Intravenous Delivery of VY1706, a CNS Penetrant AAV Gene Therapy for Alzheimer's Disease, Demonstrates Compelling Pharmacology and Safety in a 3-Month GLP Toxicology Study in NHPs

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voyager therapeutics

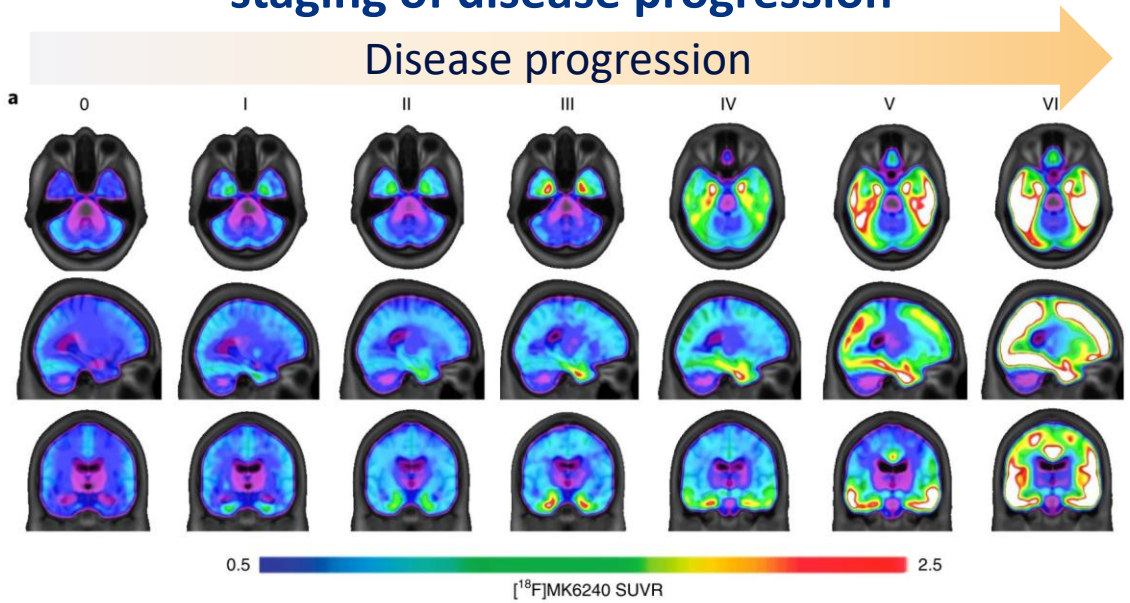
Disclosures

- Todd Carter is a full-time employee of Voyager Therapeutics, Inc.

Tau Accumulation is Associated with Alzheimer's Disease Progression

- Alzheimer's disease affects ~ 7M in the U.S.[1]
- Progressive neurodegenerative disease, causing relentless memory loss, cognitive and functional decline
- Neurofibrillary tangles (Tau) and β-amyloid plaques are key neuropathological hallmarks
- Multiple clinical trials now show slowing Tau accumulation may reduce cognitive decline.[2,3]

Accumulation of Tau measured by Tau PET imaging is associated with neuropathological staging of disease progression[4]



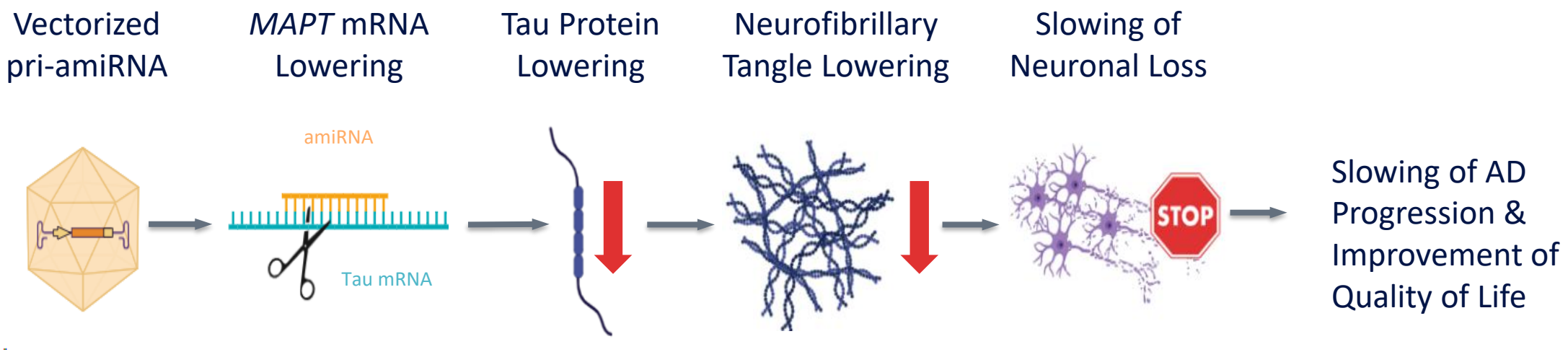
Voyager is advancing two tau-targeting programs:

VY7523 ANTI-TAU ANTIBODY

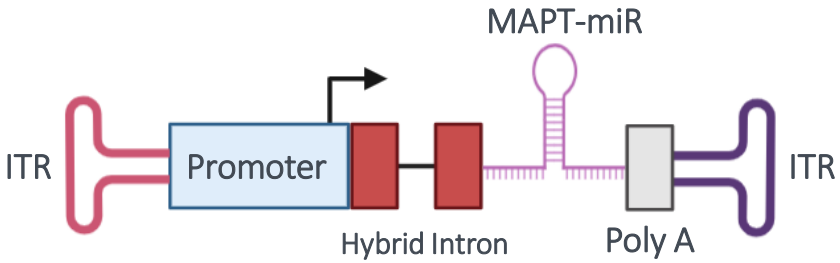
VY1706 TAU SILENCING GENE THERAPY

[1] Alzheimer's Association, Alzheimer's Facts and Figures Report | [2] Exploratory clinical outcomes from BIIB080 (MAPT ASO) phase 1b multiple ascending dose and long-term extension study in mild Alzheimer's disease. N. Ziogas, et al. [3] CTAD 2024. Results from TOGETHER, a double-blind, placebo-controlled Phase 2 study evaluating efficacy, safety and tolerability of Bepranemab in prodromal–mild Alzheimer's disease. M Citron et al. | [4] Therriault, Nature Aging. 2022.

