



Targeting Tauopathies: Robust and Widespread MAPT Silencing in CNS of Mice and NHP with TfR1-mediated Oligonucleotide Delivery

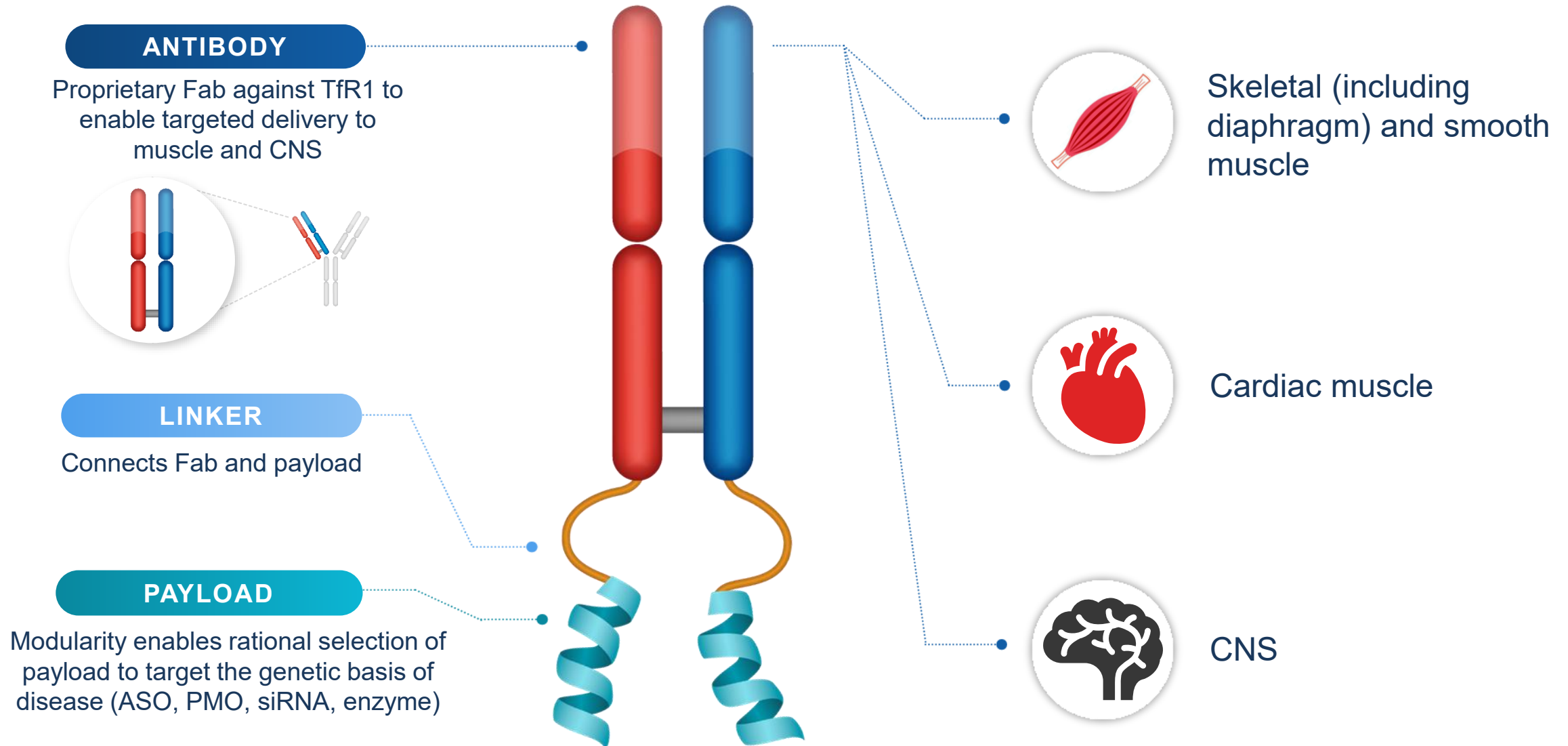
Susana Correia, PhD

ASGCT Annual Meeting | May 13, 2026

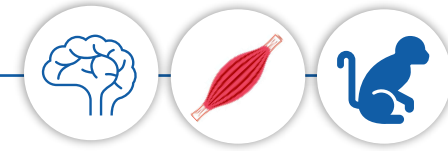
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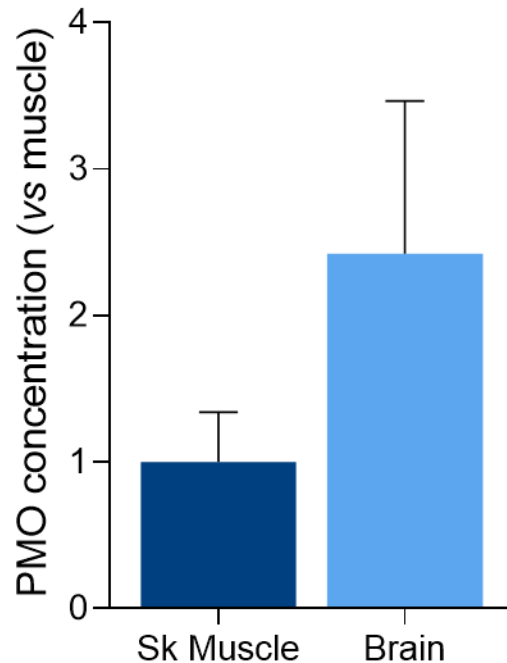
Leveraging Our FORCE™ Platform for Targeted Delivery



