



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

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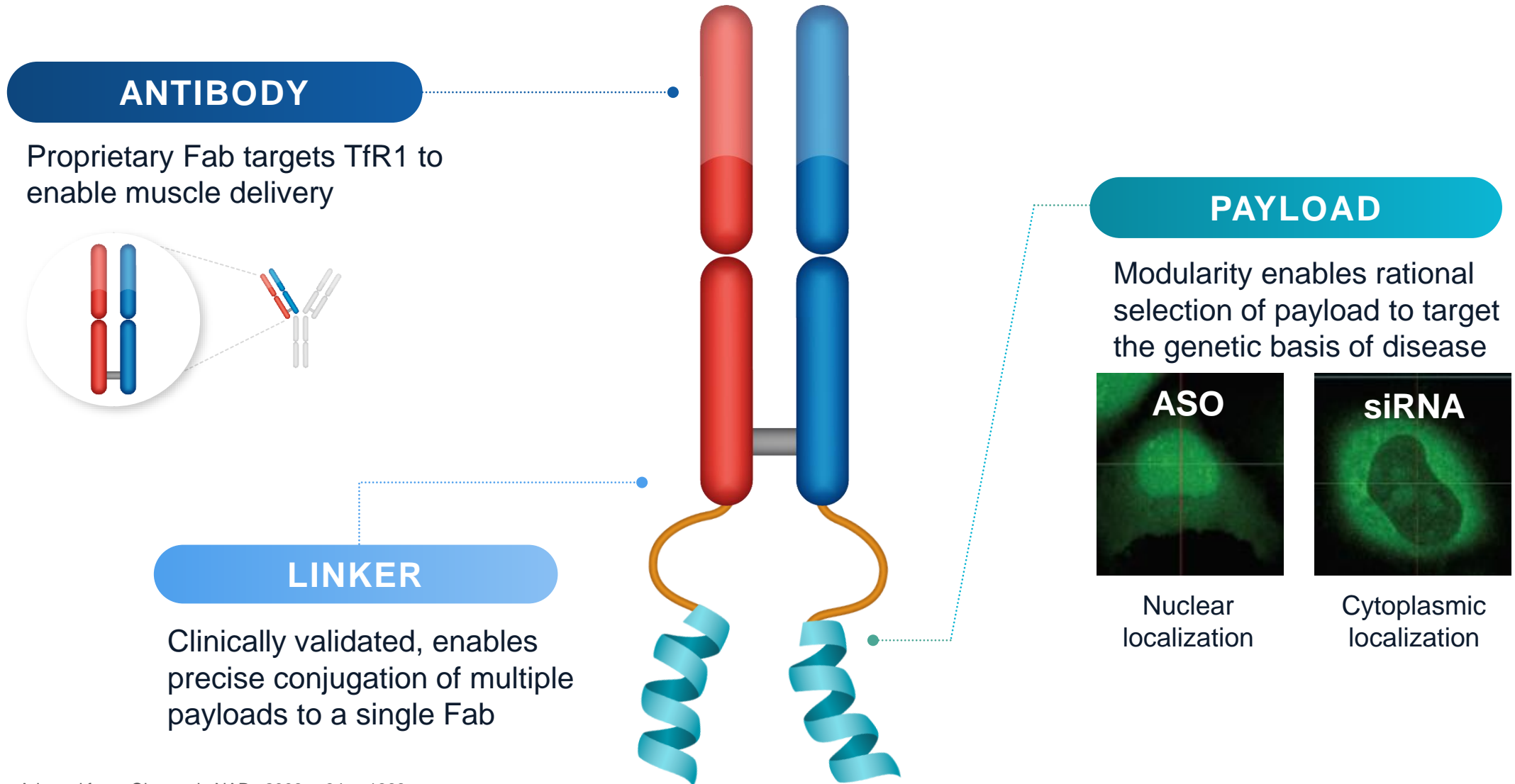
Joachim, living with DM1

# Forward-Looking Statements

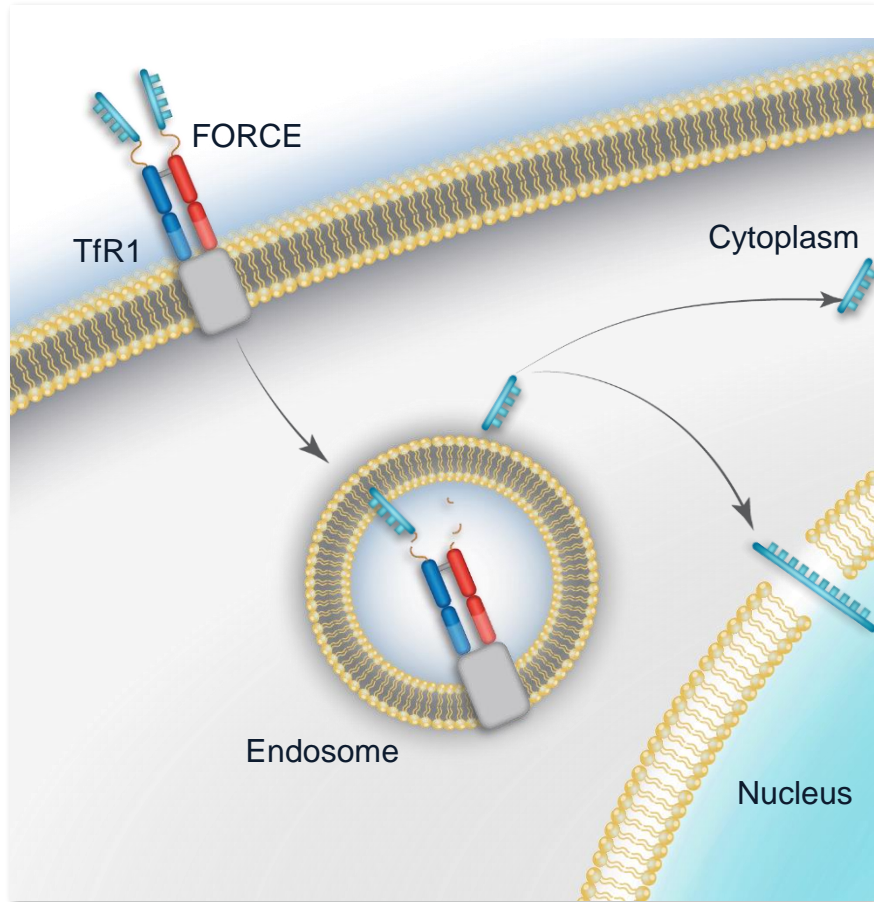
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# Dyne FORCE™ Platform: Modern Oligo Therapeutics for Neuromuscular Diseases