Single IV Dose of BBB-crossing Tau Lowering AAV Gene Therapy to Treat Alzheimer's Disease



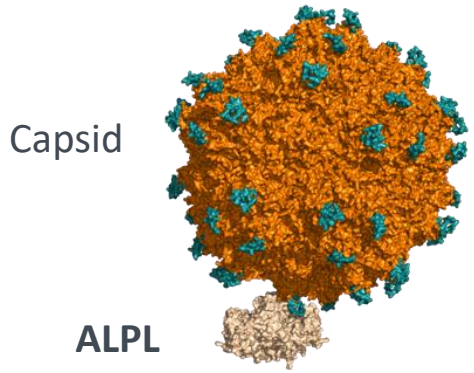
Pri-amiRNA containing siRNA530



- BBB-crossing capsid to drive brain-wide neuronal and astrocytic siRNA delivery to reduce intracellular and extracellular forms of Tau
- Liver de-targeting and potential for lower IV doses allowing reduced off-target tissue exposure
- One time IV-delivery, reducing patient burden

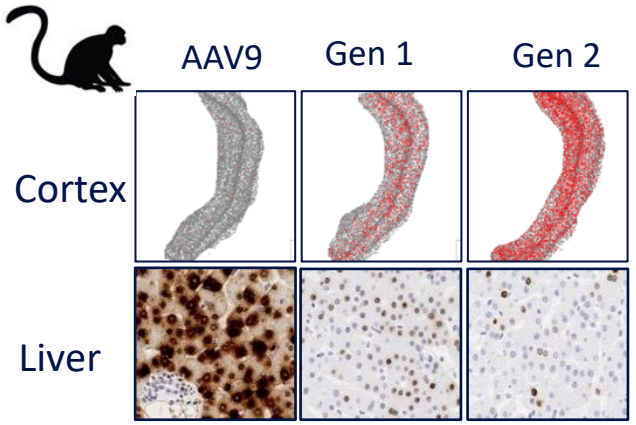
BBB-crossing Gen2 TRACER™ Capsids Demonstrate Enhanced CNS Tropism and Liver De-targeting Across Species

TRACER Capsids: Pan-Species CNS Targeting via ALPL Binding

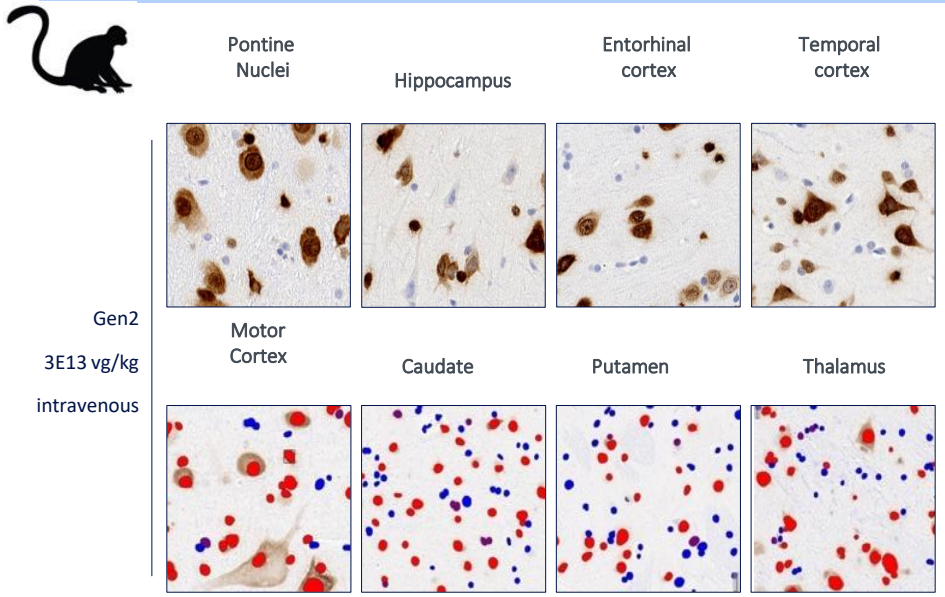


- BBB-transport enabled by capsid interaction with endothelial-enriched **ALPL**
- **Robust cross-species ALPL conservation** supporting translatability:
  - ~98% ALPL sequence homology (Cyno and Human)
  - 100% conservation of predicted capsid-ALPL interacting residues

Gen2 Capsids: Increased Brain Tropism and Liver De-targeting in NHP

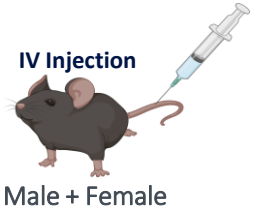


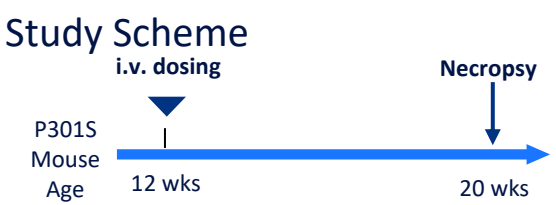
Gen2 Capsids: 50-75% of Cells Transduced Across NHP Brain Regions



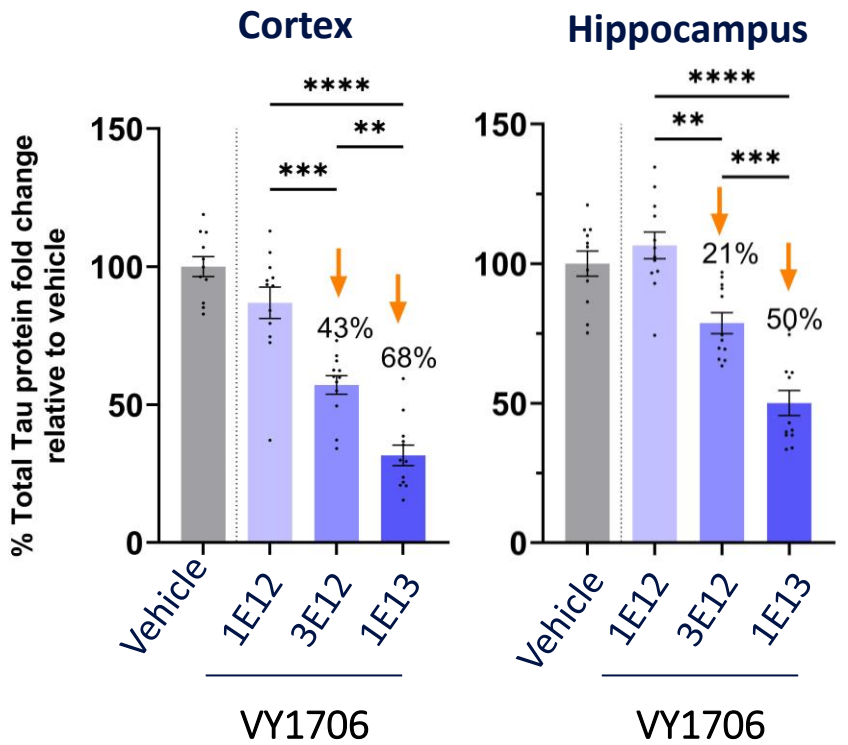
- **>40% cells** in entorhinal cortex, temporal cortex and motor cortex
- **>30% cells** in hippocampus
- >80% **astrocytes** across many CNS regions
- **~30X liver de-targeting** vs AAV9