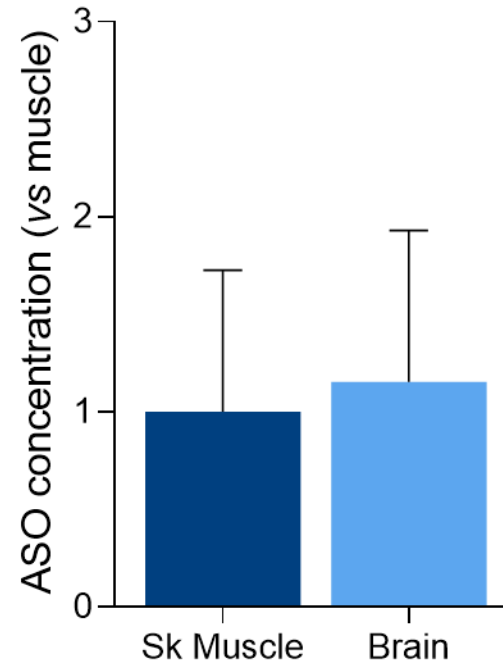
FORCE is Highly Effective for CNS and Muscle Delivery



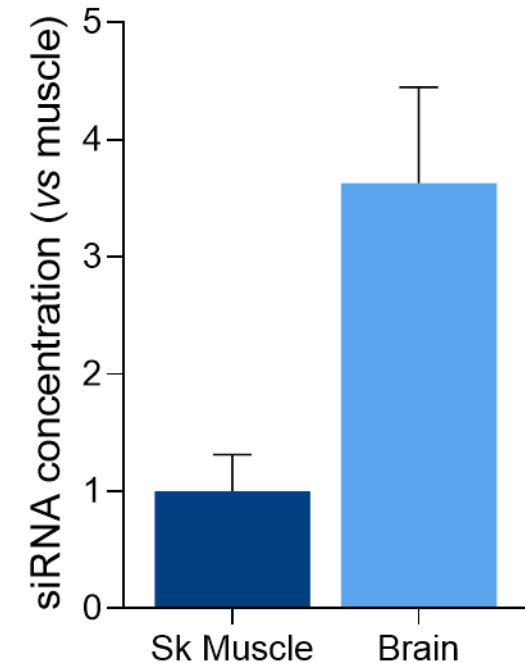
FORCE-PMO



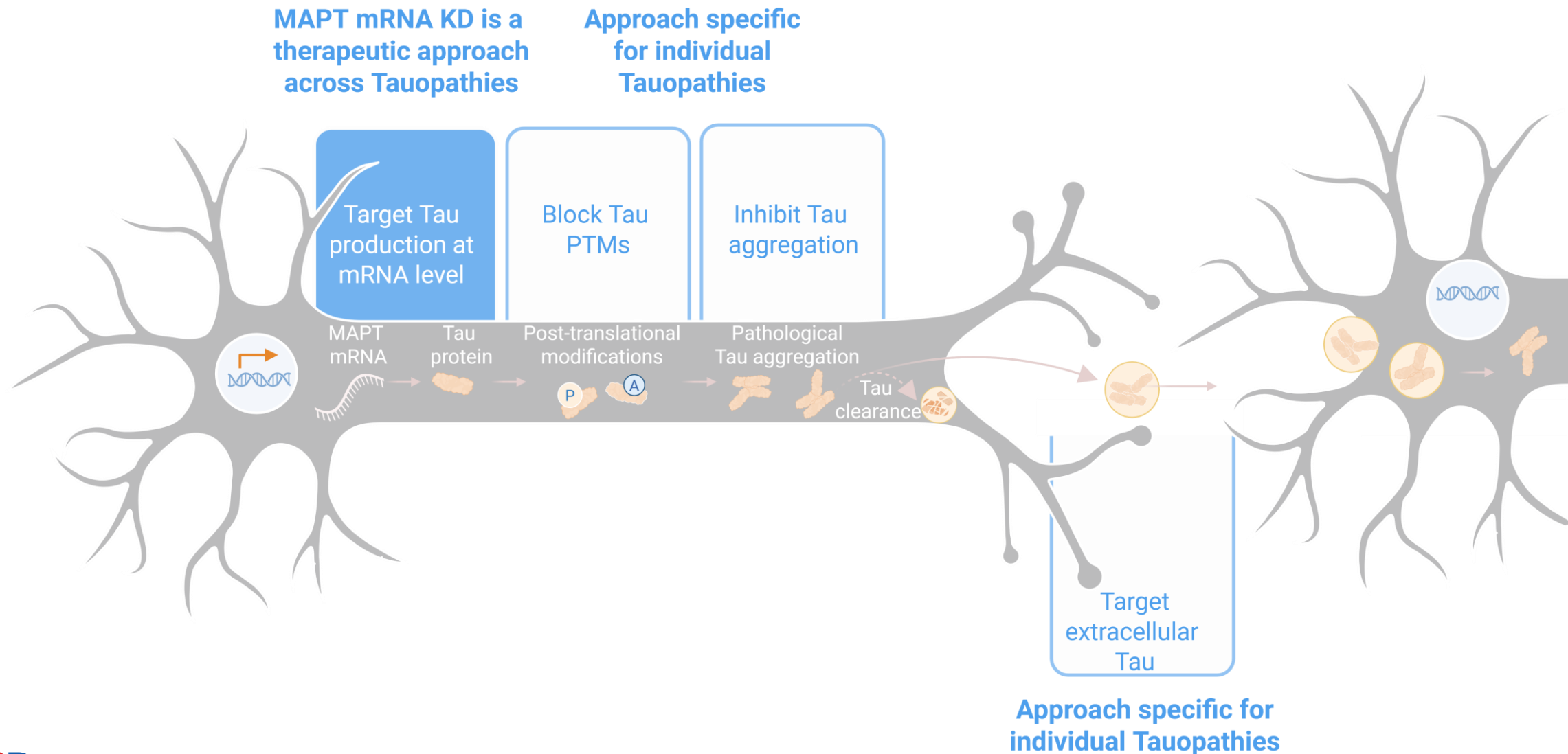
FORCE-ASO



FORCE-siRNA