# FORCE Platform Harnesses Cell Biology to Modify Disease

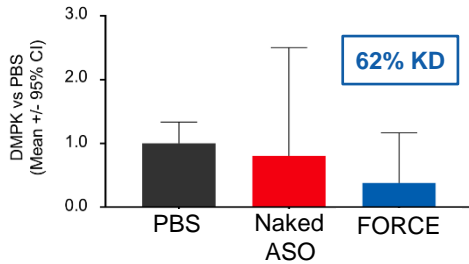


- Harnesses natural mechanism of TfR1 receptor-mediated delivery to transport therapeutics across the cell membrane
- Achieves endosomal escape without any membrane-destabilizing agents
- Distinctive pharmacokinetic profile creates opportunity for durable target engagement and wide therapeutic index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

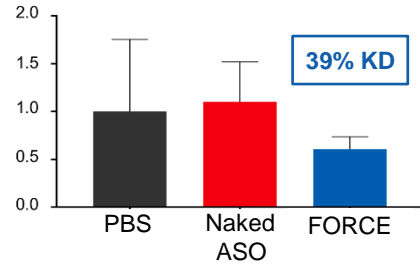
# FORCE Platform Overcomes the Barriers of Oligonucleotide Delivery to Muscle



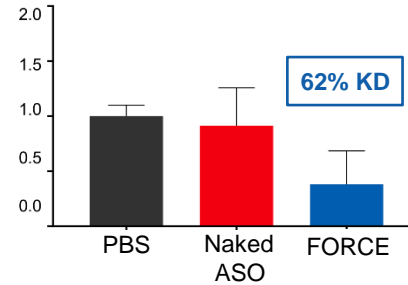
### Gastrocnemius



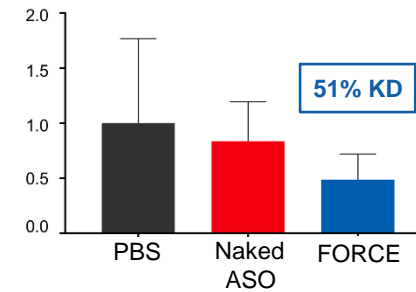
### Soleus



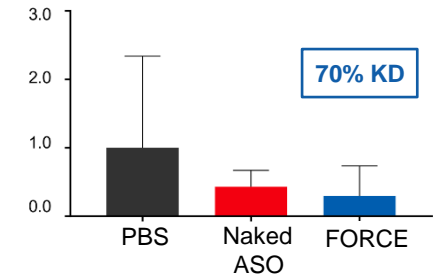
### Deep Flexor



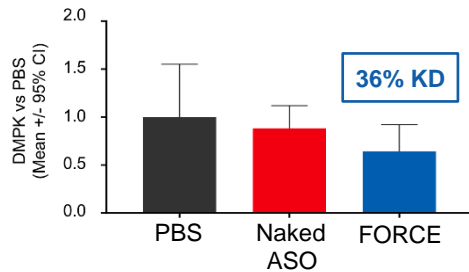
### Bicep



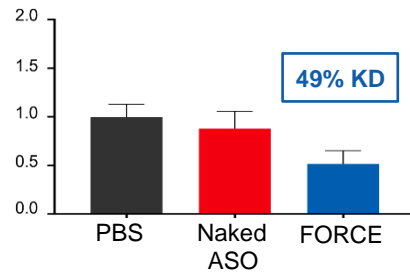
### Ileum (Near Cecum)



