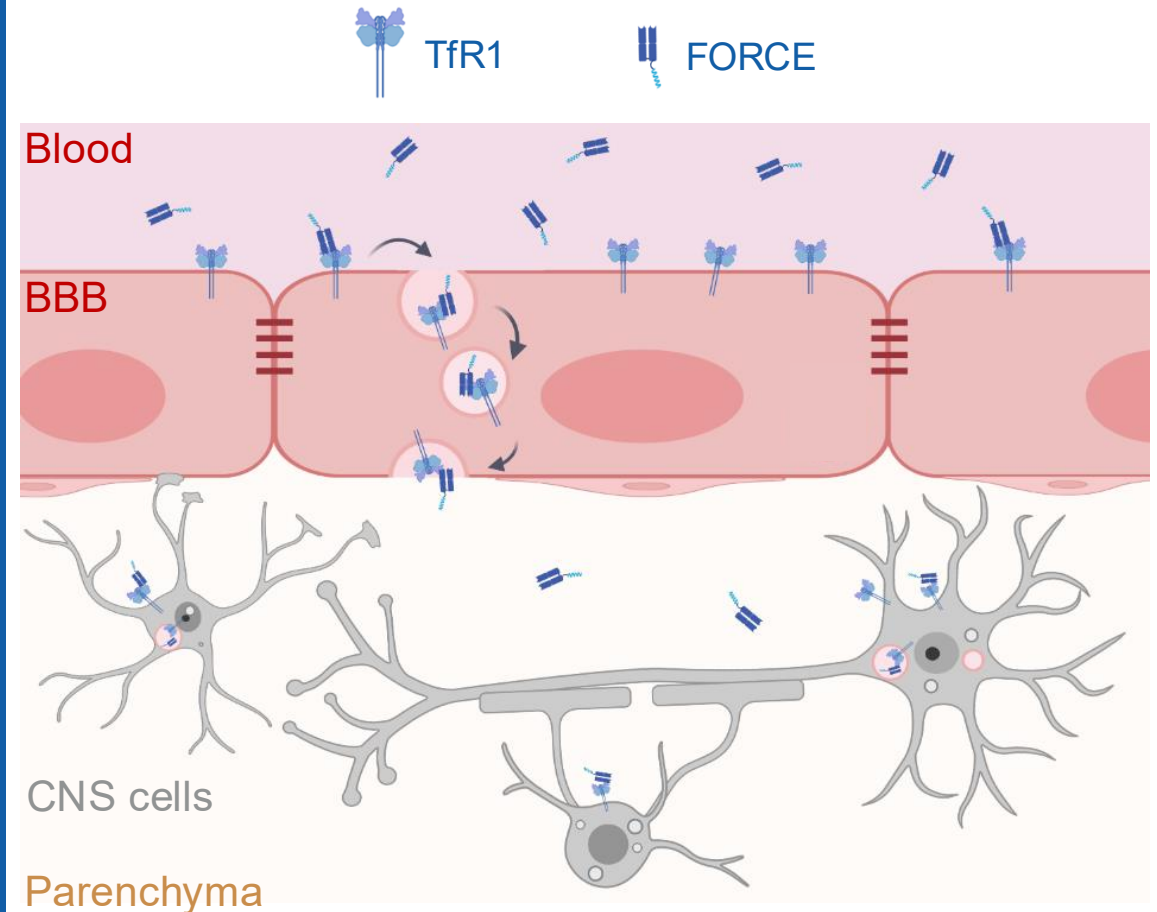


FORCE Platform has the Potential to Cross the Blood-brain Barrier (BBB) and Achieve Widespread Brain Delivery