MAPT (Tau) Reduction with an siRNA Has Potential to Address Tau Pathological Mechanisms

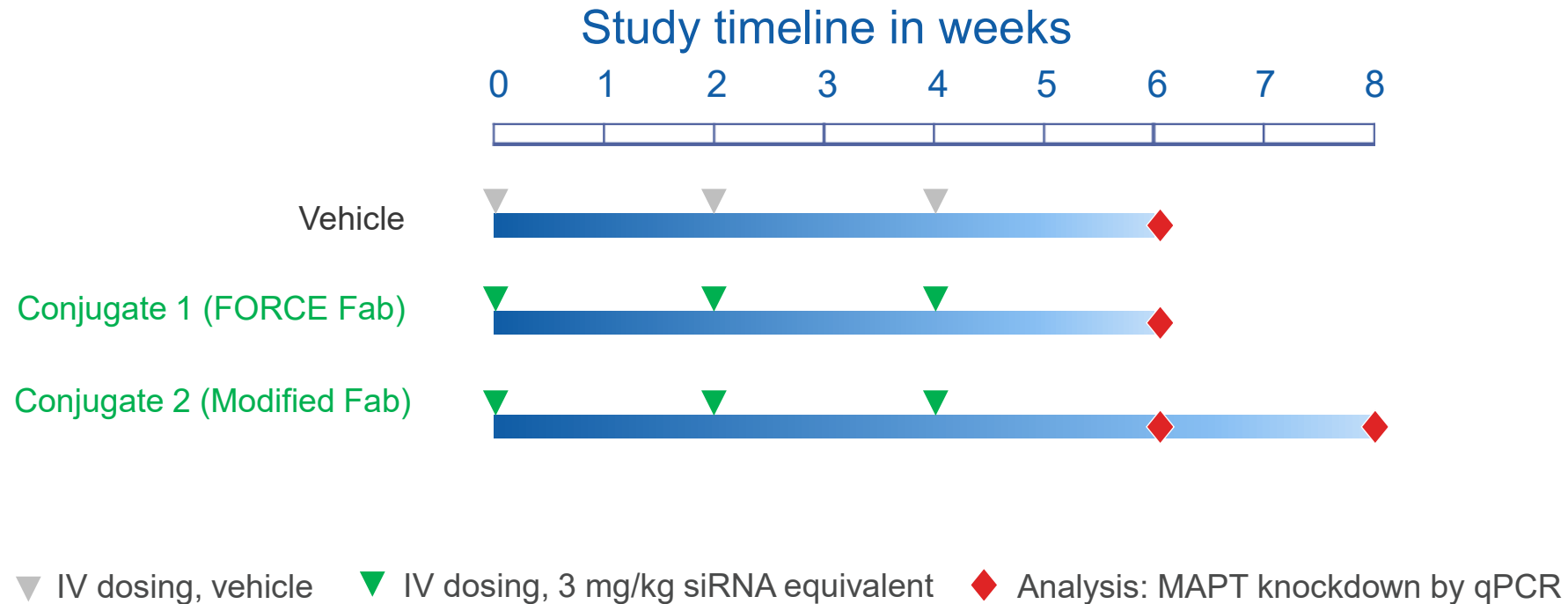


Conjugates Designed to Leverage TfR1 for Widespread Silencing of MAPT in CNS via Systemic Administration