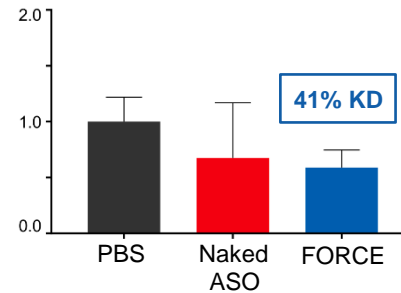
### Heart-left Ventricle



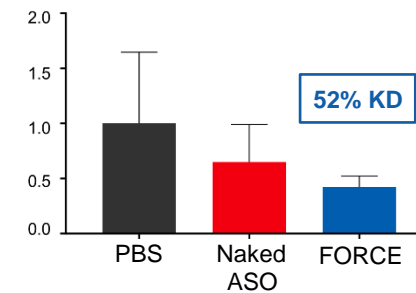
### Diaphragm



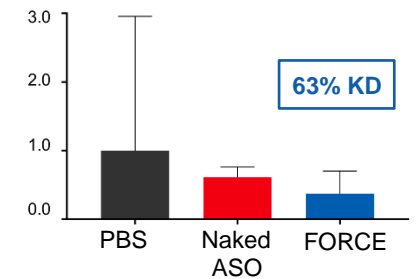
### Masseter



### Quadricep

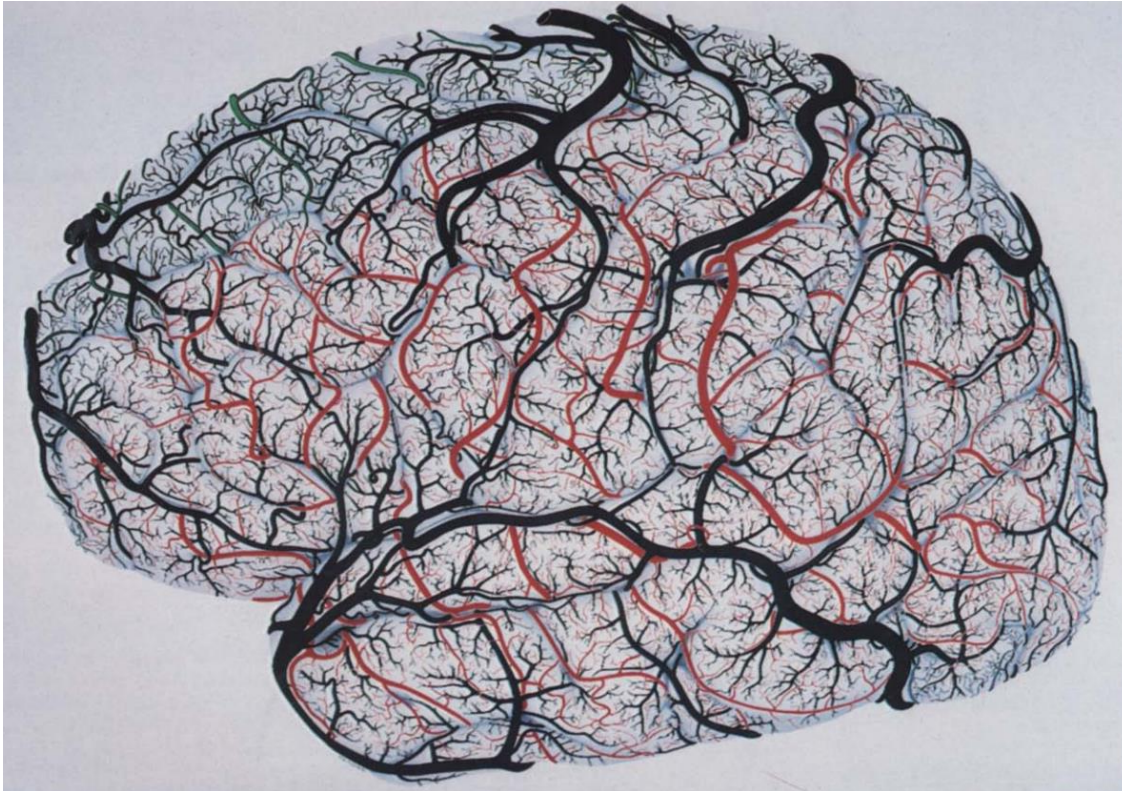