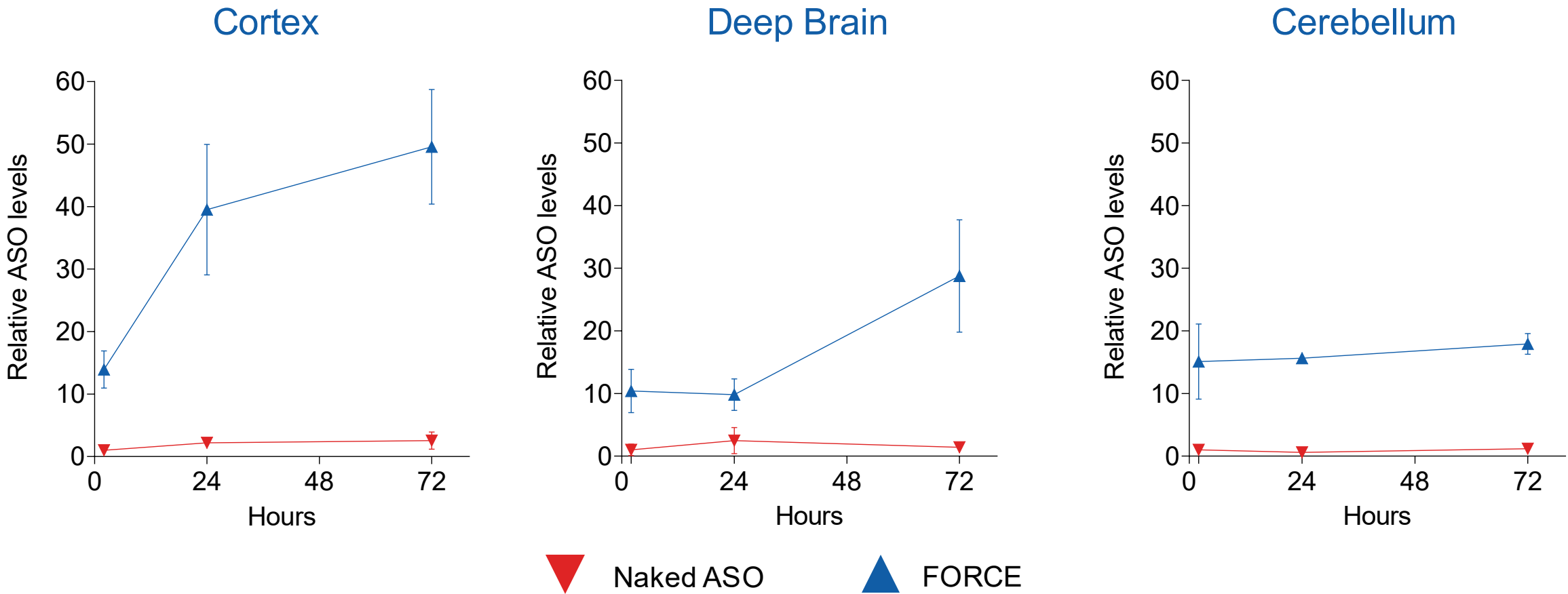
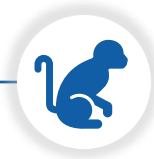
400-mile-long brain capillary network:
Enables widespread delivery



TfR1-mediated transcytosis:
Potential for crossing the BBB



FORCE Conjugate Shows Superior Delivery Compared to Naked ASO in NHP Brain After a Single IV Dose



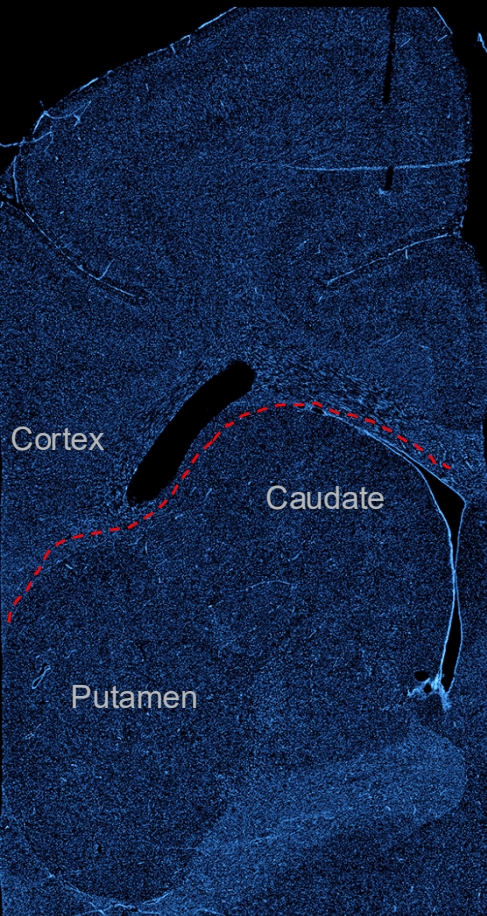
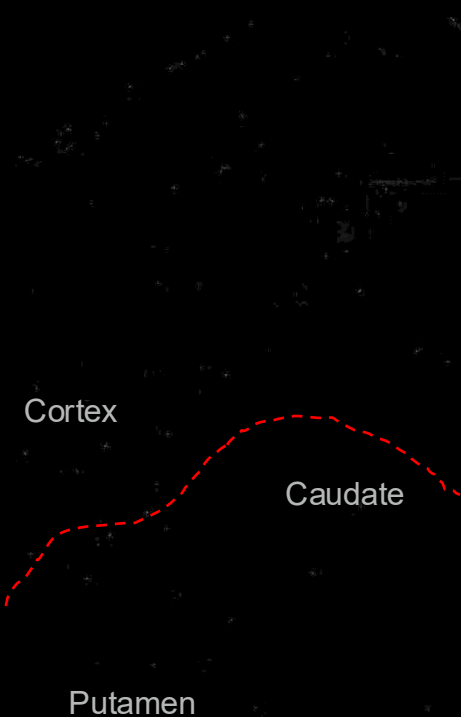
FORCE Conjugate Delivers Broadly Throughout the Brain in NHP