Component	Conjugate 1	Conjugate 2
TfR1 binder	FORCE Fab (same as clinical programs in DM1 and DMD)	Modified Fab (enhanced CNS delivery)
Linker	Same linker	
Payload	Same MAPT siRNA payload	

Conjugate 1 is designed for muscle and CNS, Conjugate 2 is further modified to enhance CNS activity

Study to Evaluate Pharmacology of Conjugate 1 and Conjugate 2 in NHP

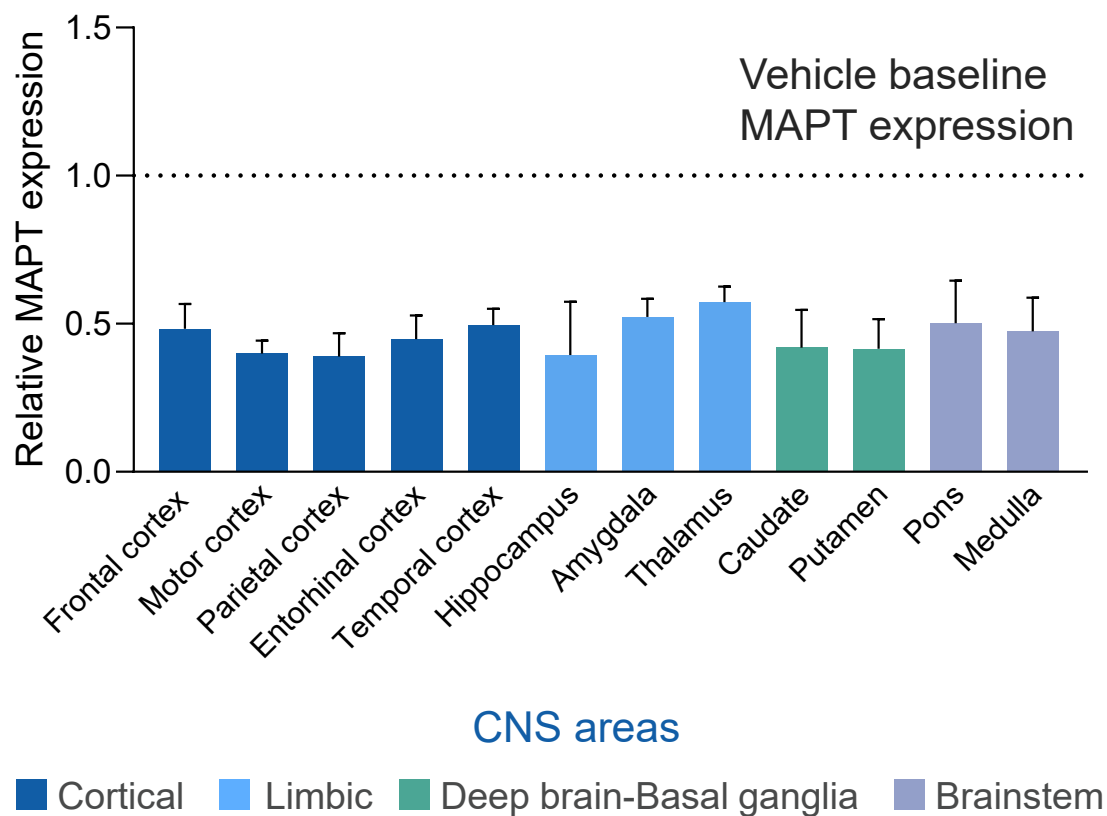


Conjugate 1 Achieved Robust and Widespread ~50% MAPT RNA Reduction in NHP CNS

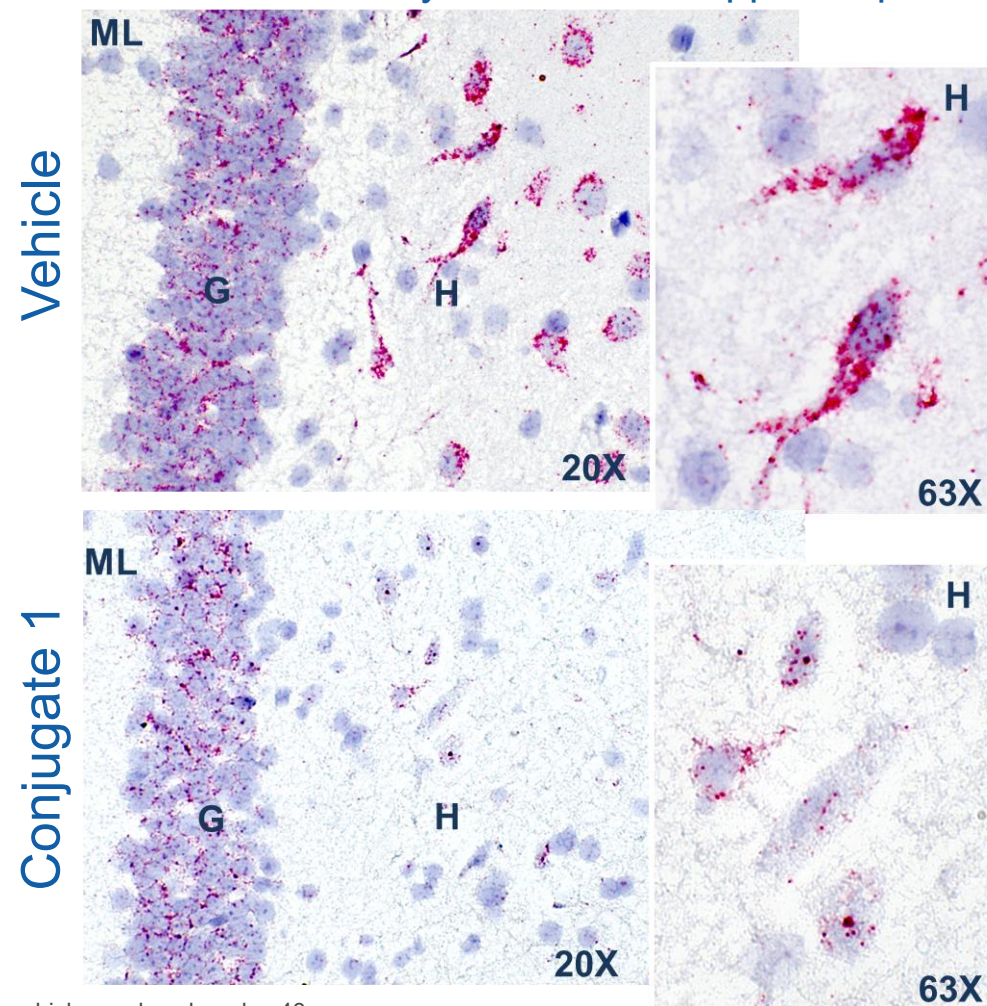


3 x 3 mg/kg siRNA Q2W, 2 weeks post-last dose

MAPT expression by qPCR



MAPT *in situ* hybridization in hippocampus



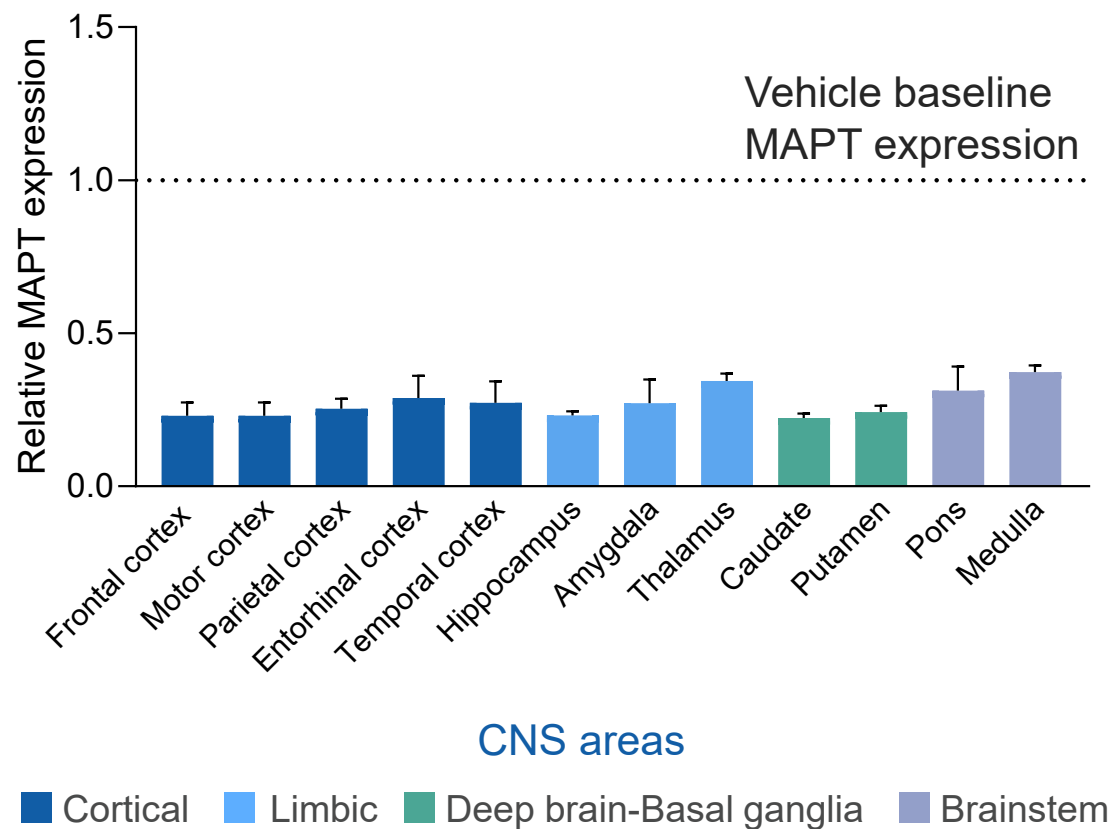
