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

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Joachim, *living with DM1*

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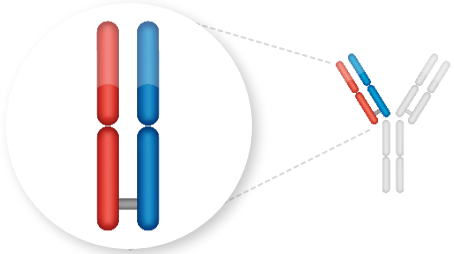
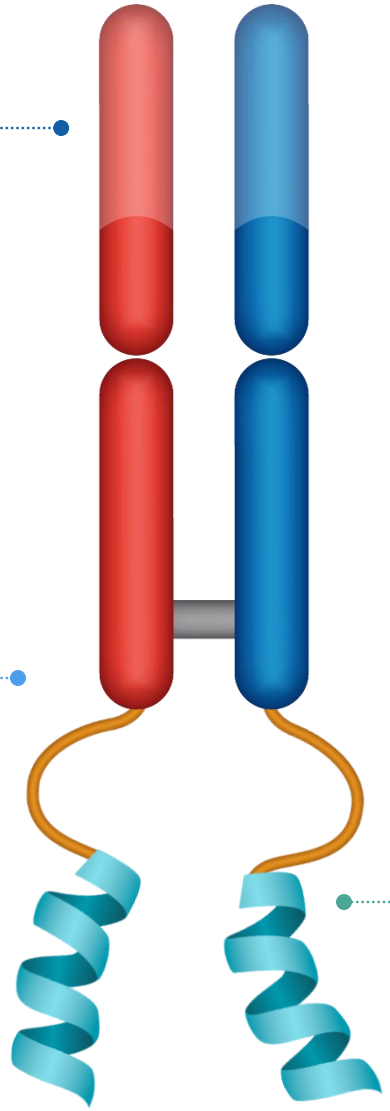
Dyne FORCE™ Platform: Modern Oligo Therapeutics for Neuromuscular Diseases