Naked ASO, IV
No ASO delivery

ASO staining

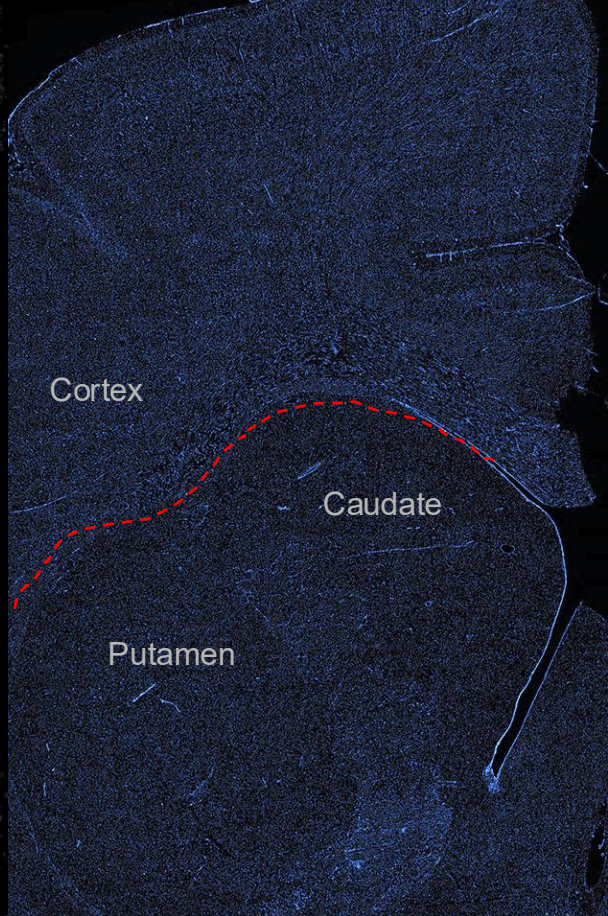
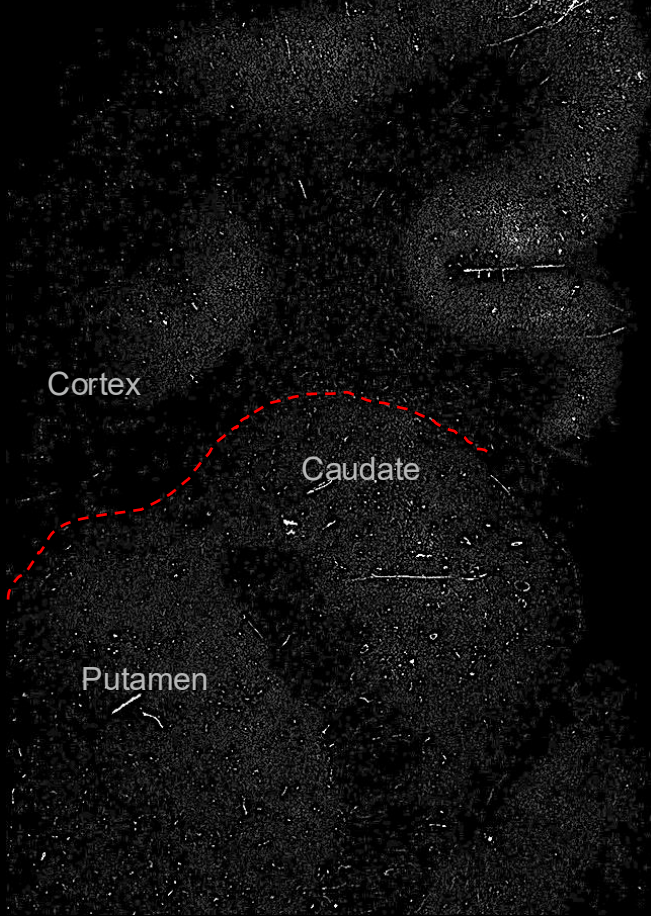
Brain morphology