MAPT RNA / Nuclei

Conjugate 2 Achieved Robust and Widespread ~75% MAPT RNA Reduction in NHP CNS

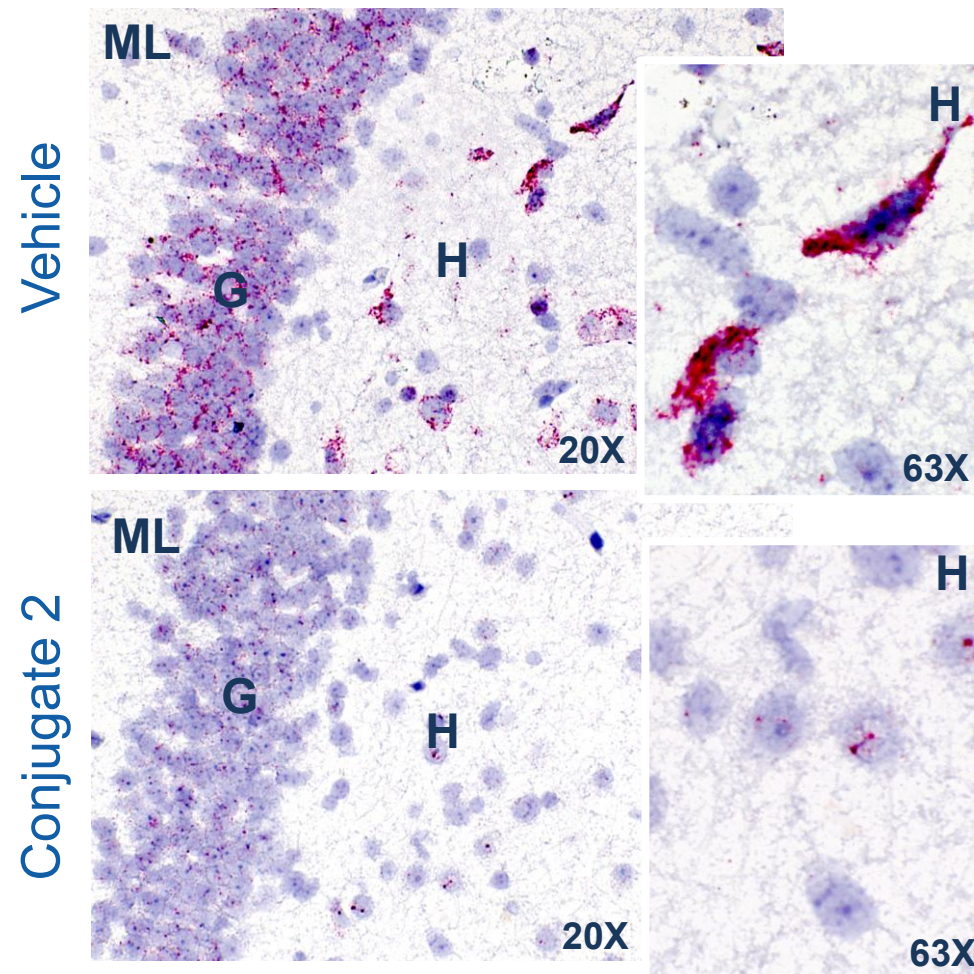


3 x 3 mg/kg siRNA Q2W, 2 weeks post-last dose

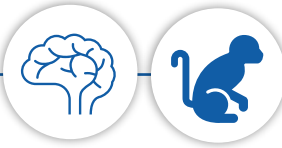
MAPT expression by qPCR



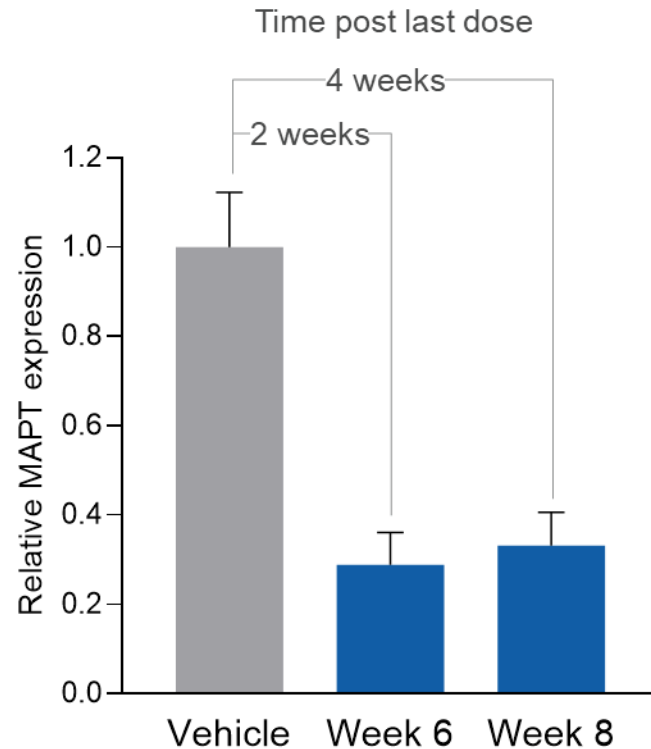
MAPT *in situ* hybridization in hippocampus