VY1706 Demonstrates Dose-dependent Reduction of Total and Pathological Tau in P301S Mice

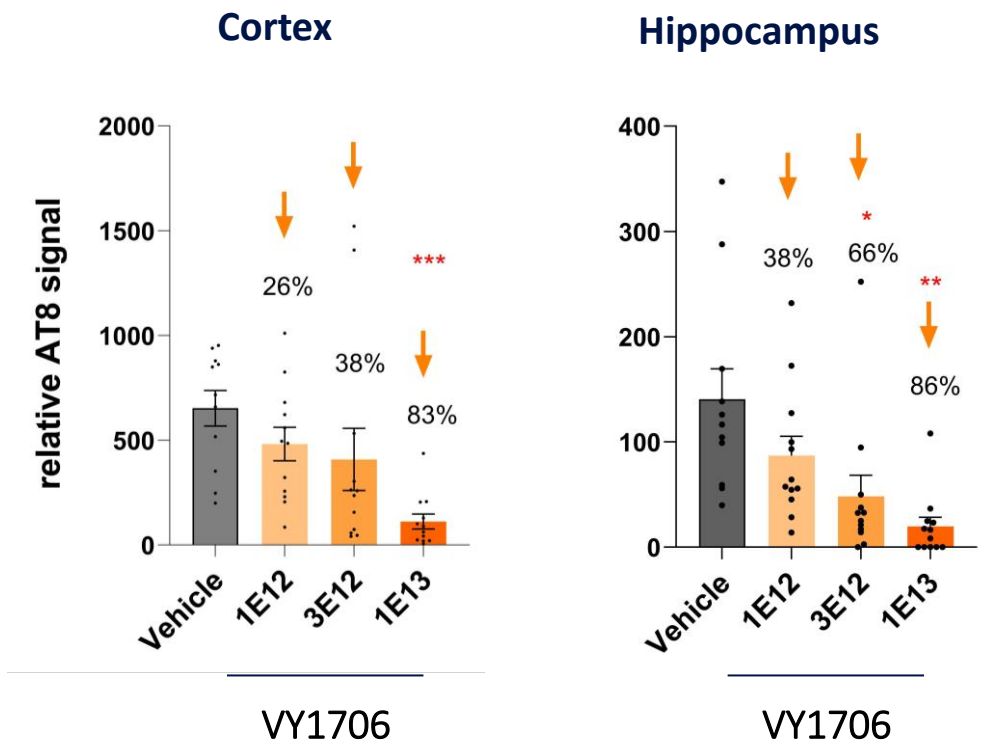




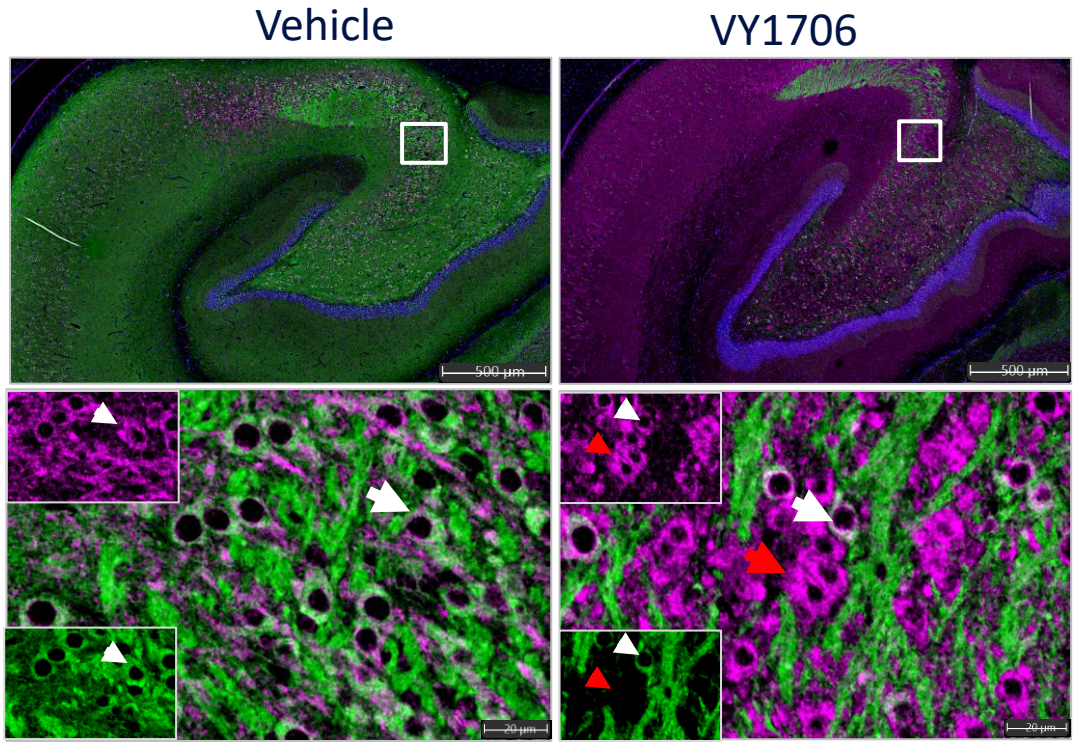
Tau Protein



Pathological Tau



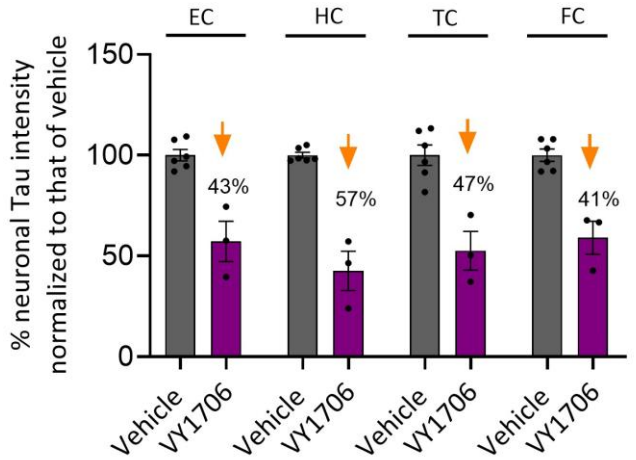
VY1706 Shows Robust Tau Protein Knockdown in Neurons Across AD-relevant Brain Regions in NHP DRF Study