### Jejunum (Duodenum Ends)

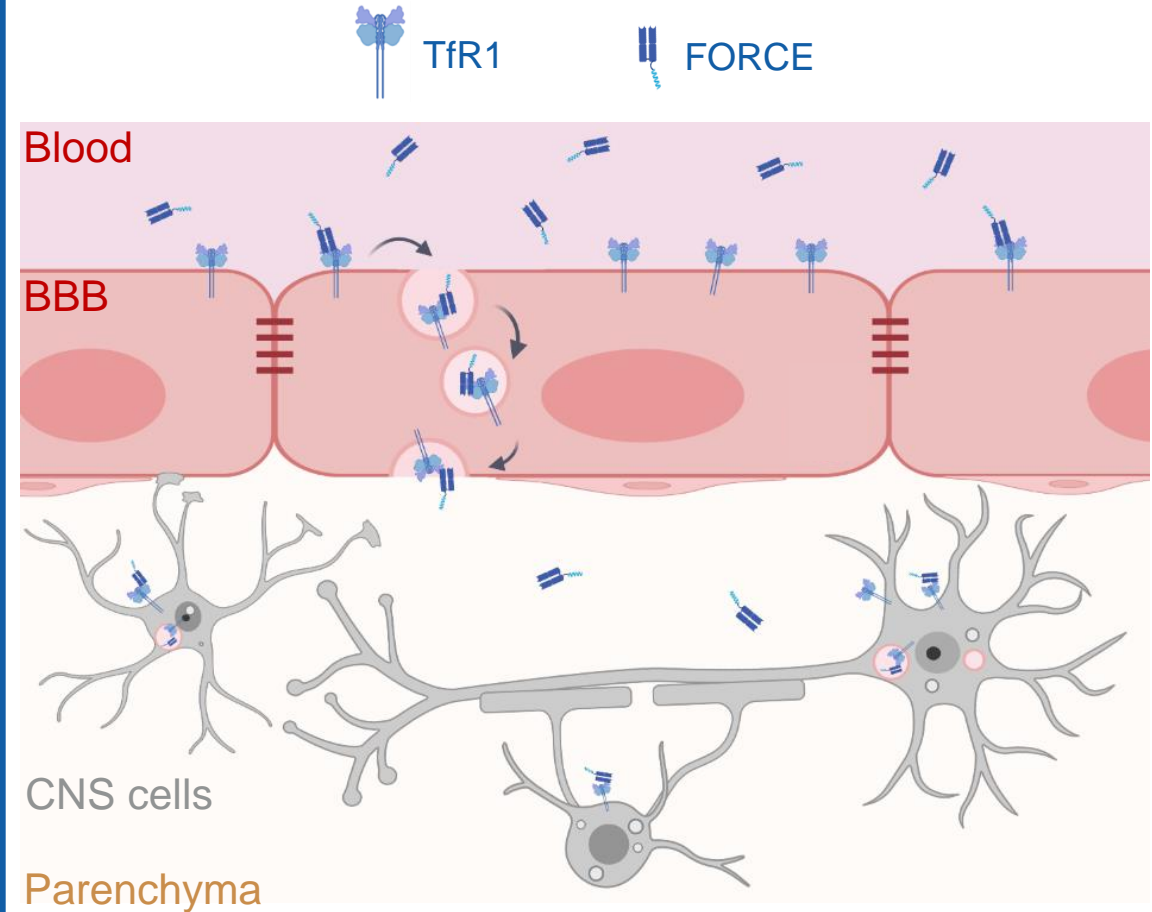


# FORCE Platform has the Potential to Cross the Blood-brain Barrier (BBB) and Achieve Widespread Brain Delivery

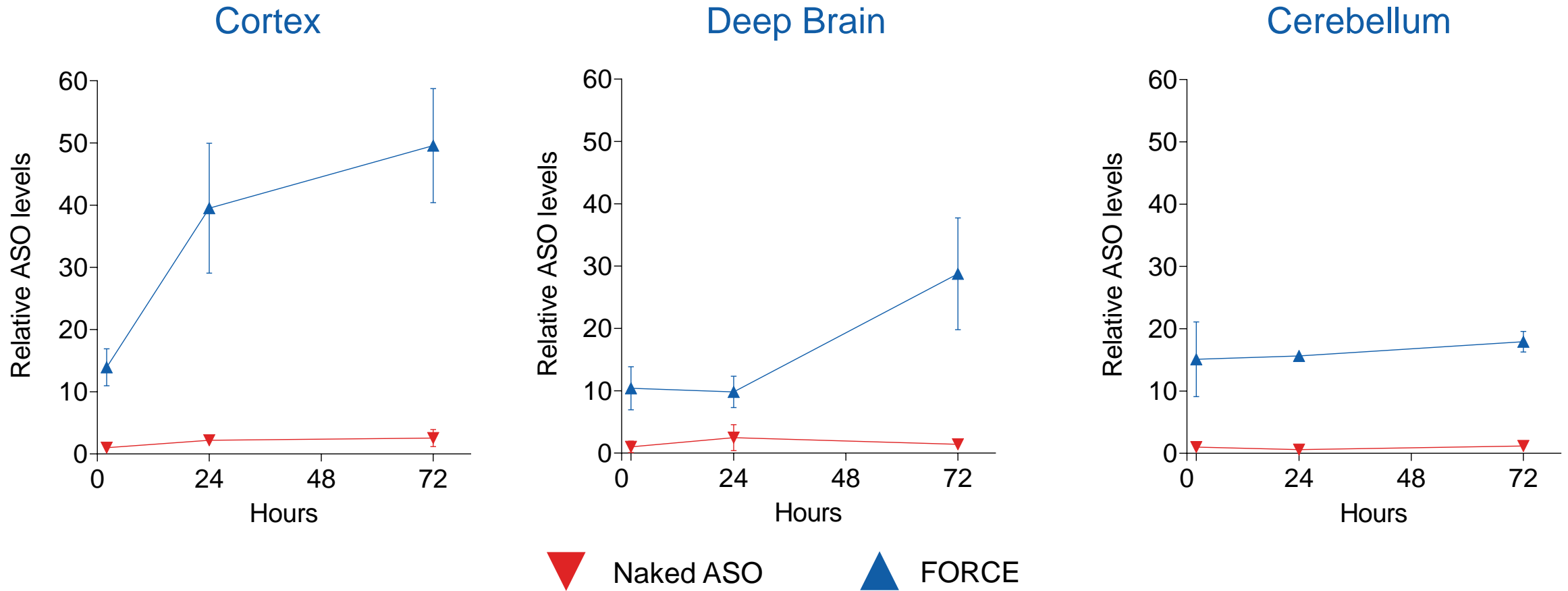