ANTIBODY

Proprietary Fab targets TfR1 to enable muscle delivery



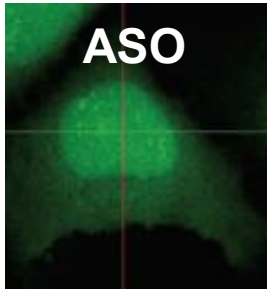


LINKER

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

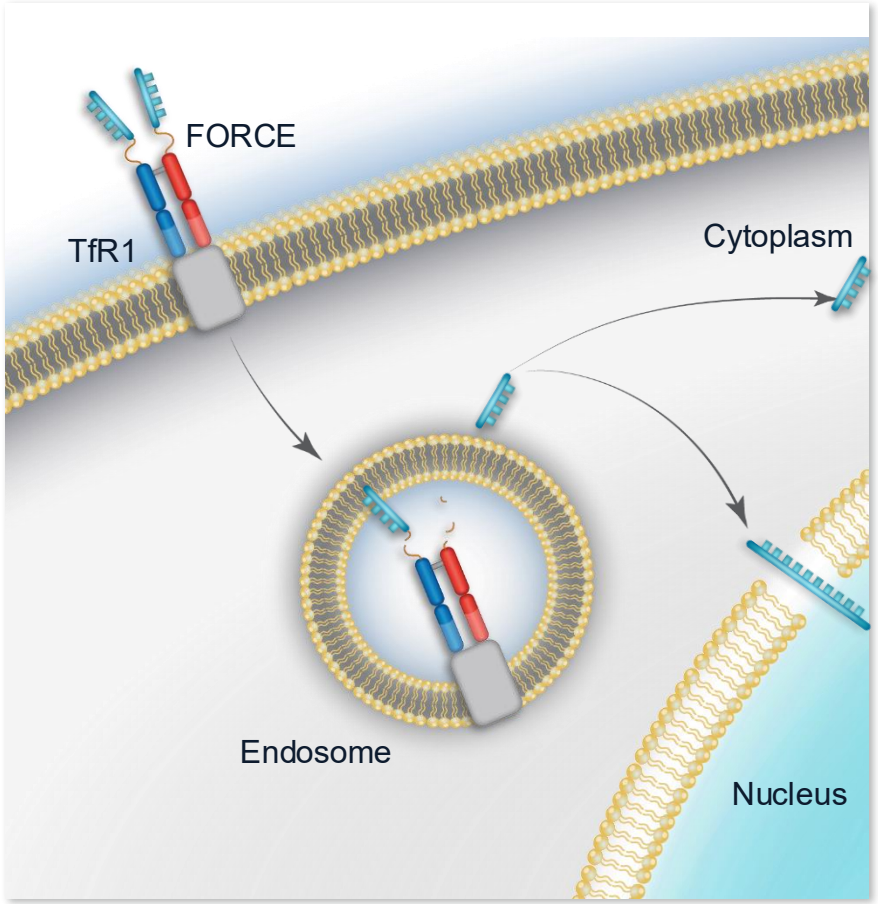


Nuclear localization

Cytoplasmic localization

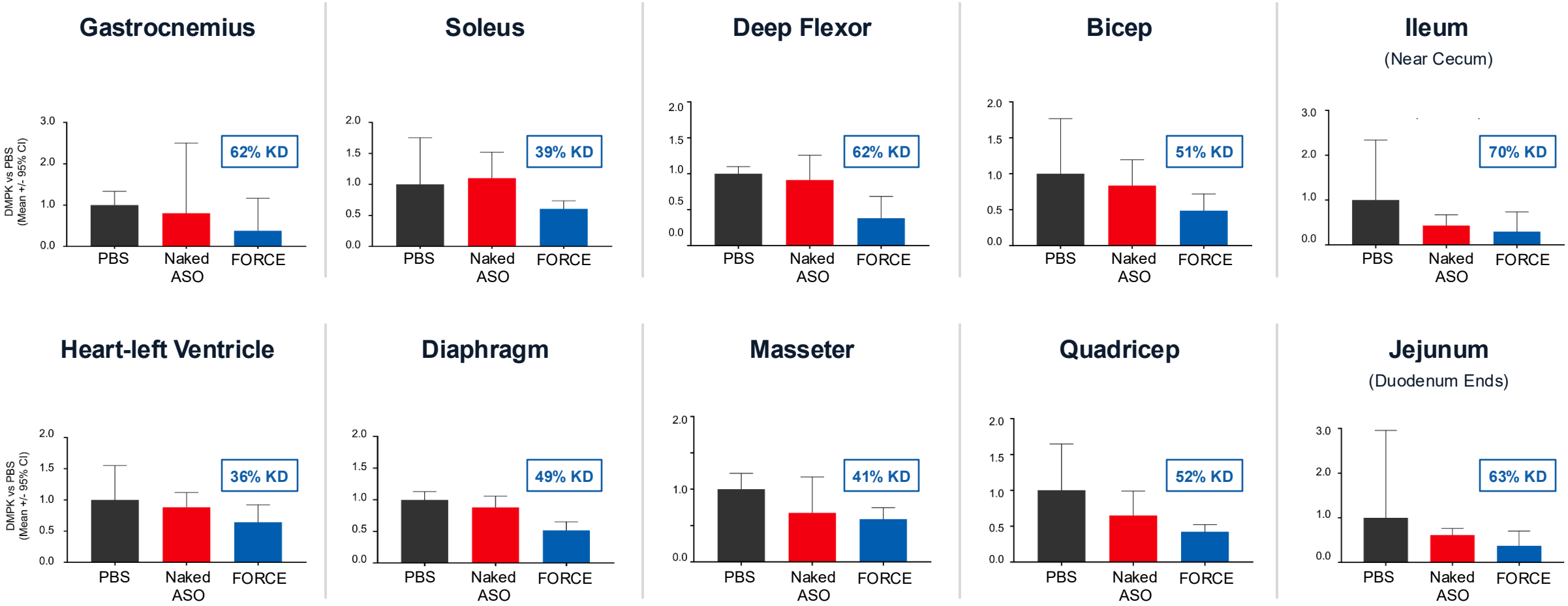
Adapted from: Ohrt et al.: NAR , 2006, v.34, p.1369

FORCE 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

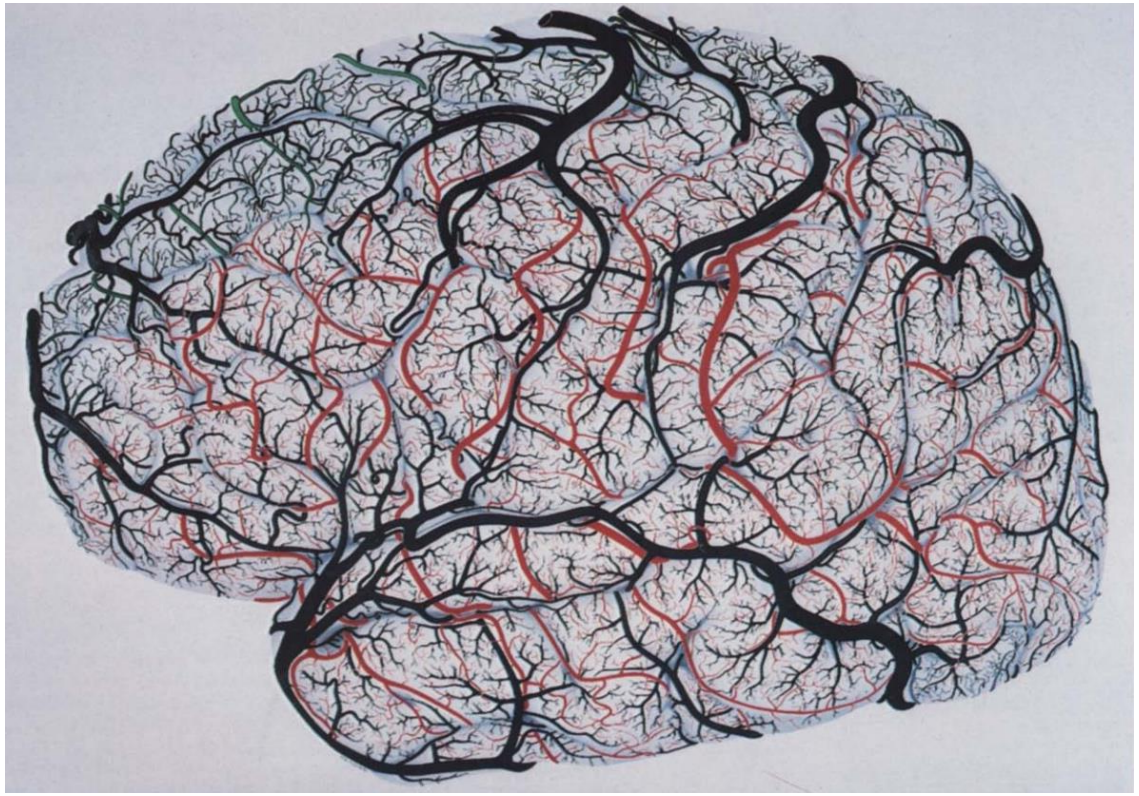
FORCE Platform Overcomes the Barriers of Oligonucleotide Delivery to Muscle