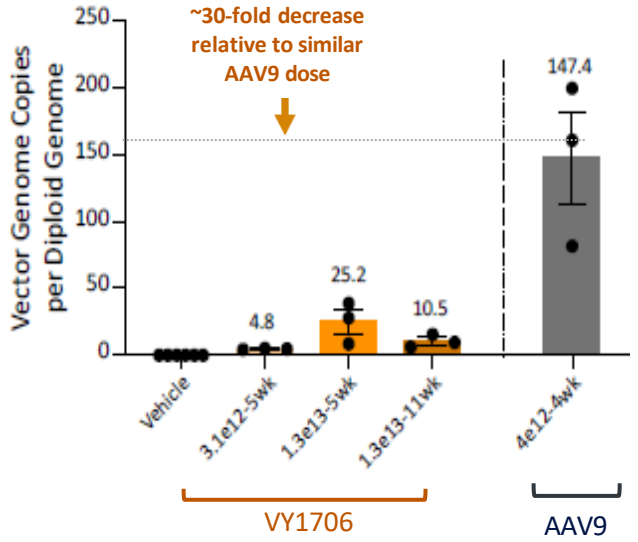
Tau Protein Expression in SMI311^{+ve} Neurons at 11 weeks:
SMI311 (neurons); TAU protein; DAPI (nuclear)

Single IV dose of 1.3e13 VG/KG; 11-week time point; non-GLP DRF study;
EC: Entorhinal Cortex; HC: Hippocampus; TC: Temporal Cortex; FC: Frontal Cortex

Neuronal Tau protein lowering



VY1706 de-targets the liver



VY1706 GLP 3-Month Toxicology Demonstrates Favorable Safety, Tolerability Profile with No Adverse Findings Across Tested Dose Range

Study design:

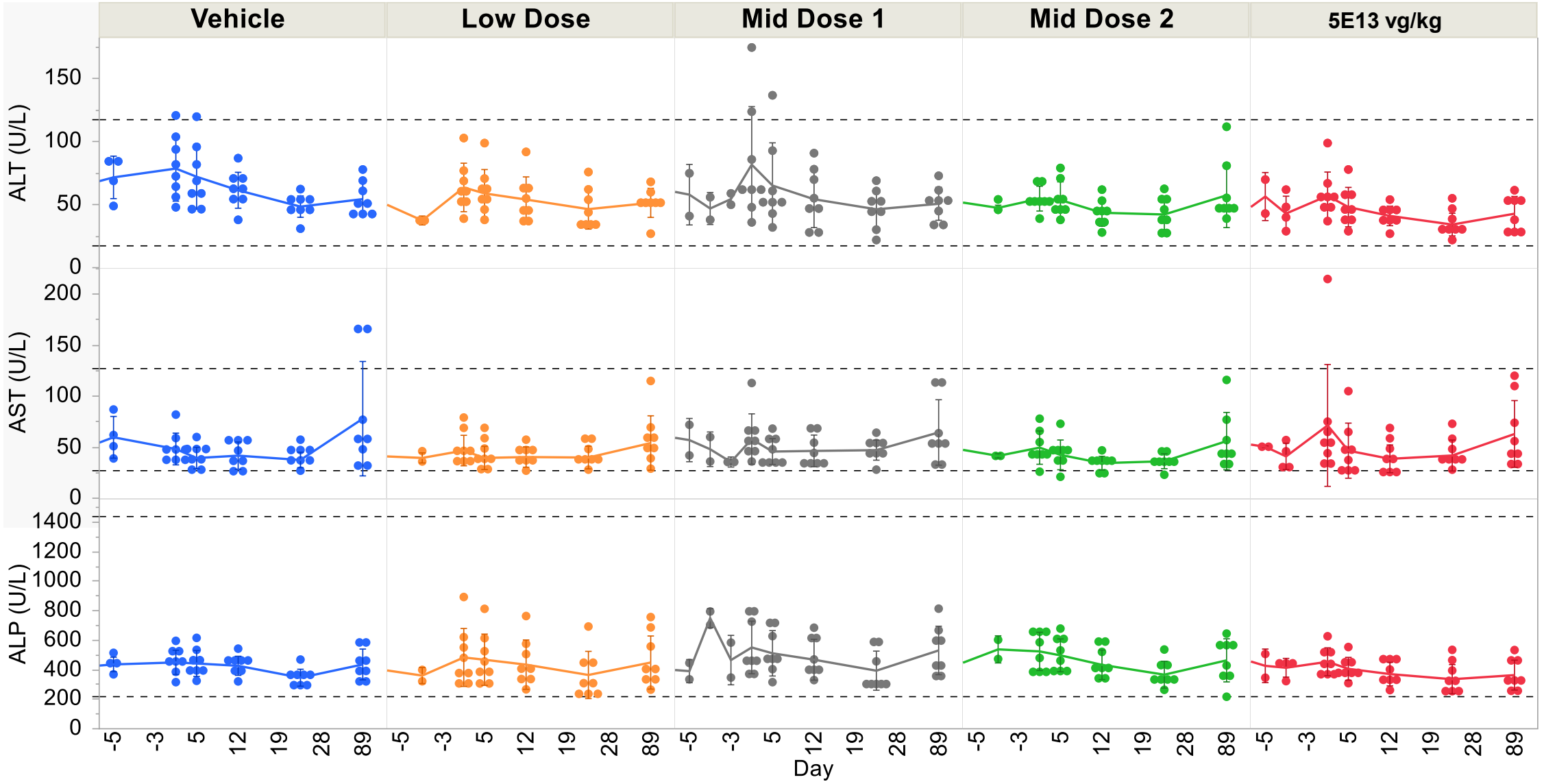
	Group	Delivery	Number of Animals	
			Males (♂)	Females (♀)
VY1706	Vehicle	Intravenous	2	2
	Low Dose		2	2
	Mid Dose 1		2	2
	Mid Dose 2		2	2
	5E13 vg/kg		2	2

Duration: 3-month
Species: Cynomolgus macaques
Animals were seronegative prior to dosing
Immunosuppression: daily oral methylprednisolone starting D-3 for 8-weeks, followed by tapering

VY1706 was safe and well-tolerated with no adverse clinical pathology or histopathological findings in the CNS, DRGs, and peripheral organs up to 5E13 vg/kg, the highest dose tested