FORCE, IV
Widespread ASO delivery

ASO staining

Brain morphology

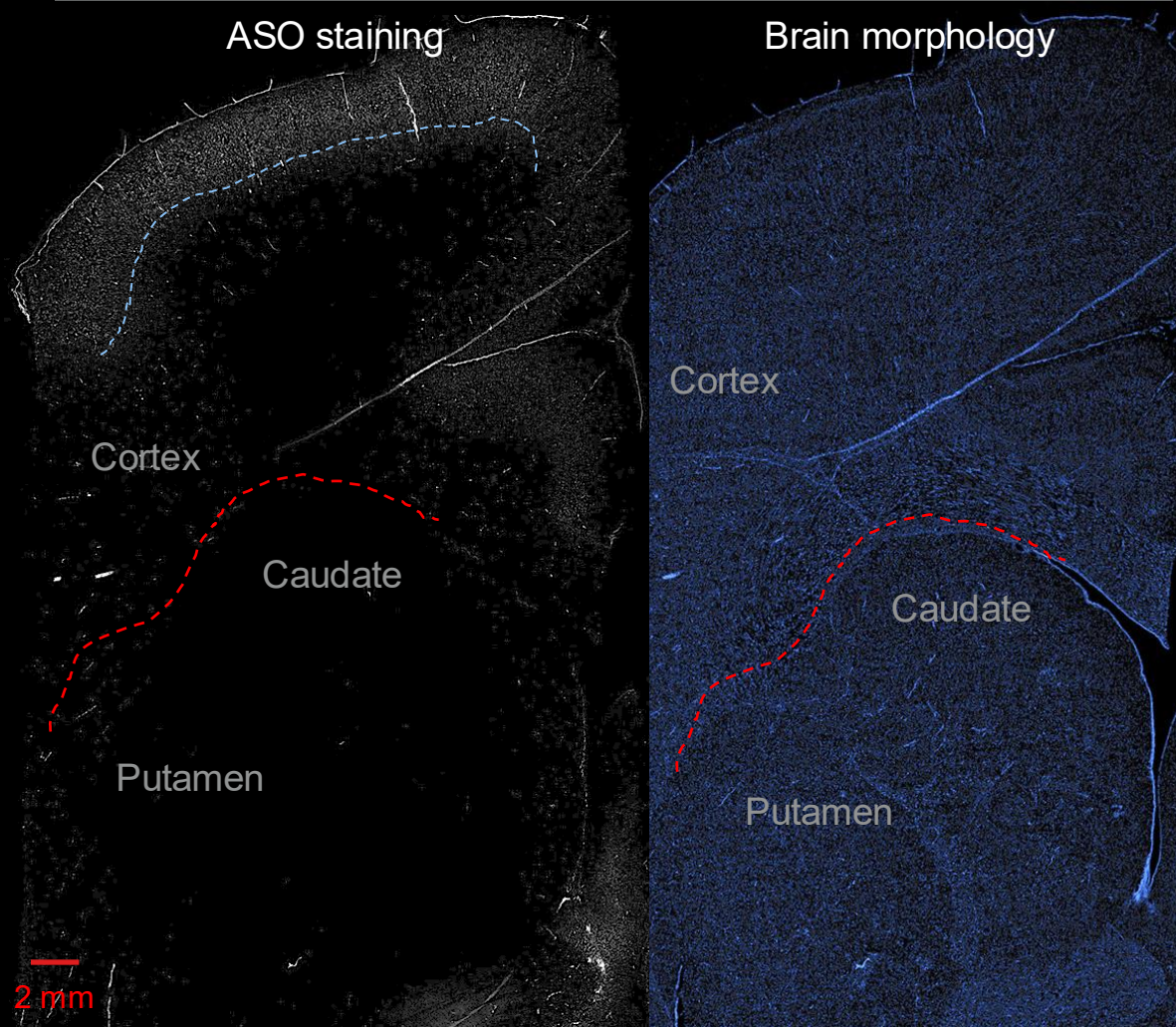


2 mm