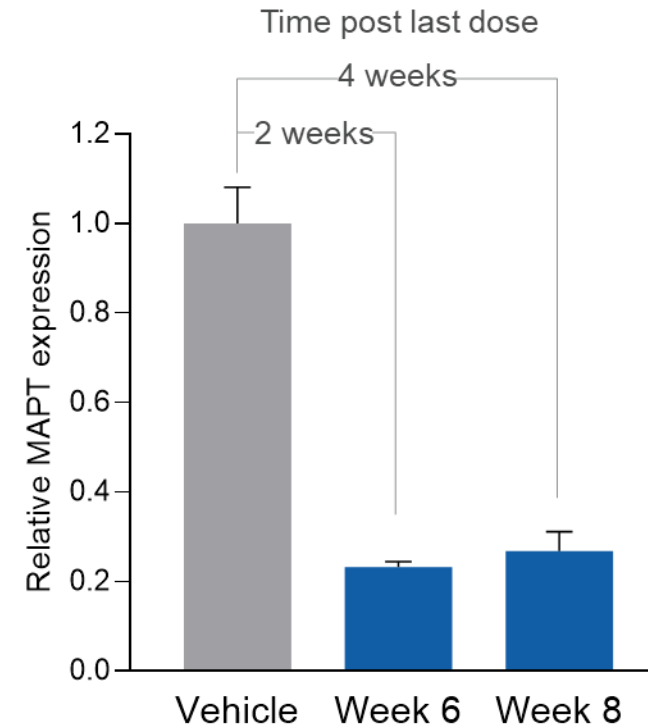
Conjugate 2 Achieves MAPT RNA Reduction Lasting Up to 4 Weeks



Entorhinal cortex



Hippocampus

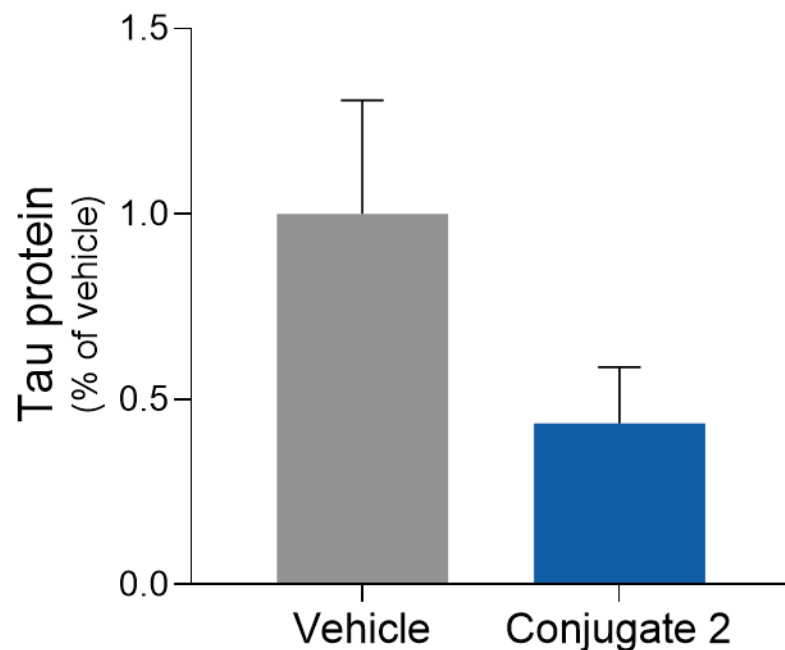


Durable *MAPT* KD observed in key brain areas affected early in Alzheimer's disease

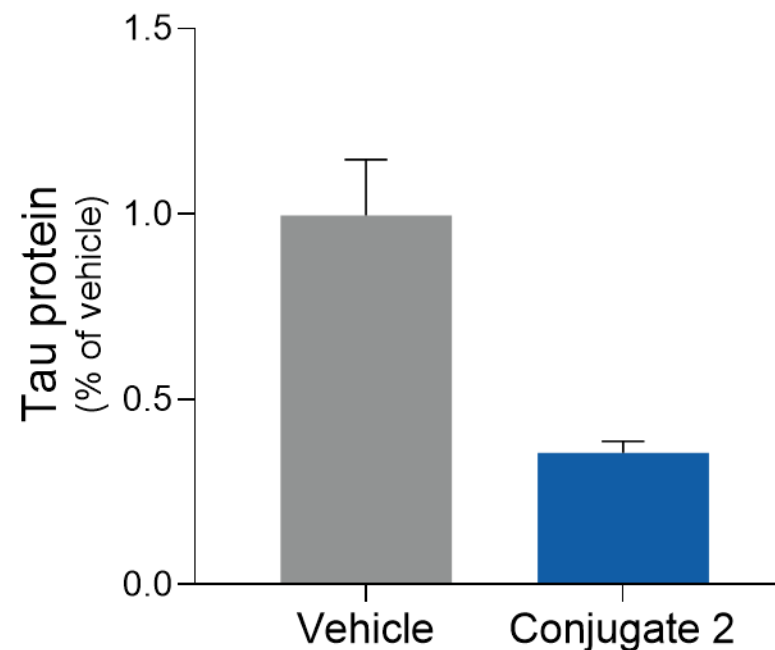
Conjugate 2 Achieved Robust Tau Protein Reduction in NHP CNS 4 weeks Post-last Dose