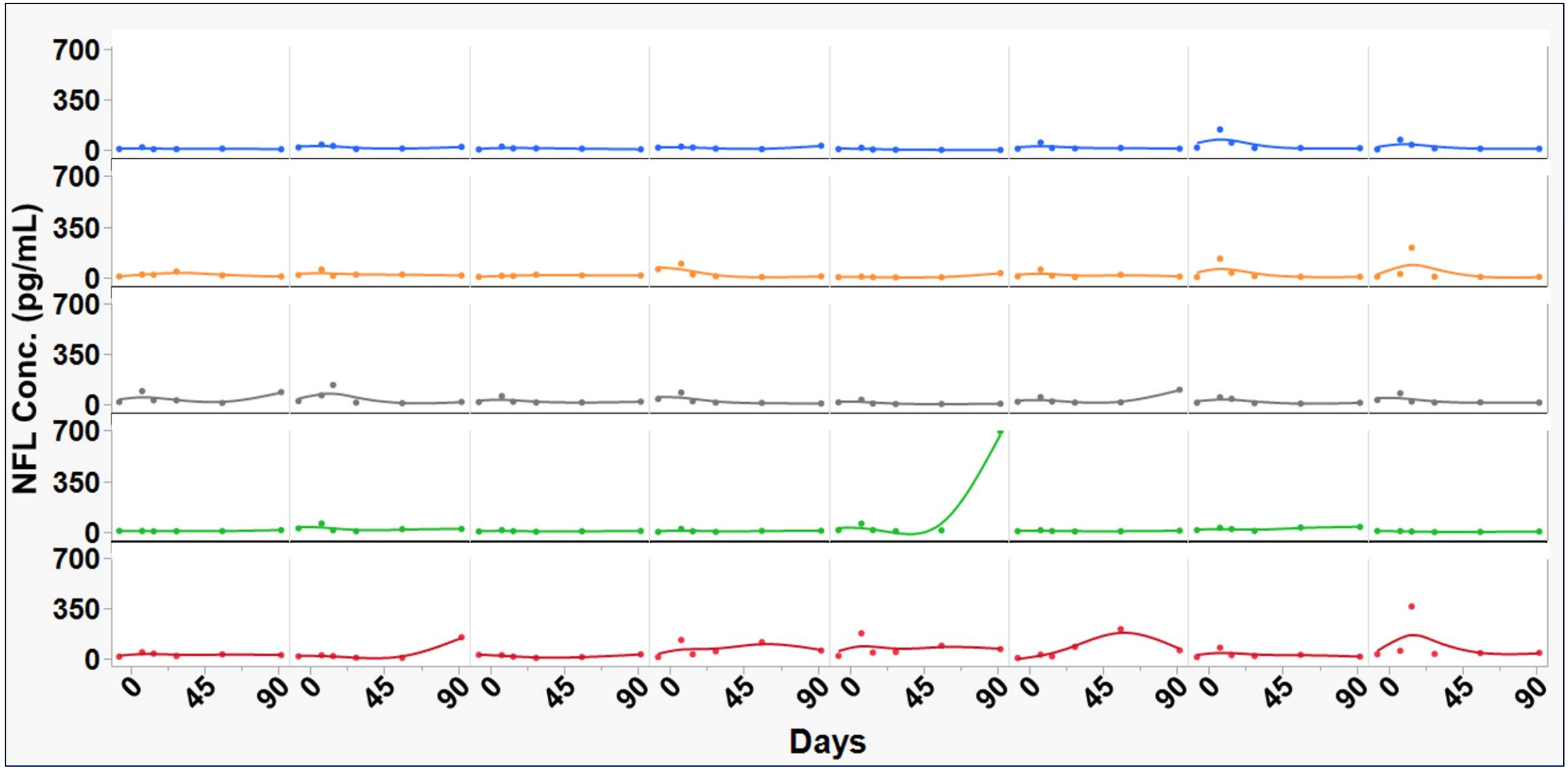
- No gross pathology or organ wt. findings; no effects on clinical pathology parameters at any dose level
- No neuro, ocular, or cardiac safety findings
- No DRG, or peripheral nerve toxicity (histopathology or electrophysiology), plasma NfL was stable with no dose-related increases
- No cellular immune activation; TAb/NAb responses were typical of AAV

