



Directed Evolution of an AAV9 Library Identifies a Capsid Variant with Enhanced Brain Tropism and Liver Detargeting in Non-Human Primates and Mice Following Systemic Administration

Dr. Tyler Moyer

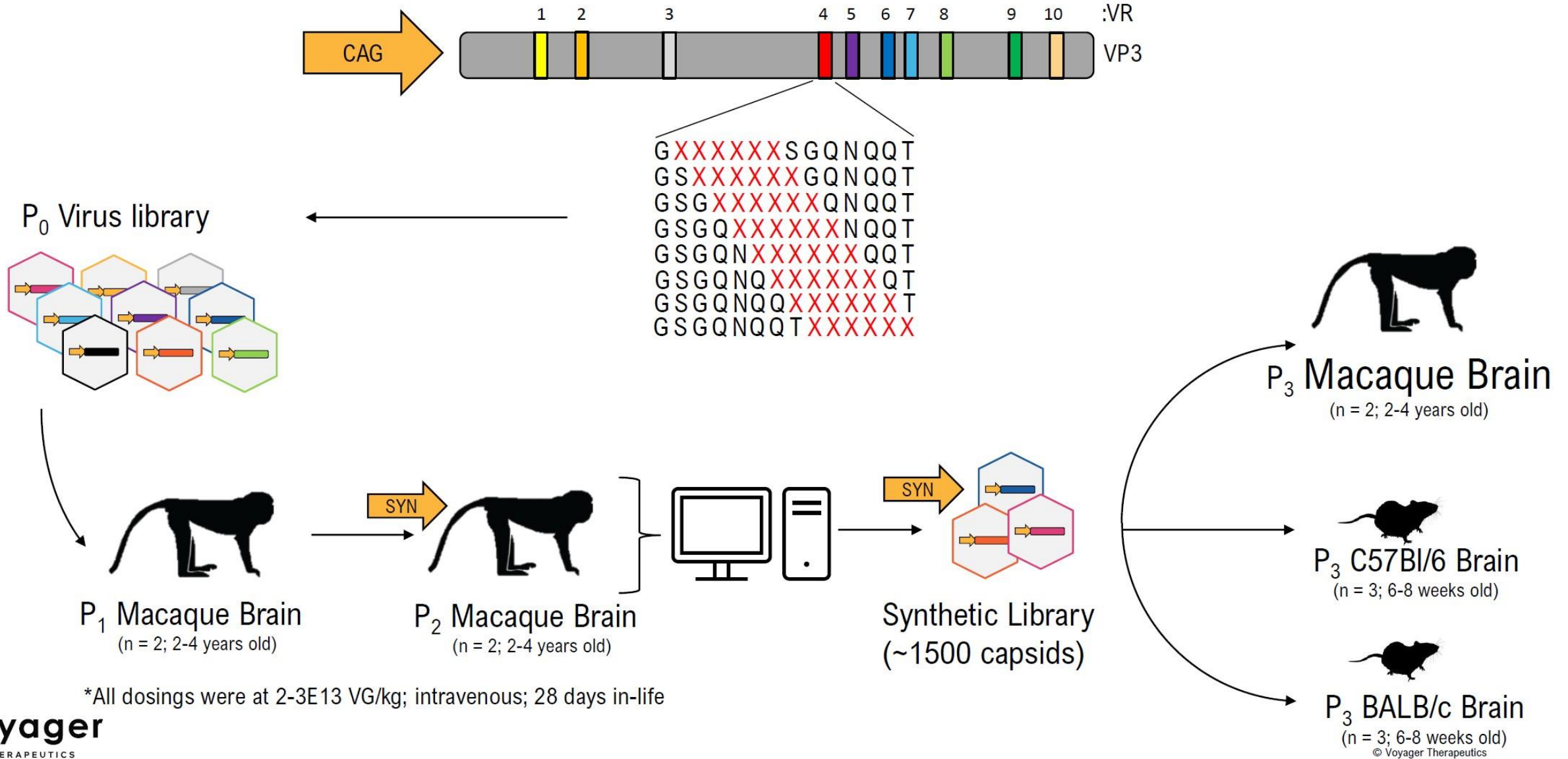
AAV Engineering for CNS Targeting

Thursday, May 18, 2023