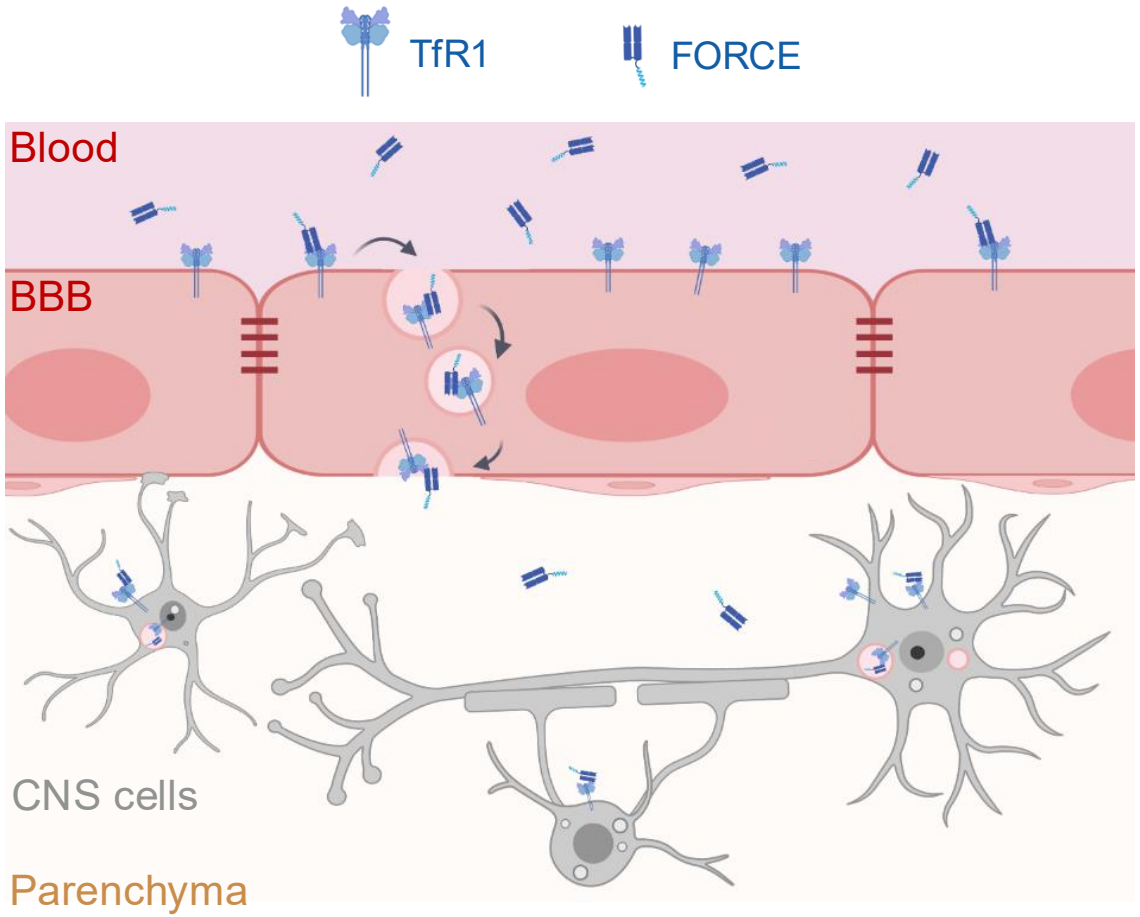
DMPK KD in cynomolgus monkeys dosed IV 10 mg/kg on day 0; analyzed day 14. Data are mean + 95% CI, n = 3 per group

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

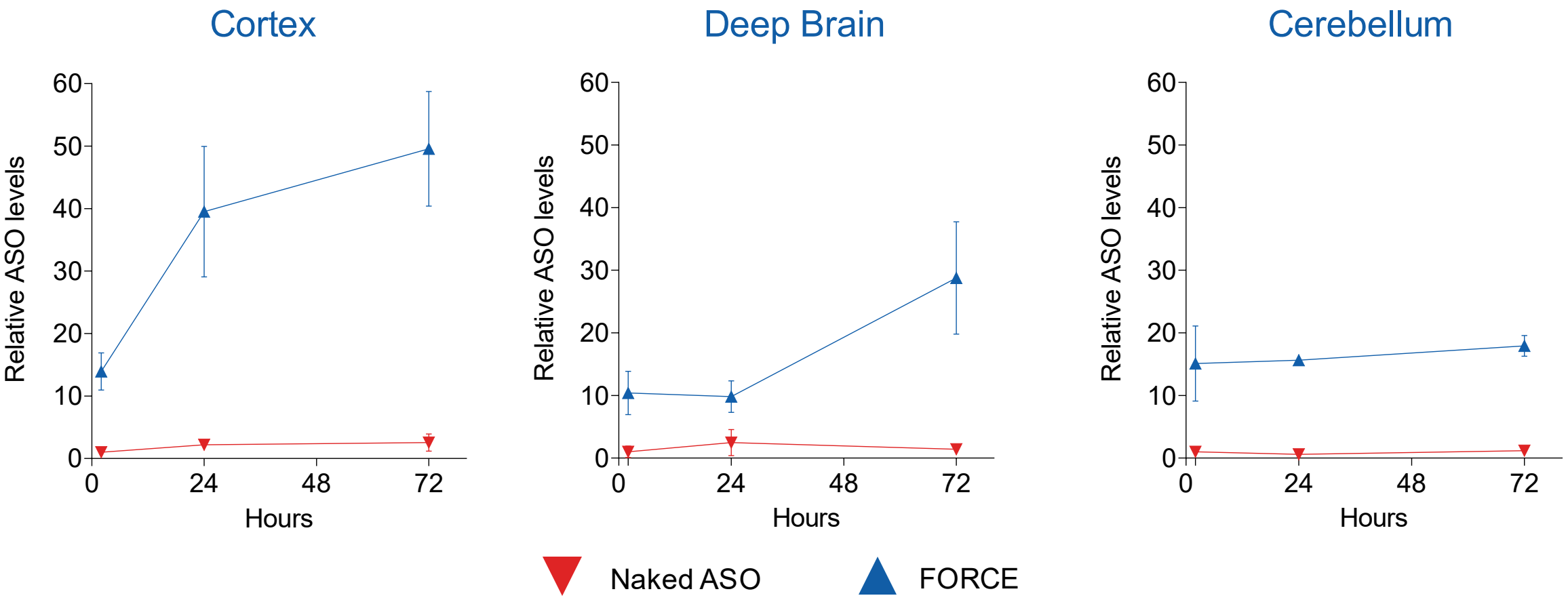


TfR1-mediated transcytosis: Potential for crossing the BBB



Brain image adapted from Duvernoy HM, Delon S, Vannson JL. *Brain Res Bull* 1981;5:519-579. Schematic created by BioRender.com