VY1706 Shows No AAV-Typical Liver Transaminase Elevations at All Doses Tested

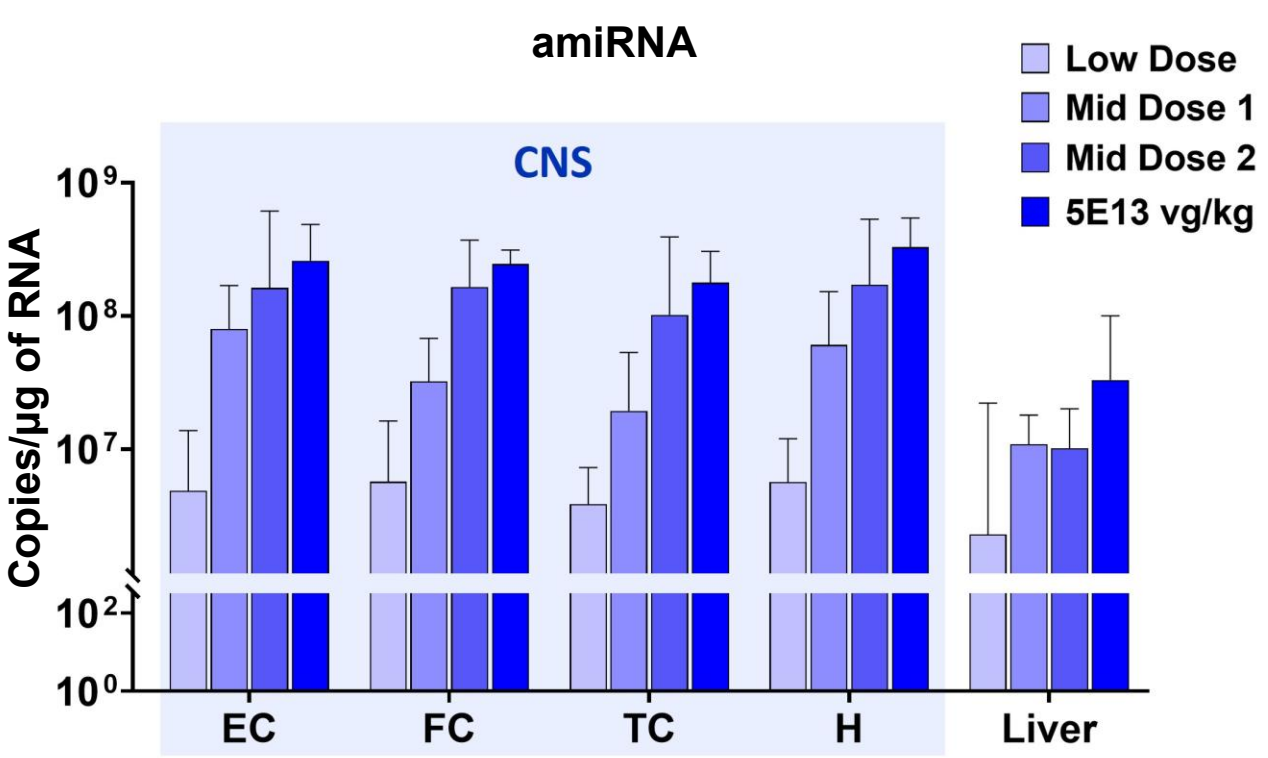


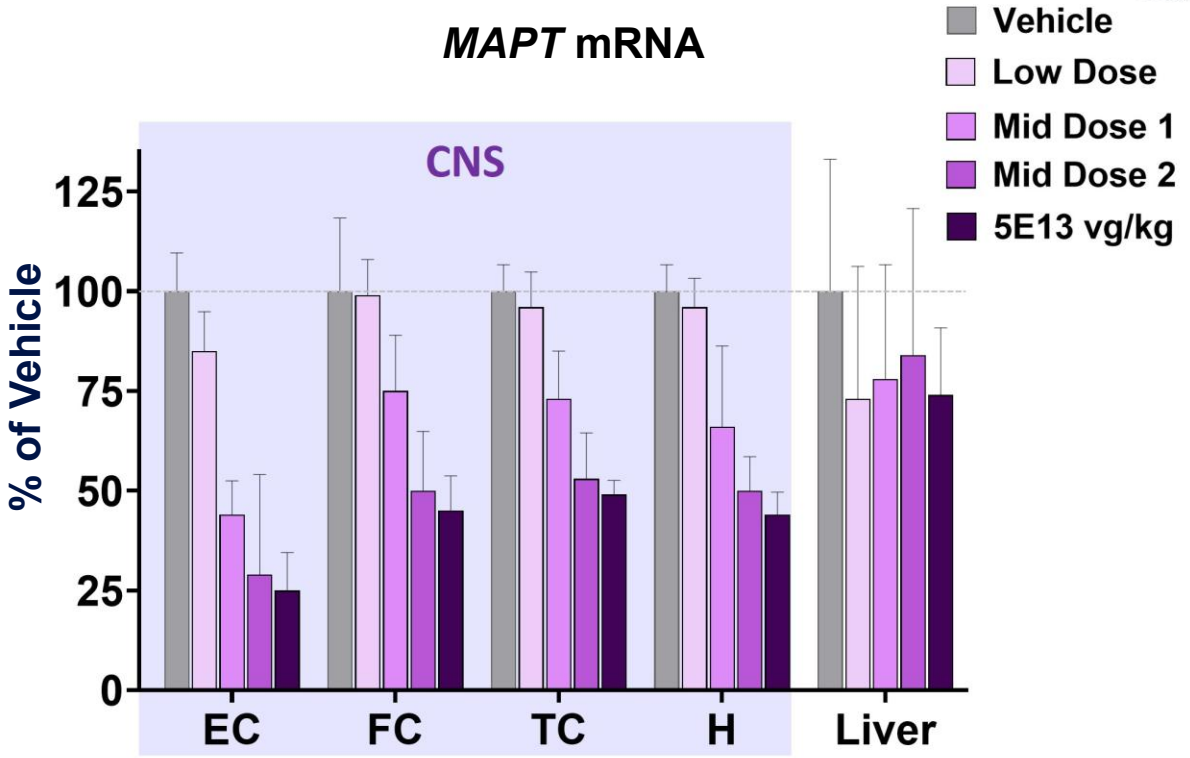
Timepoints: Predose, Day 3, Day 5, Week 2, Week 4, Week 13

VY1706 Demonstrates Stable Plasma NfL with No Dose-related Elevations



VY1706 Shows Dose-Dependent Increase in miRNA Level and Lowering of MAPT mRNA in AD-relevant Brain Regions in NHP

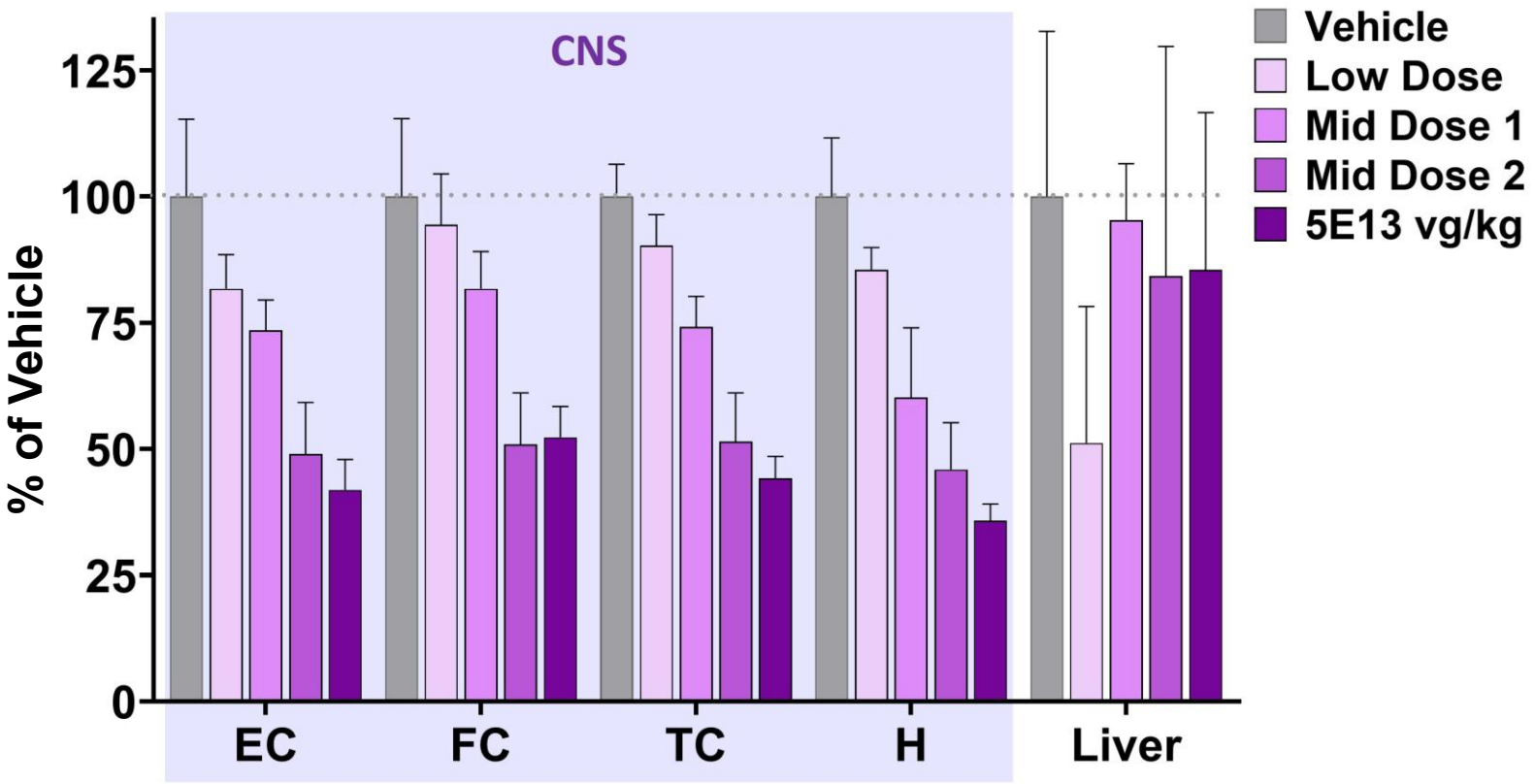




VY1706 demonstrated broad CNS biodistribution and robust dose-dependent *MAPT* mRNA lowering of up to 51-75% in AD-relevant brain regions