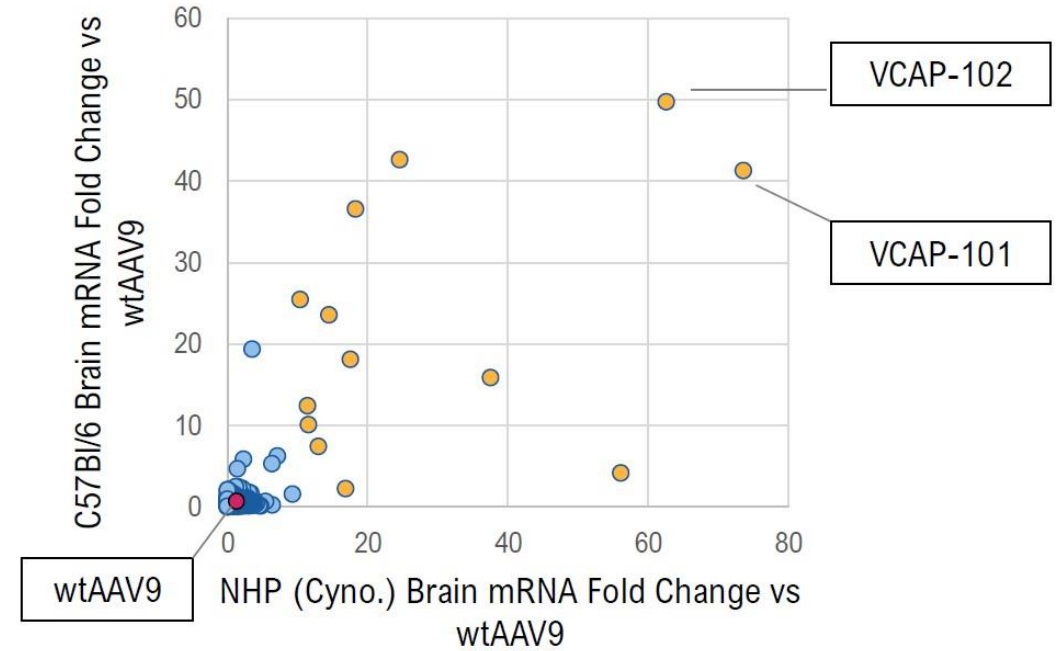
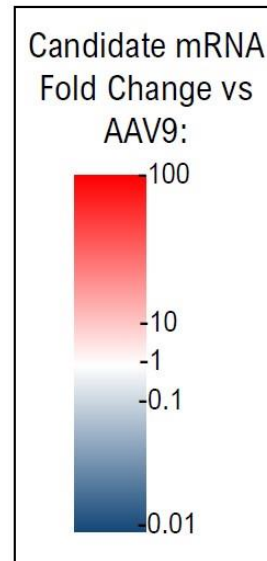
Abstract #105

Disclosure: Tyler Moyer is a full-time employee of Voyager Therapeutics.

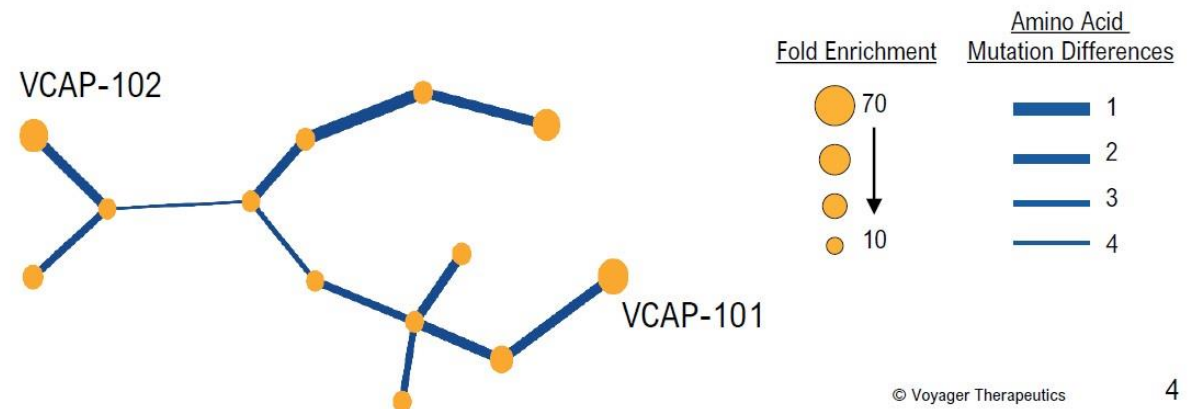
AAV9 VR-IV Peptide Insertion Scan Library Design and Dosing Strategy