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

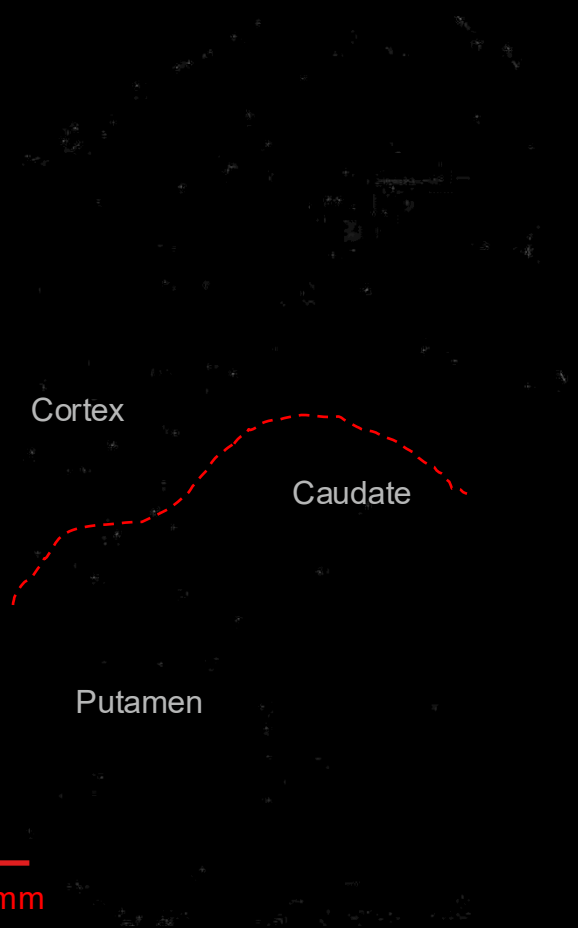


Cynomolgus monkeys dosed IV 10 mg/kg at time 0. Data are mean ± SEM relative to naked ASO at 2h; n = 2

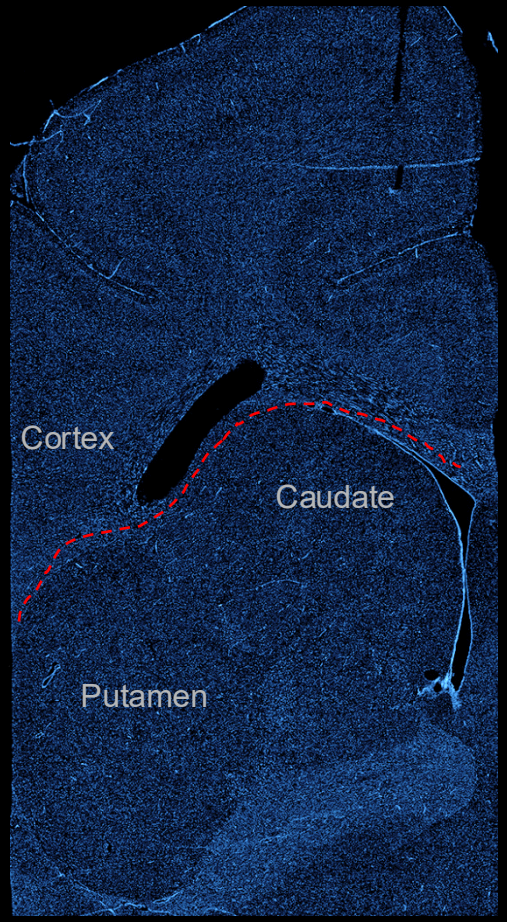
FORCE Conjugate Delivers Broadly Throughout the Brain in NHP