400-mile-long brain capillary network:  
Enables widespread delivery



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

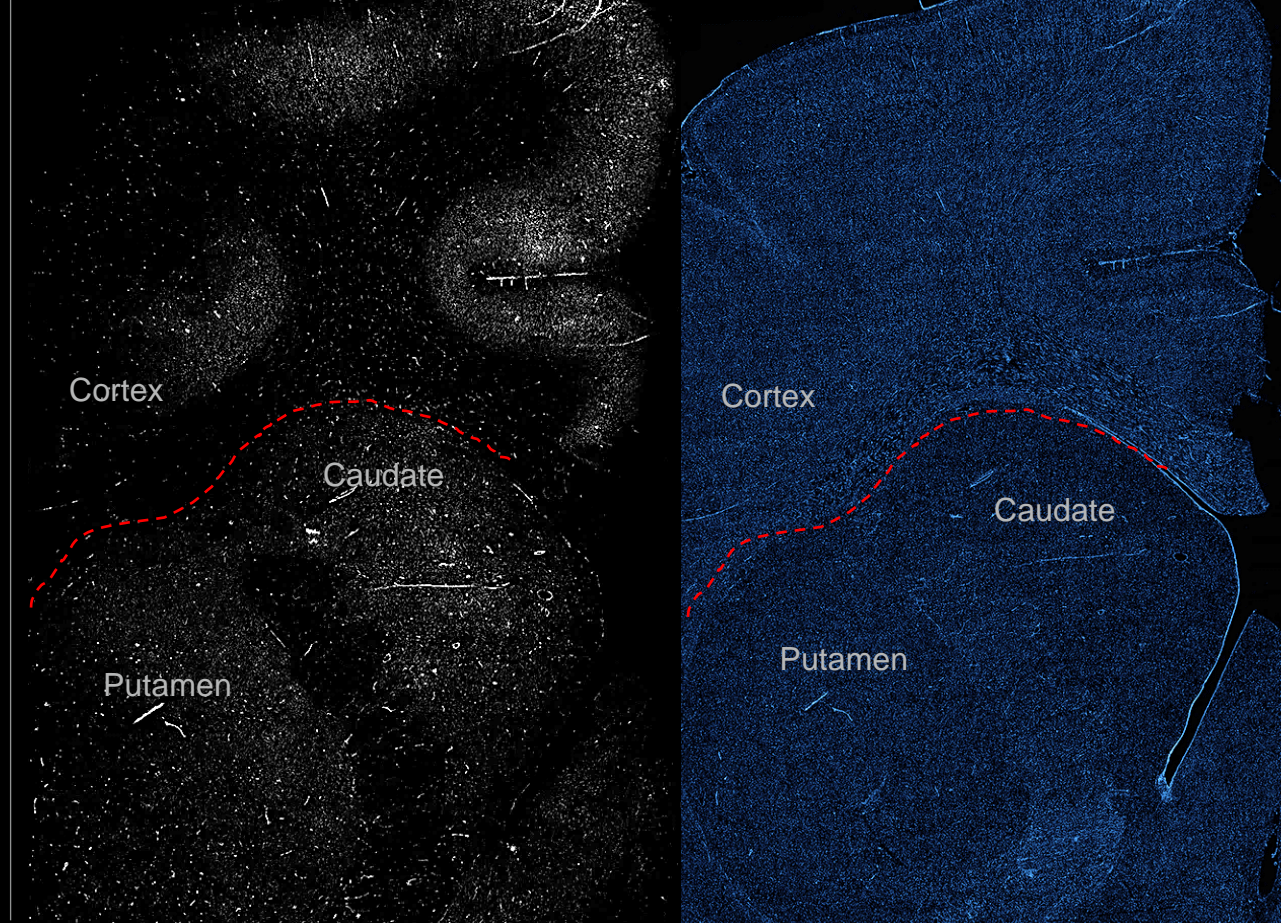
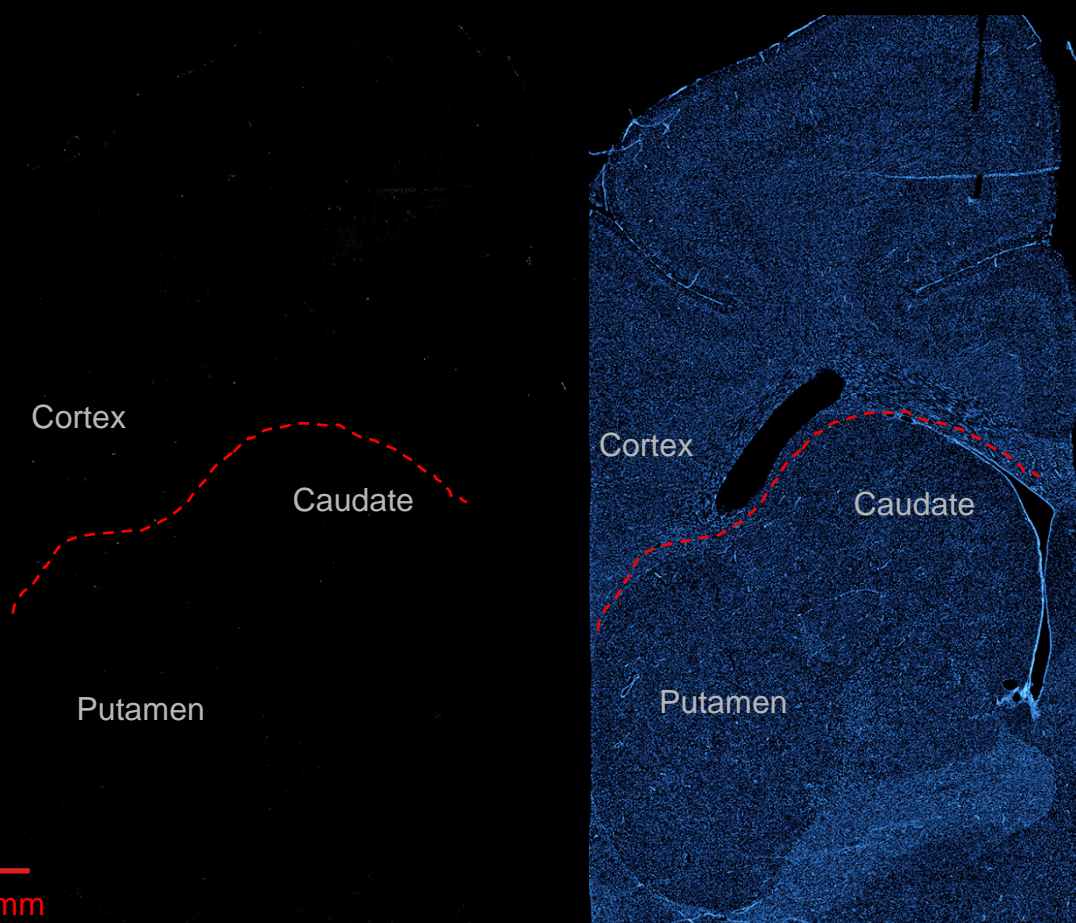
FORCE, IV  
Widespread ASO delivery