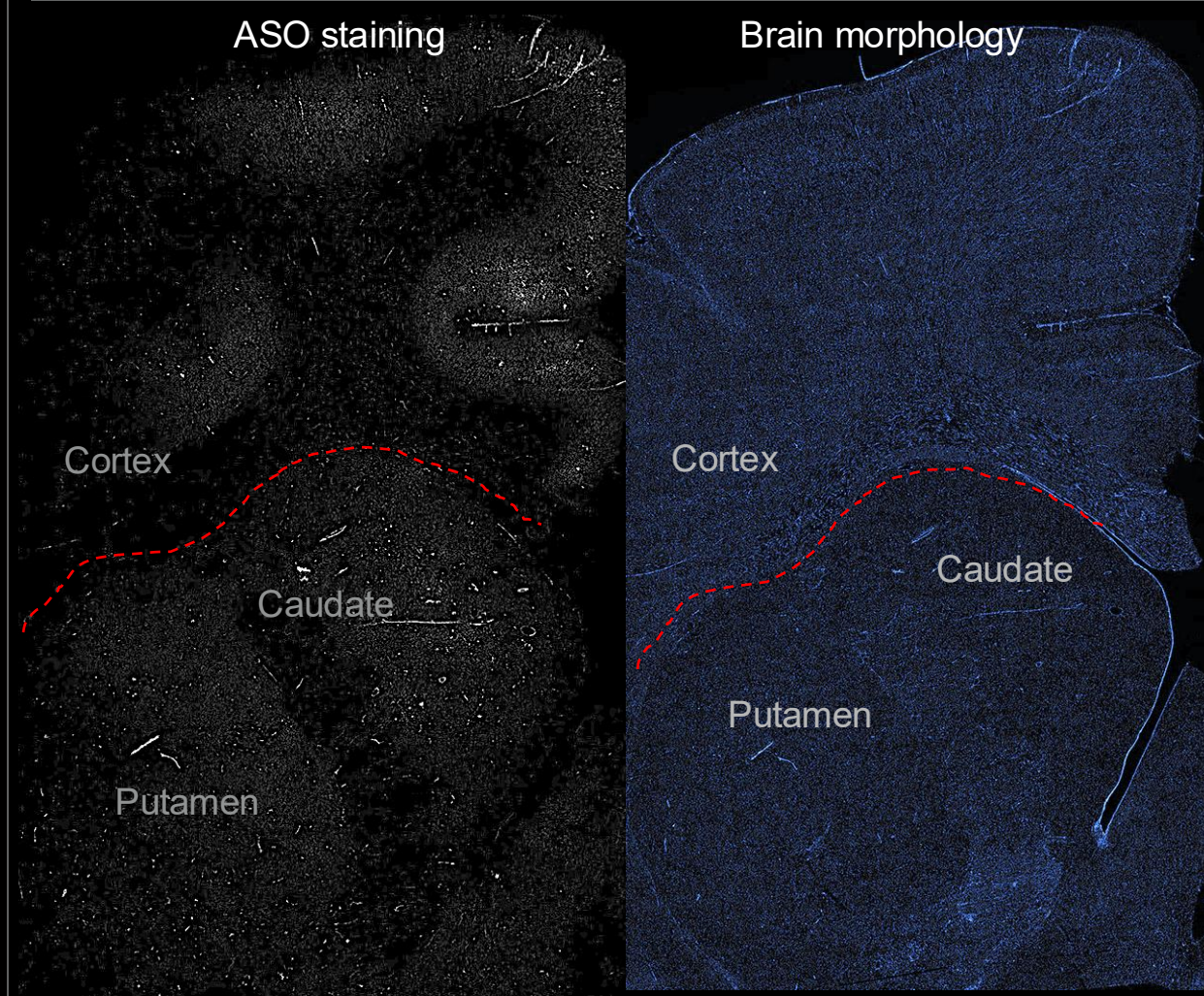
FORCE Conjugate Achieves Broader Delivery Compared to IT Administration of Naked ASO in NHP