Naked ASO, IV
No ASO delivery

ASO staining

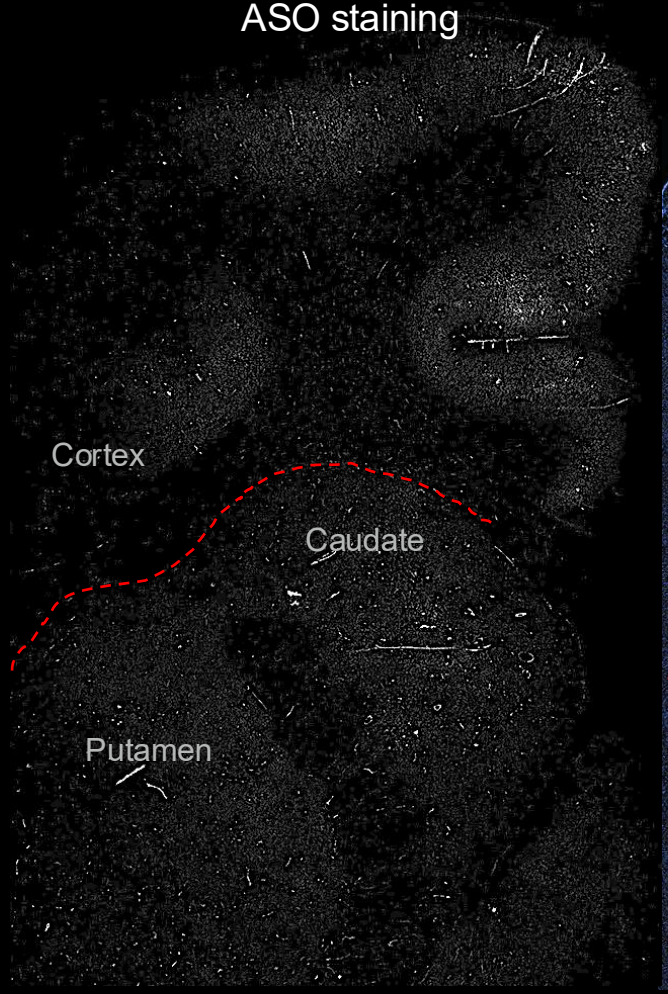


Brain morphology

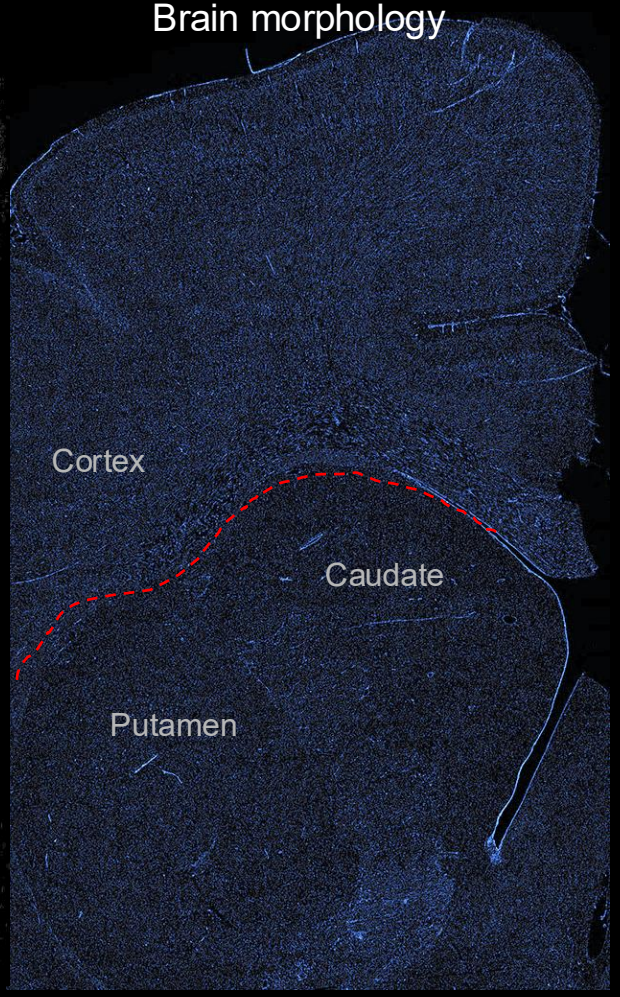


FORCE, IV
Widespread ASO delivery

ASO staining



Brain morphology

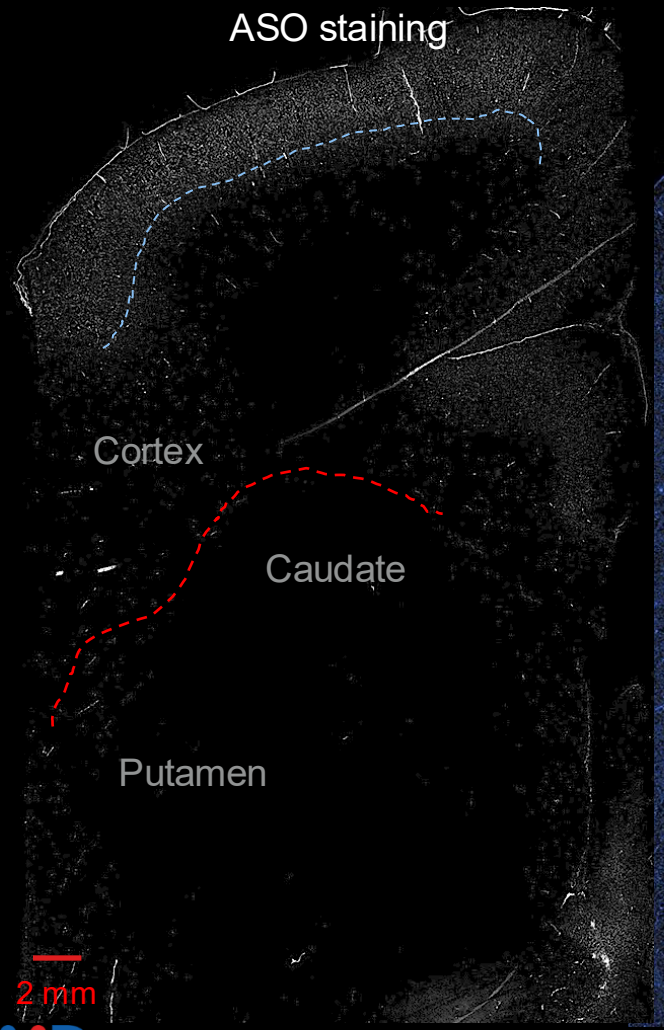


2 mm

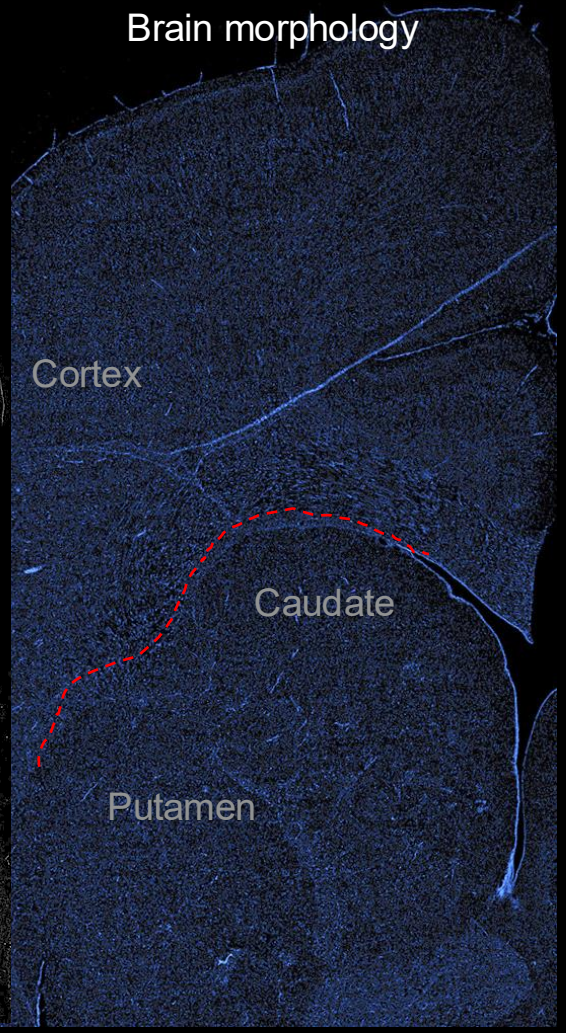
FORCE Conjugate Achieves Broader Delivery Compared to IT Administration of Naked ASO in NHP