ASO staining

Brain morphology

ASO staining

Brain morphology

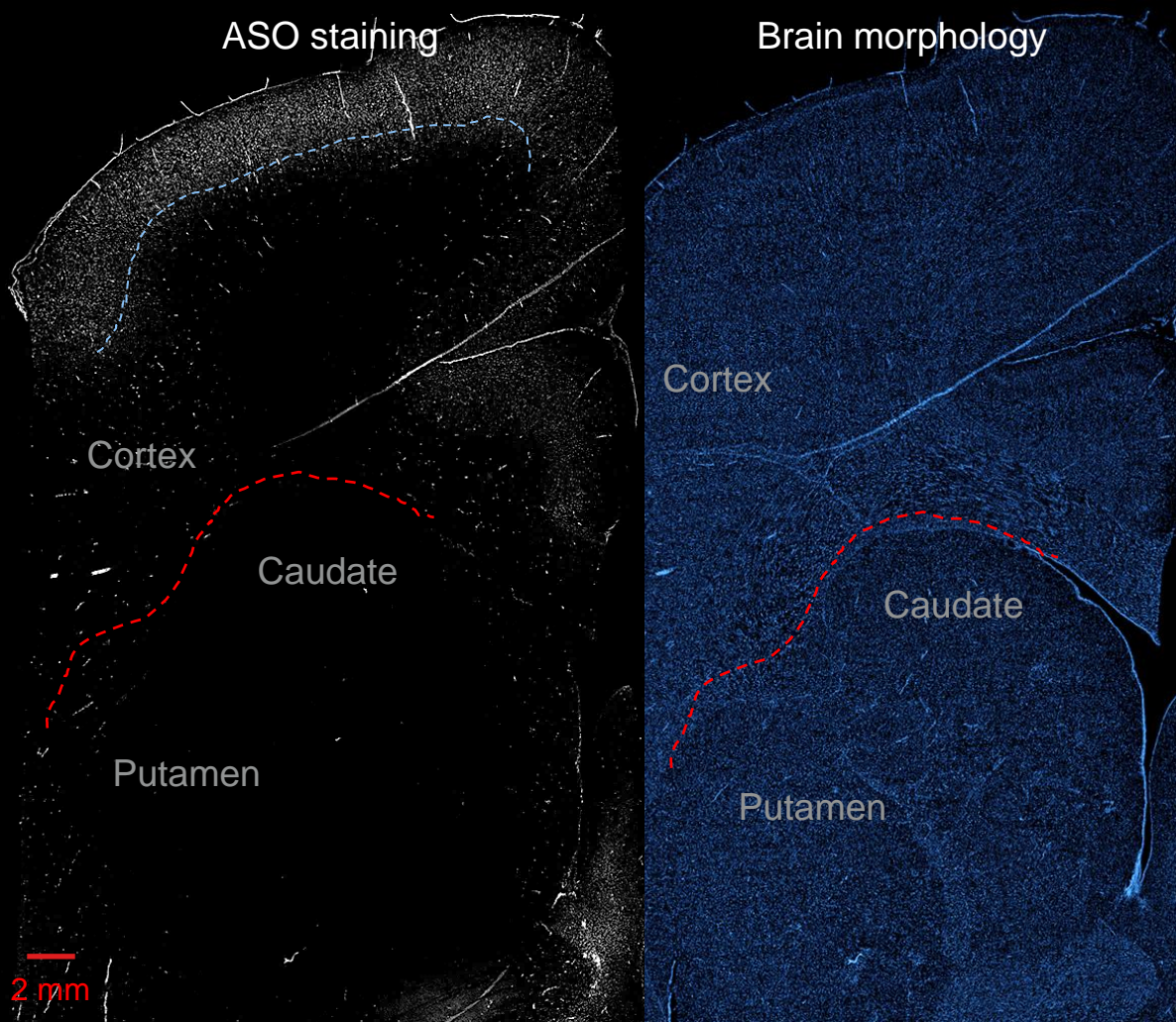




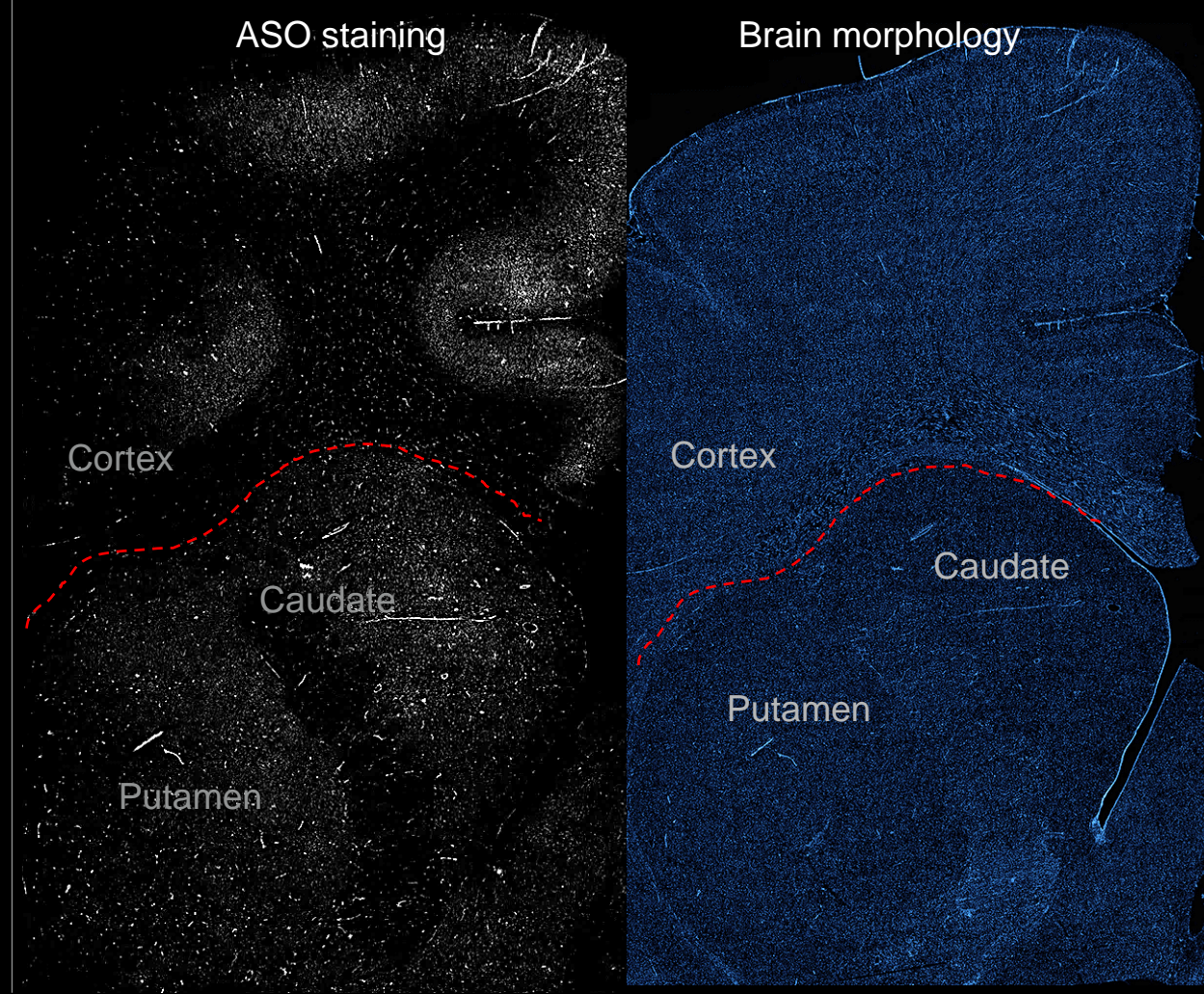
# FORCE Conjugate Achieves Broader Delivery Compared to IT Administration of Naked ASO in NHP