Naked ASO IT
Limited ASO distribution

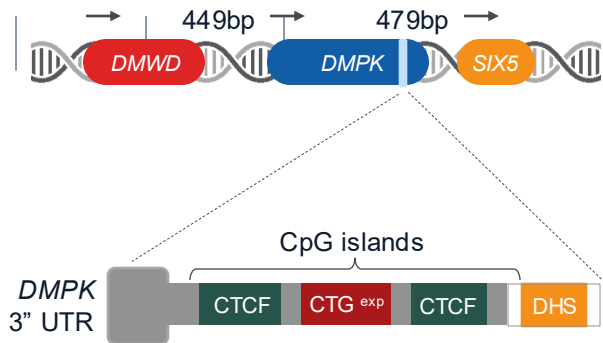


FORCE, IV
Widespread ASO distribution

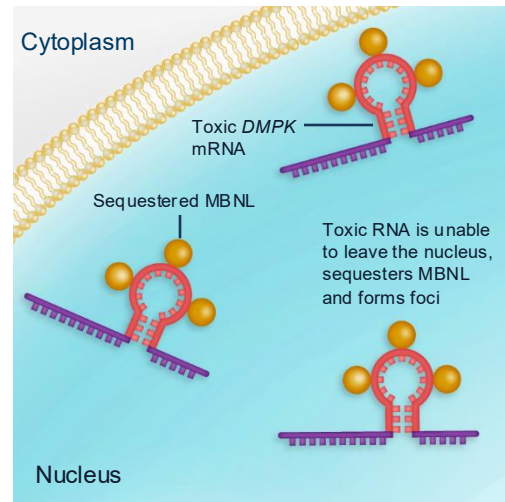


DM1 is a Spliceopathy with Muscle and CNS Clinical Manifestations

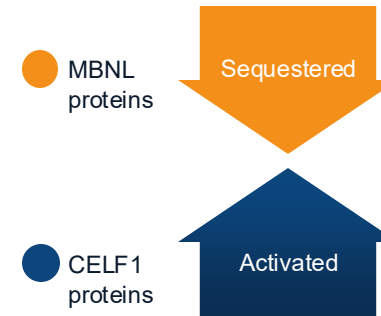
DNA Triplet Repeats



Toxic RNA Forms Foci in Nucleus



RNA Binds Splicing Proteins



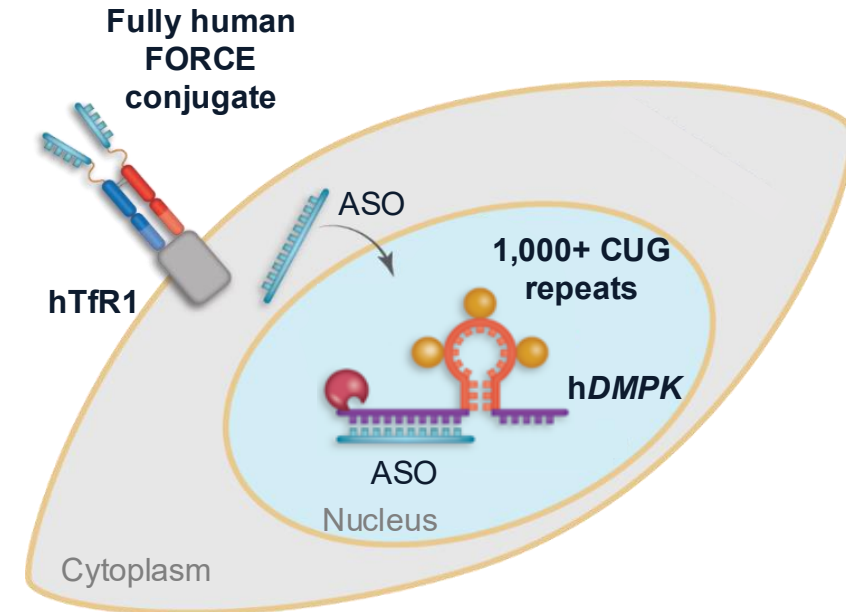
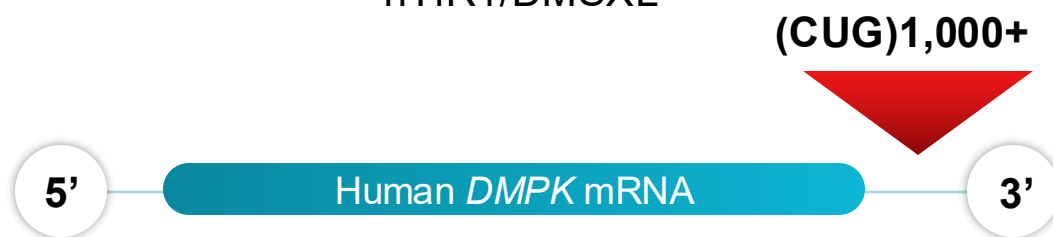
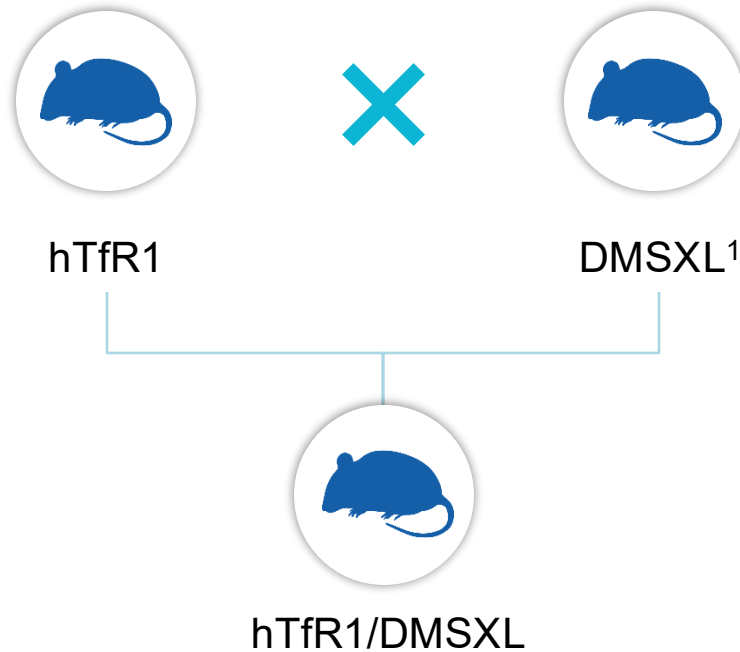
Clinical Presentation

- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities
- CNS manifestations

hTfR1/DMSXL Mice: DM1 Model to Evaluate PD of FORCE in Muscle and Brain



Uptakes human TfR1 targeting Fabs Expresses human toxic *DMPK*



- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Expresses human toxic *DMPK* in muscle and brain^{2,3}

Approach to Investigate FORCE Delivery to CNS in the hTfR1/DMSXL Model of DM1

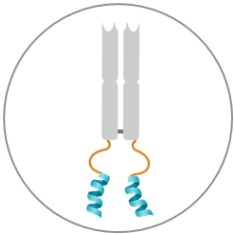


Tool molecules



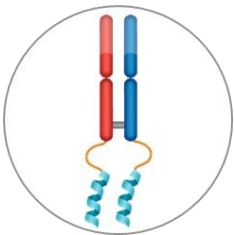
Naked ASO

- Gapmer ASO for human *DMPK*



Negative Control

- Fab recognizes HIV protein



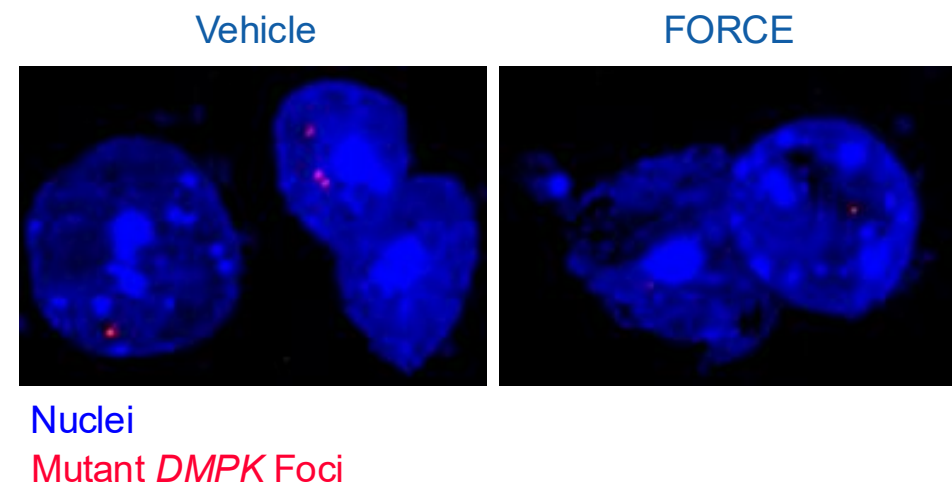
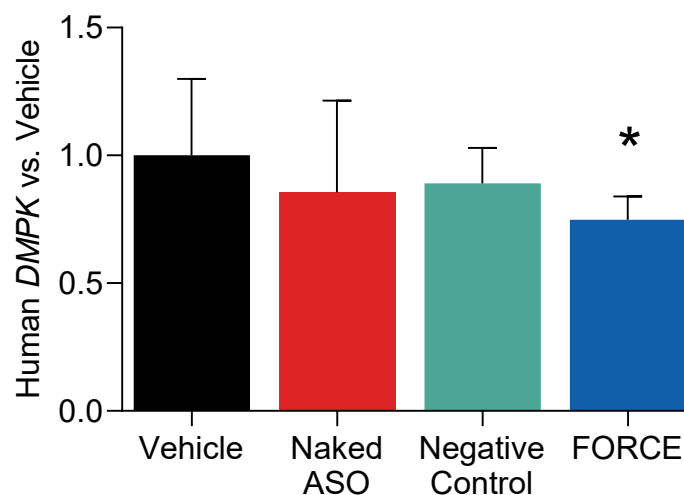
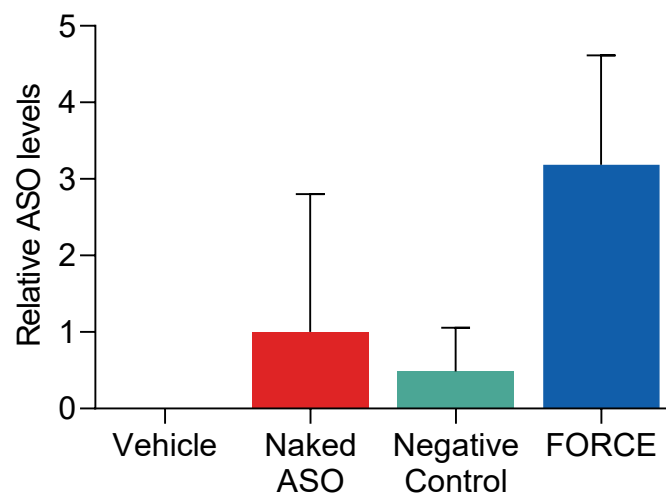
FORCE