Naked ASO IT
Limited ASO distribution

ASO staining

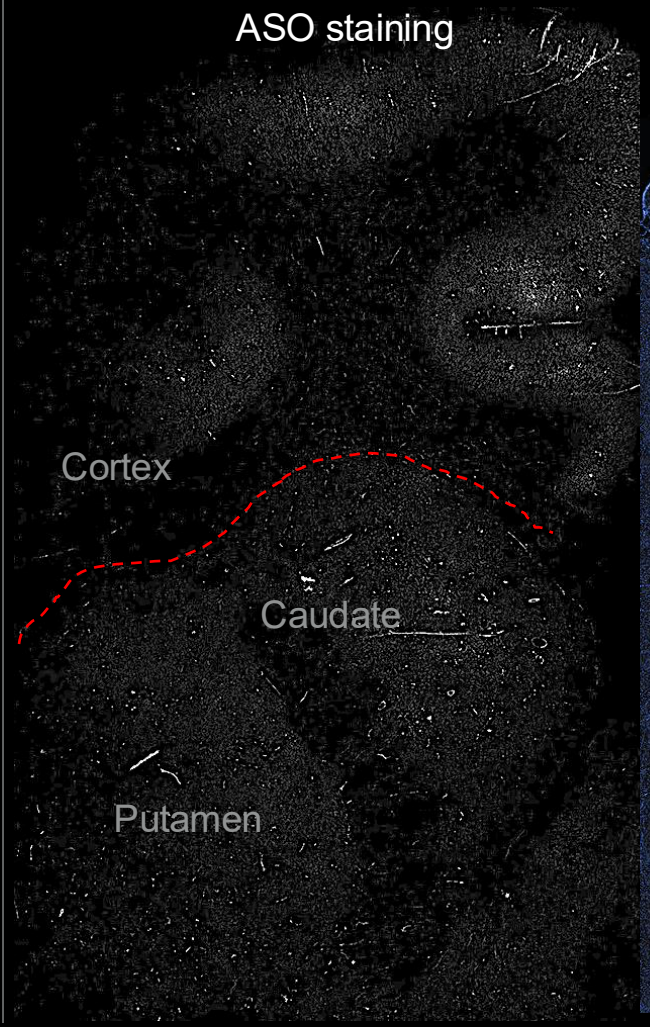


Brain morphology

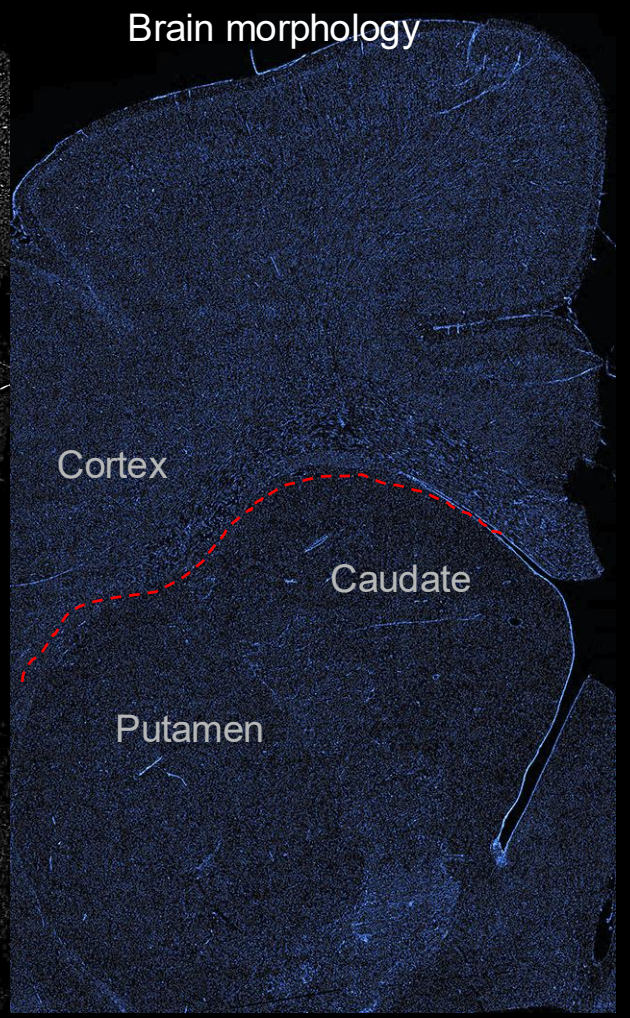


FORCE, IV
Widespread ASO distribution

ASO staining

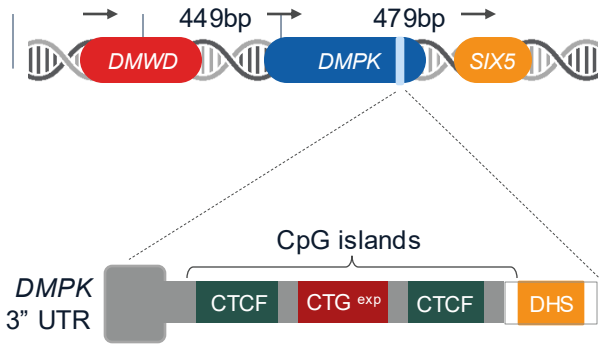


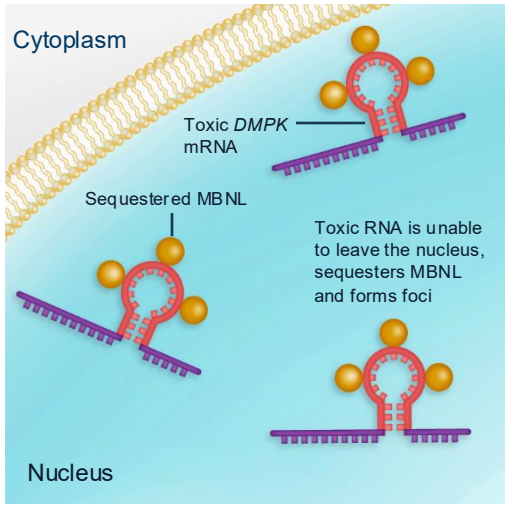
Brain morphology

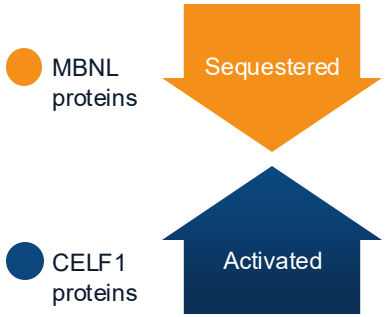


DM1 is a Spliceopathy with Muscle and CNS Clinical Manifestations

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