GLP Tox Study (3 month); n=4/group; Plots show mean + SD
EC: Entorhinal Cortex; FC: Frontal Cortex; TC: Temporal Cortex; H: Hippocampus

VY1706 Shows Dose-Dependent Lowering of Tau Protein in AD-Relevant Brain Regions in NHP

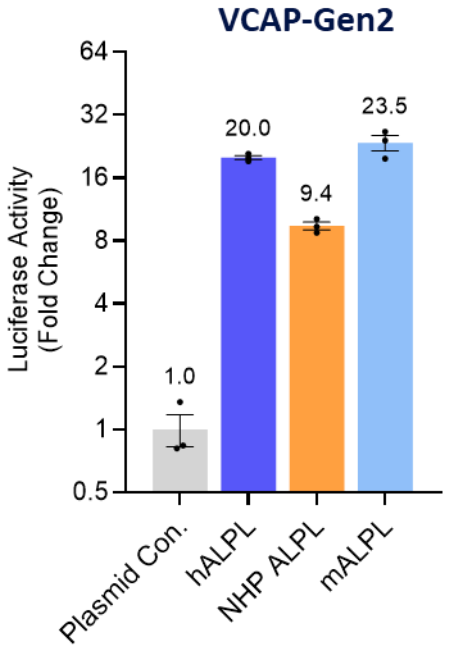


VY1706 demonstrated robust dose-dependent Tau protein lowering in the range of up to 48-64% in AD-relevant brain regions

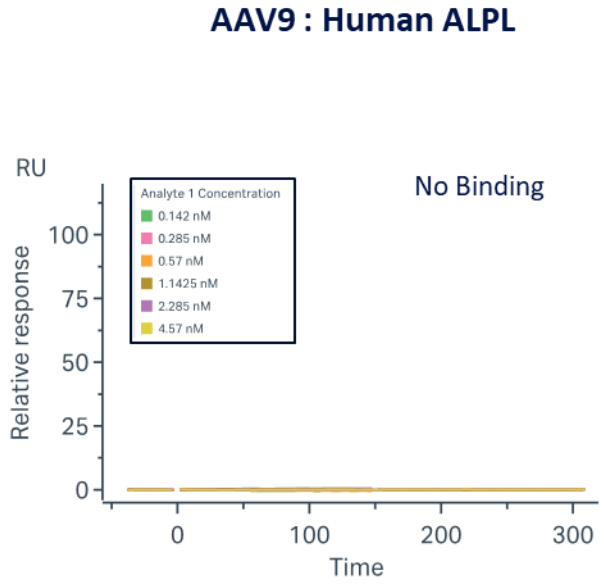
GLP Tox Study (3 month); n=4/group; Plots show mean + SD
EC: Entorhinal Cortex; FC: Frontal Cortex; TC: Temporal Cortex; H: Hippocampus

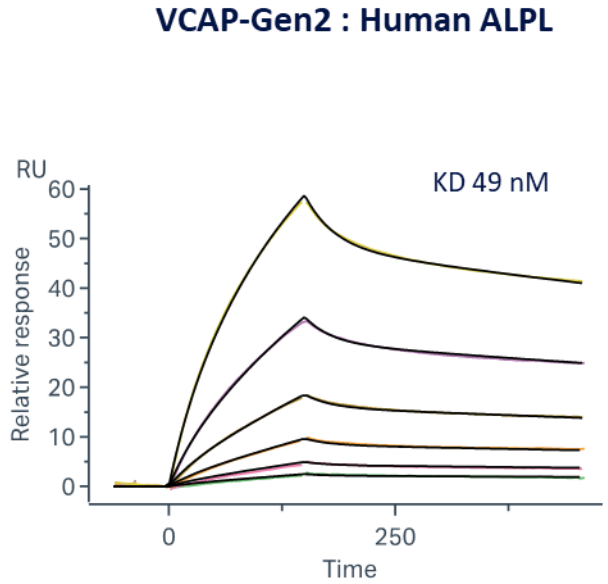
VY1706 Capsid Demonstrates Cross-species Translatability of Capsid-ALPL Interaction

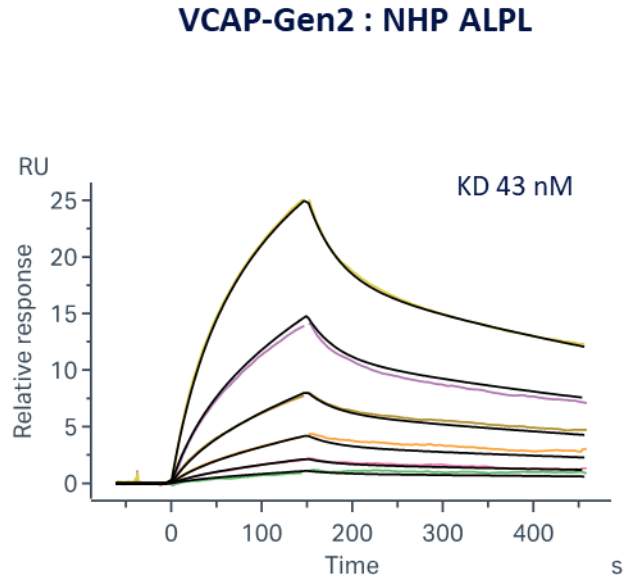
Transduction Assay



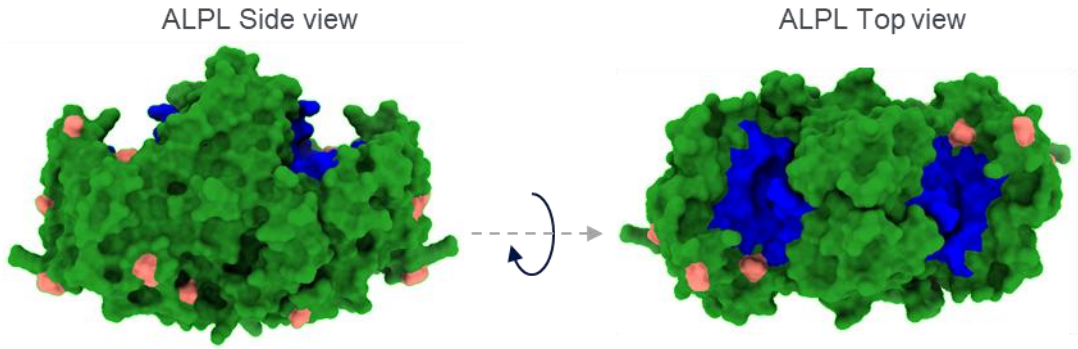
Binding Assay (SPR)