**Naked ASO IT**  
Limited ASO distribution

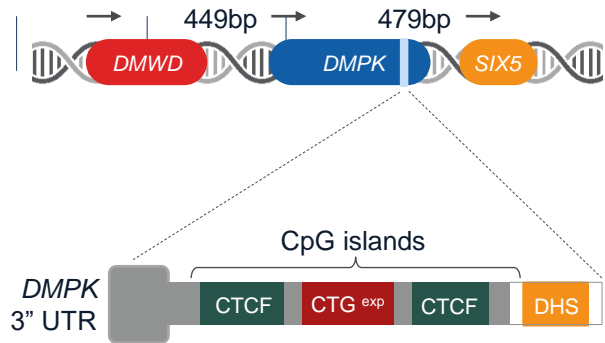


**FORCE, IV**  
Widespread ASO distribution

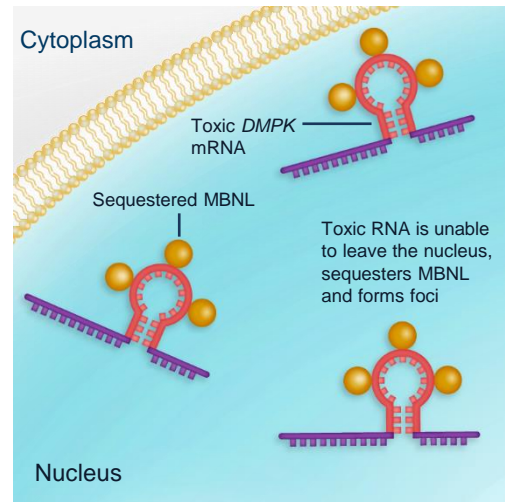


# DM1 is a Spliceopathy with Muscle and CNS Clinical Manifestations

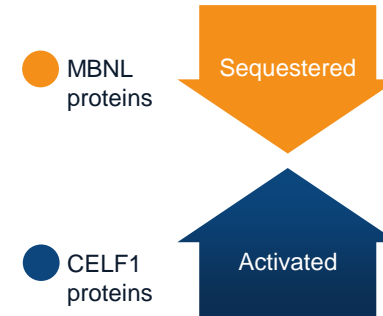
DNA Triplet Repeats



Toxic RNA Forms Foci in Nucleus



RNA Binds Splicing Proteins



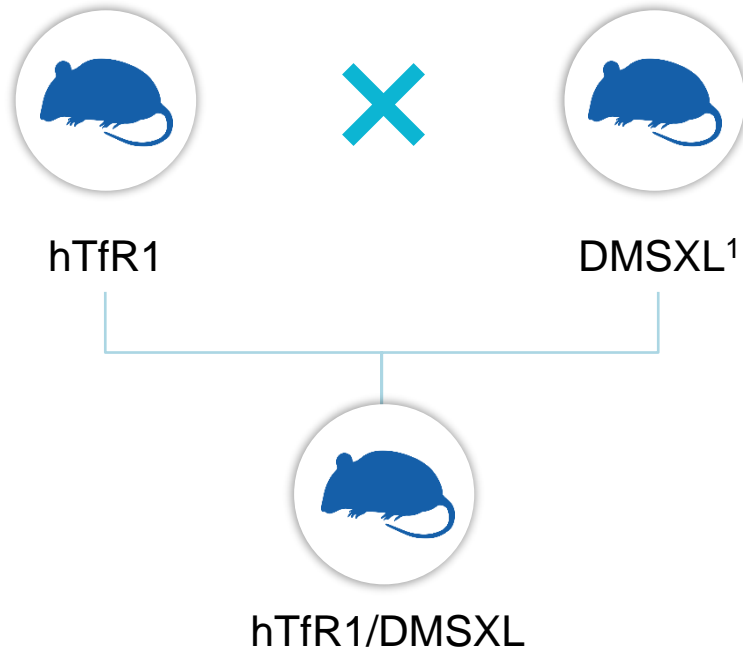
Clinical Presentation

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

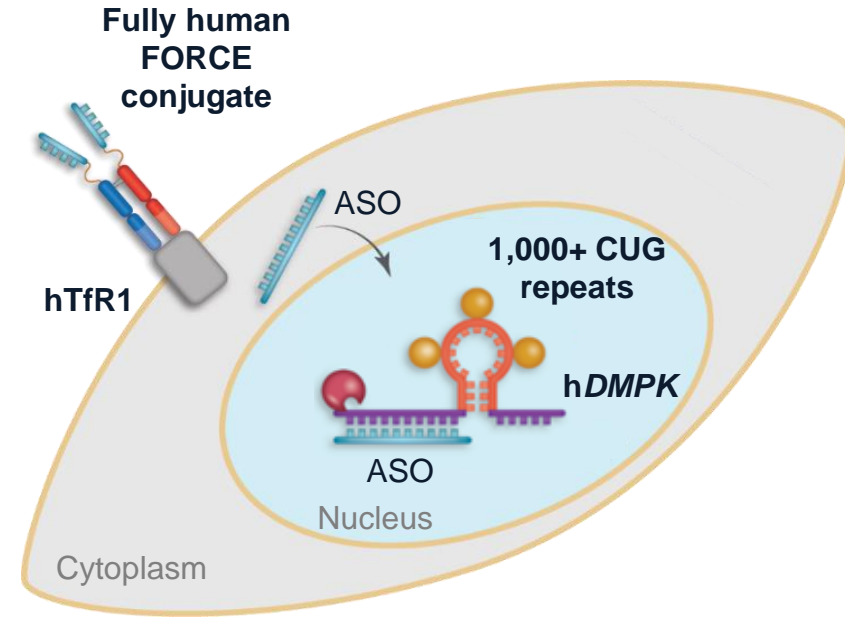
# hTfR1/DMSXL Mice: DM1 Model to Evaluate PD of FORCE in Muscle and Brain



Uptakes human TfR1 targeting Fabs      Expresses human toxic *DMPK*



(CUG)<sub>1,000+</sub>



- Expresses human TfR1 receptor, enabling use of human TfR1-targeting Fabs
- Expresses human toxic *DMPK* in muscle and brain<sup>2,3</sup>