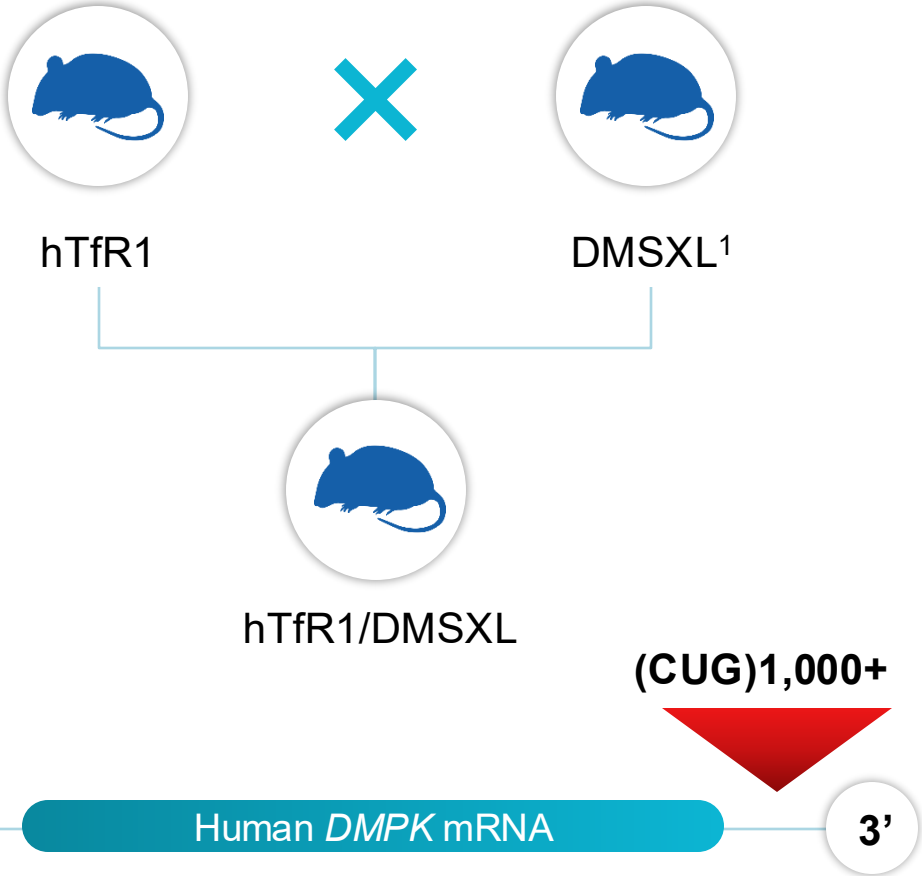


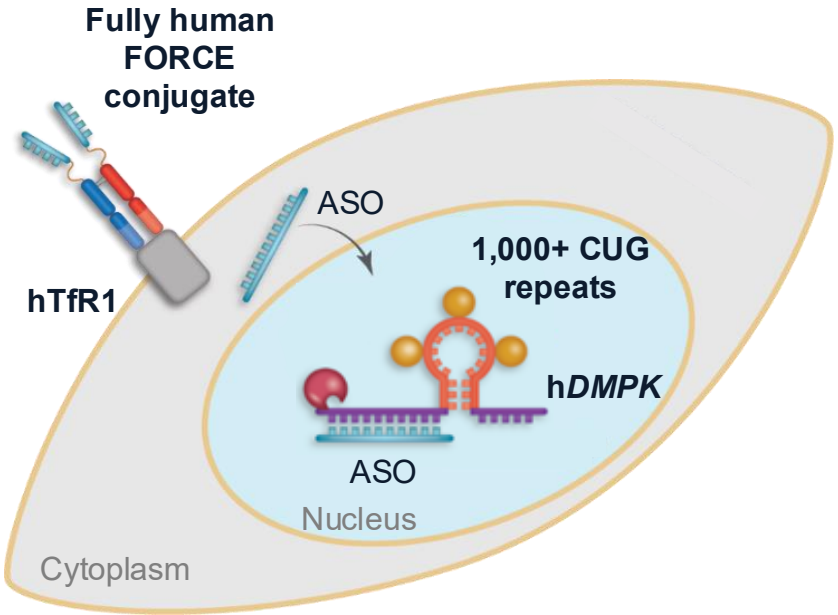
- Myotonia
- Muscle weakness
- Cardiac arrhythmia
- Pulmonary abnormalities
- CNS manifestations

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]

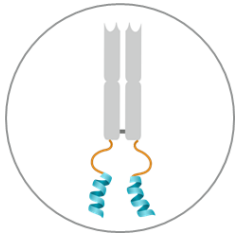
1. Huguet A, et al. *PLOS Genetics* 2012;8:e1003043; 2. Hernández-Hernández O, et al. *Brain* 2013;136:957-970; 3. Sicot G, et al. *Cell Rep* 2017;19:2718-2729.