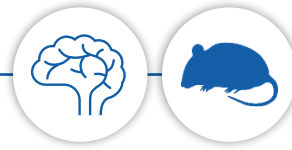
Tau protein in entorhinal cortex



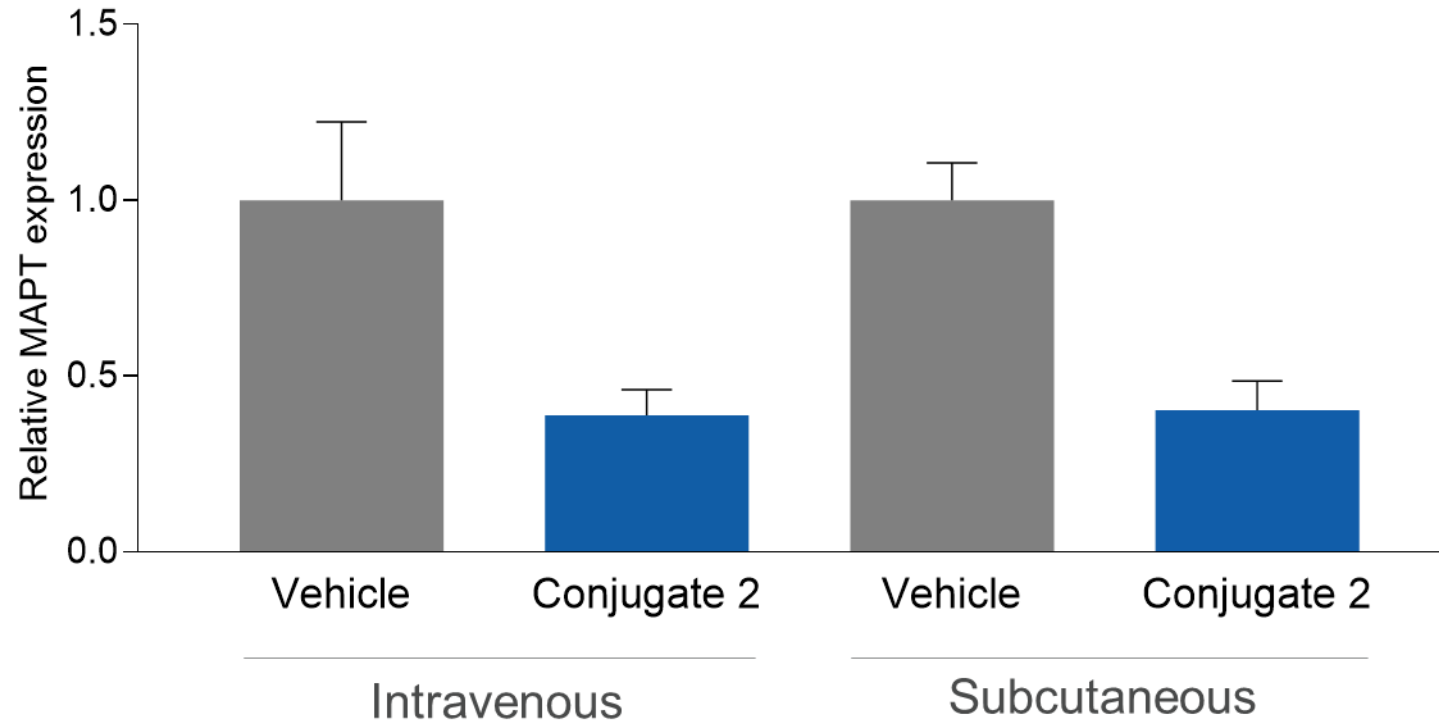
Tau protein in hippocampus



Conjugate 2 Has Comparable CNS Activity with Subcutaneous and Intravenous Administration



MAPT KD in brain of humanized hTfR1/hMAPT mice



Conjugate 1 also demonstrated comparable CNS activity with subcutaneous and intravenous administration

Conclusions

- The FORCE platform was designed for the treatment of neuromuscular diseases and effectively delivers to both muscle and the CNS
- Reducing tau levels via *MAPT* silencing is emerging as a highly promising approach for the treatment of Tauopathies including Alzheimer's disease
- Conjugate 1 and Conjugate 2 achieved robust and widespread silencing of *MAPT* across CNS via systemic administration
- Our data highlight the potential of TfR1-mediated delivery to enable disease-modifying therapies for neurological diseases

Acknowledgements

Dyne R&D