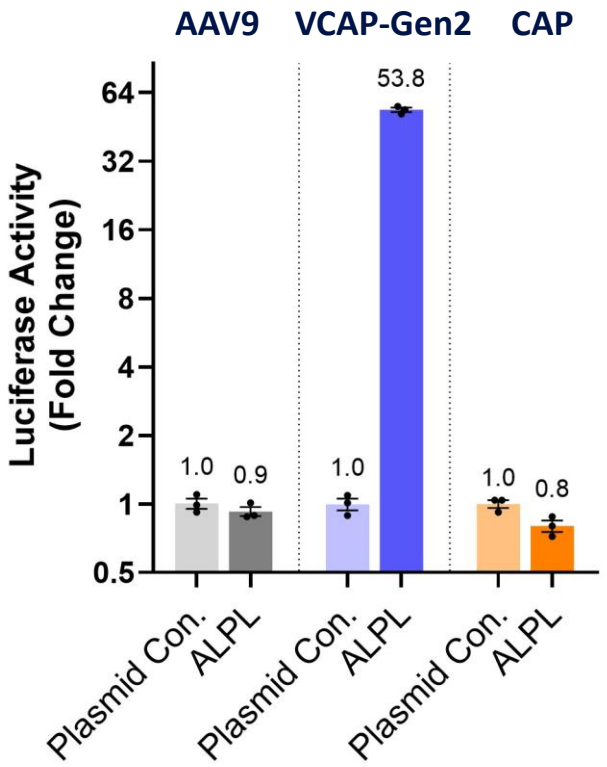
ALPL Binding Model



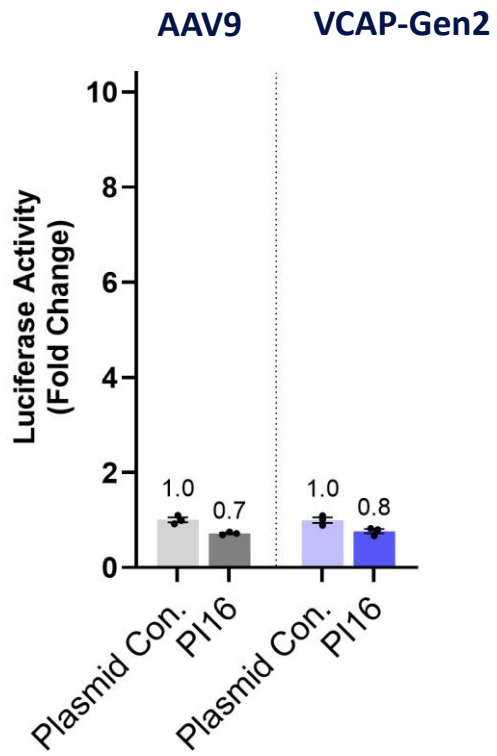
VY1706 Capsid Engages an Endothelial Receptor Distinct from Published Capsida Vector

- We examined the receptors mediating BBB transport of the two capsids:
  - VY1706 uses ALPL as its primary BBB receptor
  - Identification of CAP receptor as ADAM15, not the patent reported PI16
  - **No receptor cross-reactivity between VCAPGen2 and CAP capsids**

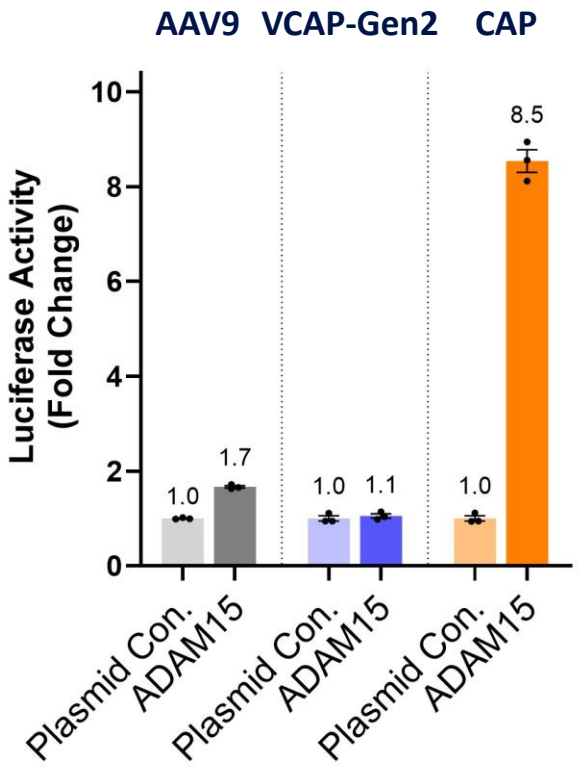
ALPL



PI16



ADAM15



CAP refers to the capsid described by Capsida with the STXBP1 payload published in WO2025213064A1
Patent application (WO2025231383) suggested PI16 as a potential BBB transport receptor for CAP
ADAM15 was identified as a potential BBB transport receptor for CAP through a receptor screen

Conclusions

- Single IV dose of VY1706 achieved broad CNS delivery of vectorized MAPT siRNA in multiple nonclinical species
- ALPL, a well conserved endothelial receptor, mediates VY1706 blood-brain barrier transport, supporting cross-species translatability
- VY1706 was safe and well-tolerated in the 3-month GLP toxicology study, with no adverse clinical pathology or histopathological findings in the CNS, DRGs, and peripheral organs (including liver) up to the highest dose tested (5E13 vg/kg)
- Dose-dependent reduction of up to 51-75% *MAPT* mRNA and 48-64% Tau protein in key brain regions was observed in NHPs, 3-months following single IV doses
- Dose-dependent reduction of *MAPT* mRNA, Tau protein and pathological Tau was observed in a mouse model of tauopathy
- Nonclinical package supports advancement to first-in-human evaluation in patients with Alzheimer's disease
- **IND process on track for Q2 2026; clinical entry expected H2 2026**

Team Acknowledgements

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Andrew Cameron
Kim Parthum
Toby Ferguson
Al Sandrock

Explore More of Voyager's Science at ASGCT:

- **Oral #422: Directed evolution of muscular and neuromuscular capsid variants in both mice and non-human primates. Friday, May 15, 8:00 a.m**

- Poster #1028: Engineering an AAV9-derived muscle-tropic capsid to evade pre-existing human neutralizing antibodies.
- Poster #1460: Intravenous delivery of a bi-functional AAV gene therapy to reduce endogenous ApoE4 and express ApoE2 in ApoE4 humanized mice.
- Poster #2027: Leveraging artificial intelligence to design AAV mutant capsids optimized for antibody evasion.
- Poster #3139: Optimized transfection platform with improved productivity and transgene packaging for scalable rAAV production.
- Poster #3148: Exploiting an AAV capsid specific receptor to develop stable cell lines for transduction based assays for gene therapies.
- Poster #3161: Evaluating affinity chromatography media for capture of novel blood-brain-barrier penetrant AAV capsids.