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

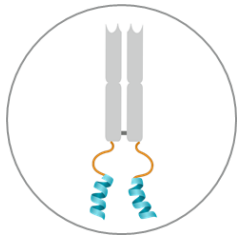


## Tool molecules



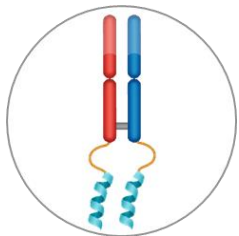
### Naked ASO

- Gapmer ASO for human *DMPK*



### Negative Control

- Fab recognizes HIV protein



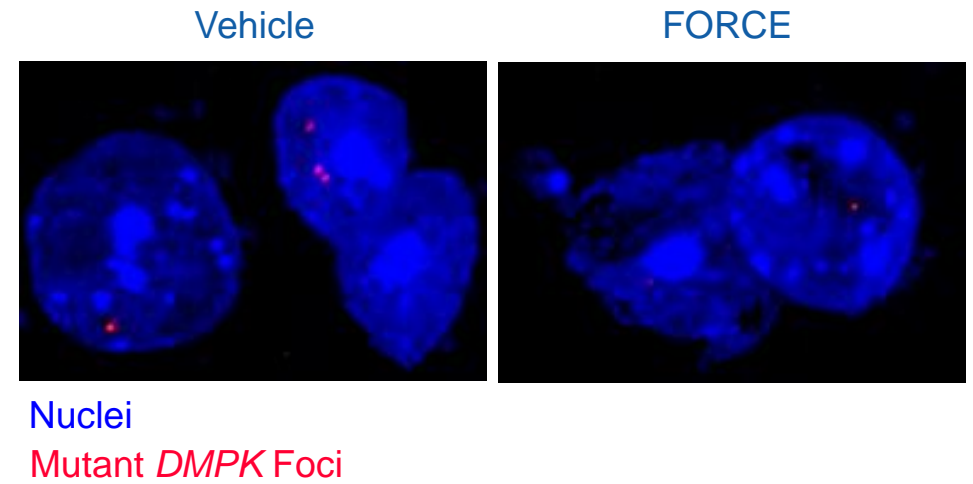
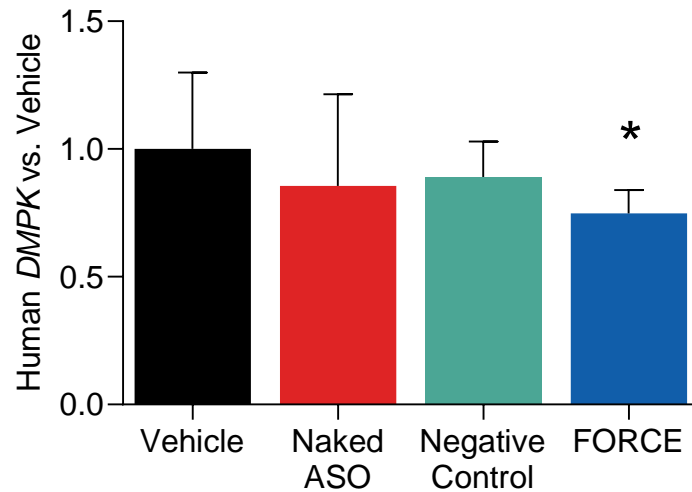
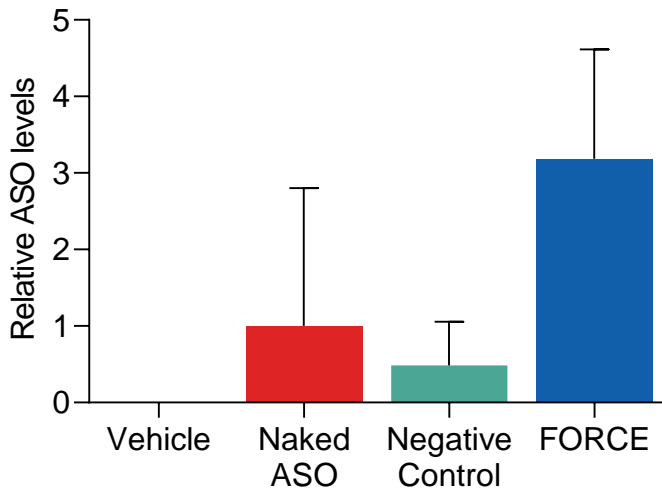
### FORCE

- Fab recognizes human/cyno TfR1

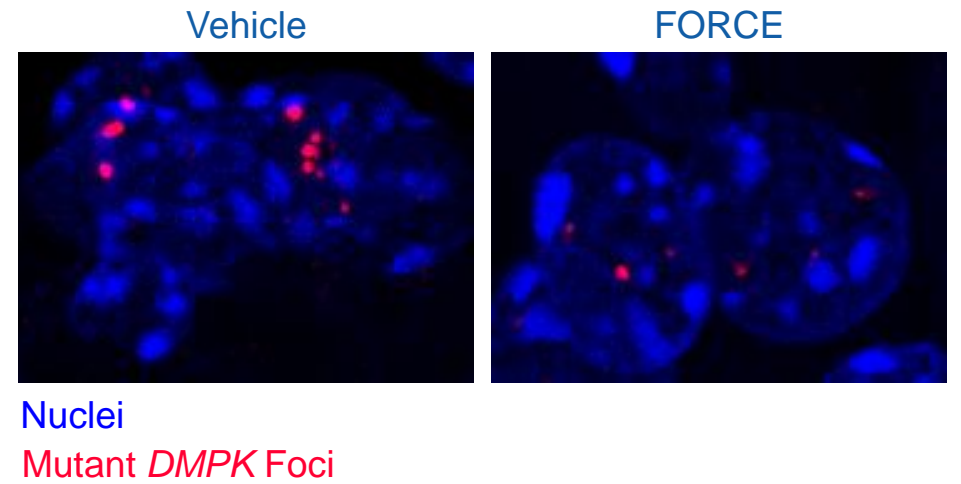
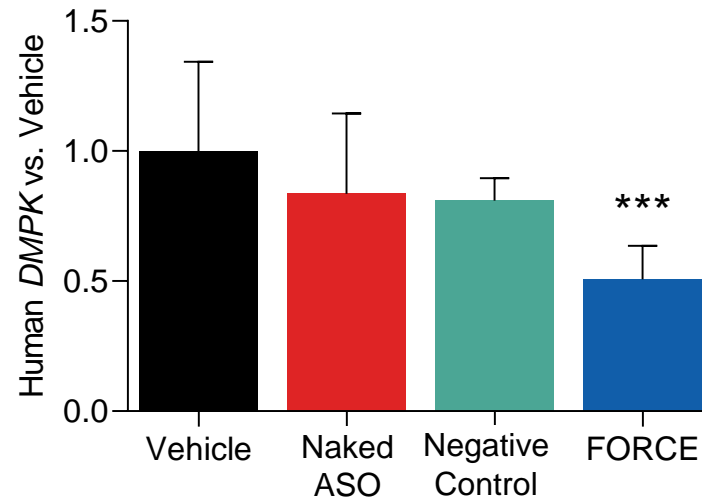
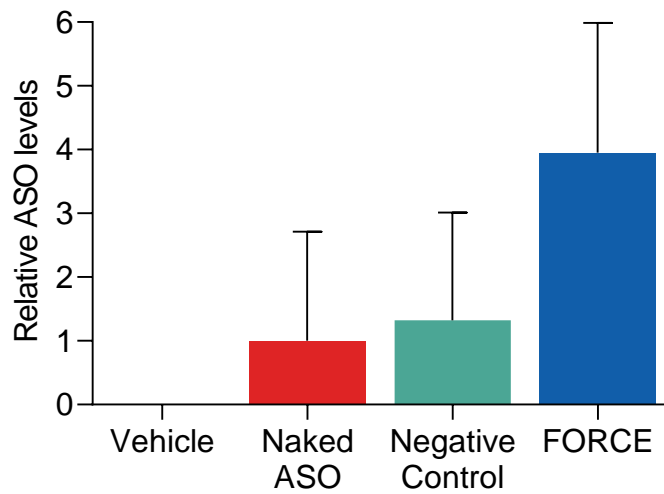
## Endpoints

- 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



# Conclusions

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- 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

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- Pei-Ni Tsai
- Timothy Weeden

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- Kim Tang