- Fab recognizes human/cyno TfR1

Endpoints

- ASO levels in brain and cerebellum
- Toxic human *DMPK* expression
- *DMPK* foci area in brain cells

FORCE Conjugate Delivers to Brain Cortex and Achieves Toxic Human Nuclear *DMPK* KD and Foci Reduction in hTfR1/DMSXL Mice



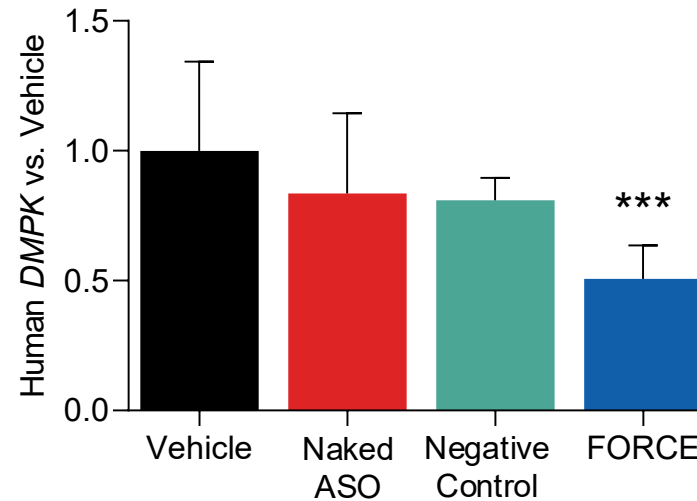
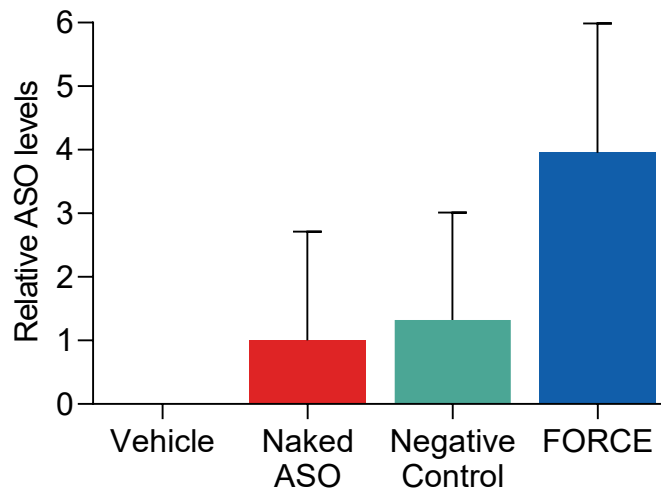
FORCE Conjugate Delivers to Cerebellum and Achieves Toxic Human Nuclear *DMPK* KD and Foci Reduction in hTfR1/DMSXL Mice



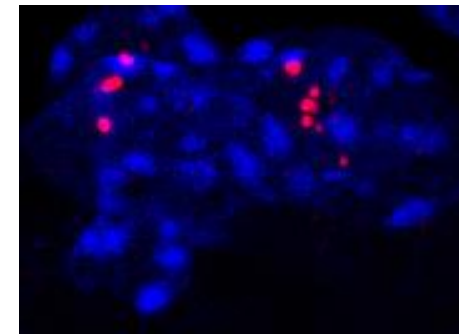
ASO delivery

DMPK KD

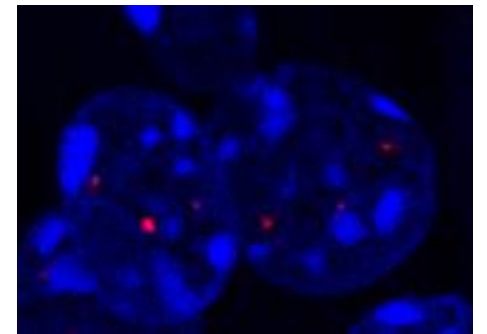
DMPK foci area reduction by ~60%*



Vehicle



FORCE



Nuclei
Mutant *DMPK* Foci

Conclusions

- The FORCE platform demonstrated robust delivery of oligonucleotides to skeletal, cardiac, smooth muscle and CNS leveraging a TfR1-mediated mechanism
- Superior and widespread delivery compared to naked ASO administered IV or IT in NHP
- In DM1 model, FORCE conjugate achieved *DMPK* KD and foci reduction in the brain
- The FORCE platform has the potential to overcome barriers of oligonucleotide delivery to the brain, which is critically important for the treatment of neuromuscular disorders, including DM1

Acknowledgements

Dyne Neuromuscular Research

- Jin Cui
- Jenn Johnson
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- Pei-Ni Tsai
- Timothy Weeden

Dyne Platform Pharmacology

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- Kim Tang