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

Tool molecules

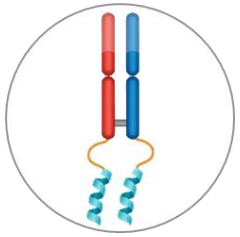
Naked ASO

- Gapmer ASO for human *DMPK*



Negative Control

- Fab recognizes HIV protein



FORCE

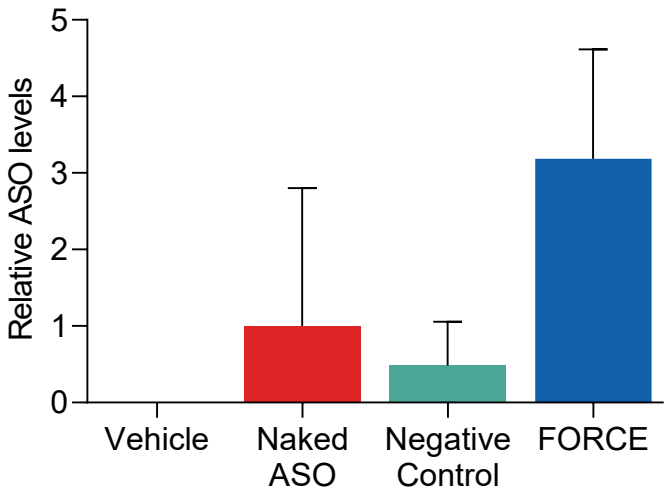
- Fab recognizes human/cyno TfR1

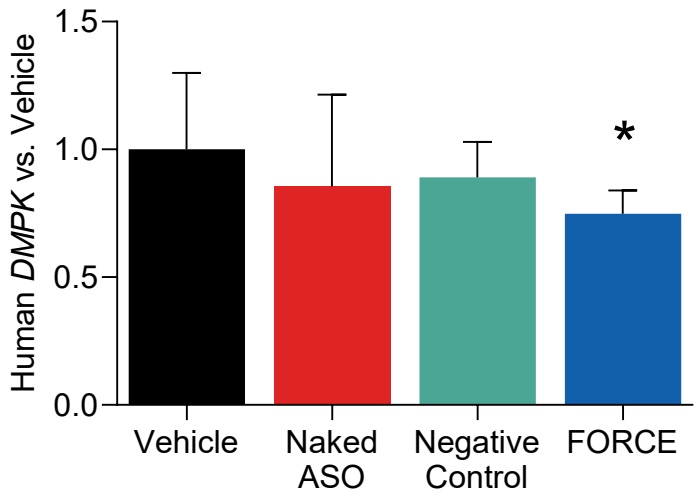
Endpoints

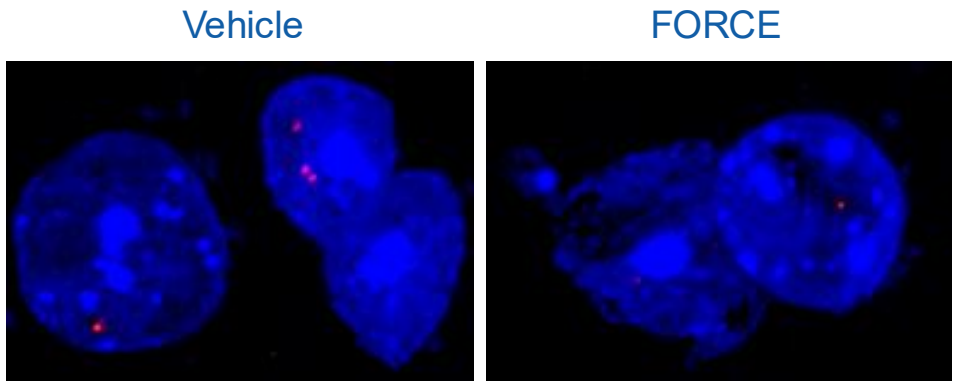
- ASO levels in brain and cerebellum
- Toxic human *DMPK* expression
- *DMPK* foci area in brain cells

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

ASO delivery → *DMPK* KD → *DMPK* foci area reduction by ~65%**





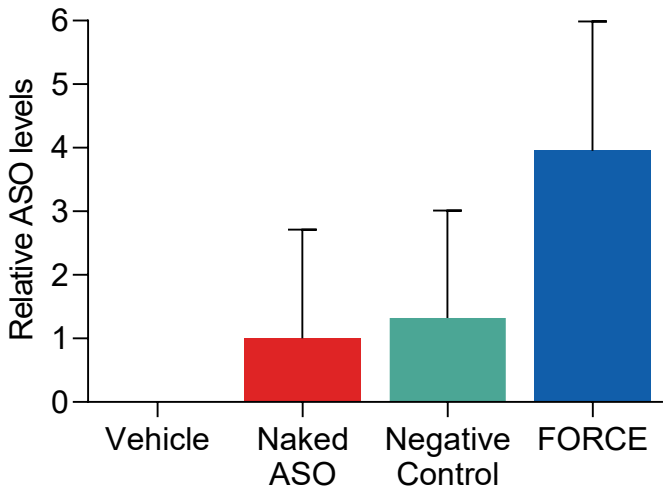


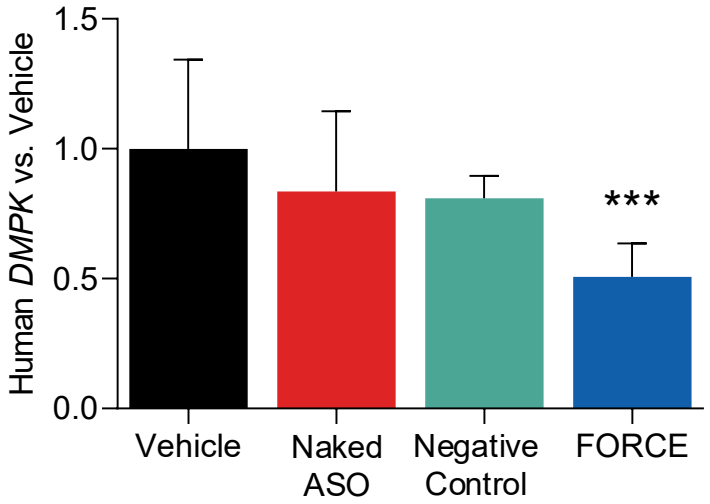
Nuclei
Mutant *DMPK* Foci

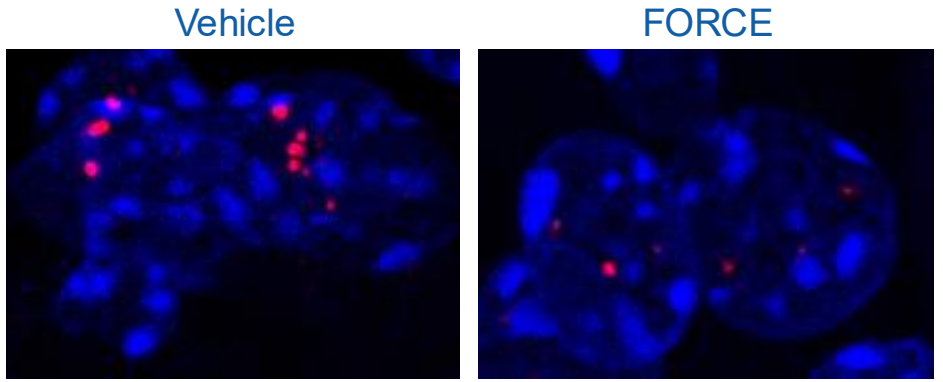
hTfR1/DMSXL mice dosed 10 mg/kg on day 0 and day 7, analyzed day 35. Data are mean + SD, n = 7. *$p < 0.05$, **$p < 0.01$ FORCE vs. vehicle

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%*







hTfR1/DMSXL mice dosed 10 mg/kg on day 0 and day 7, analyzed day 35. Data are mean + SD, n = 7. ***$p < 0.001$, *$p < 0.05$ FORCE vs. vehicle

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

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