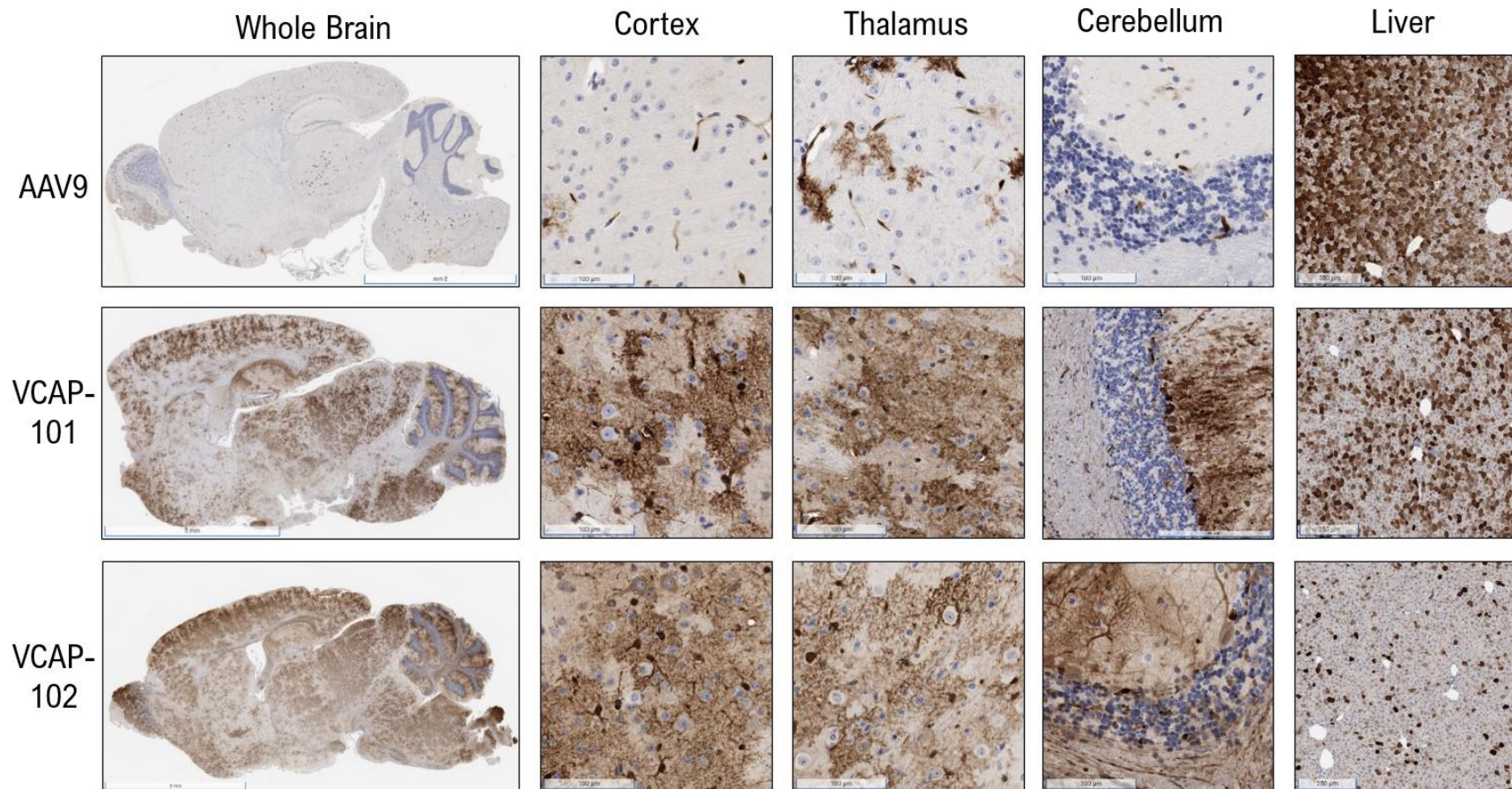
VCAP-101 and VCAP-102 Demonstrate Increased CNS Tropism in Both Macaques and Rodents



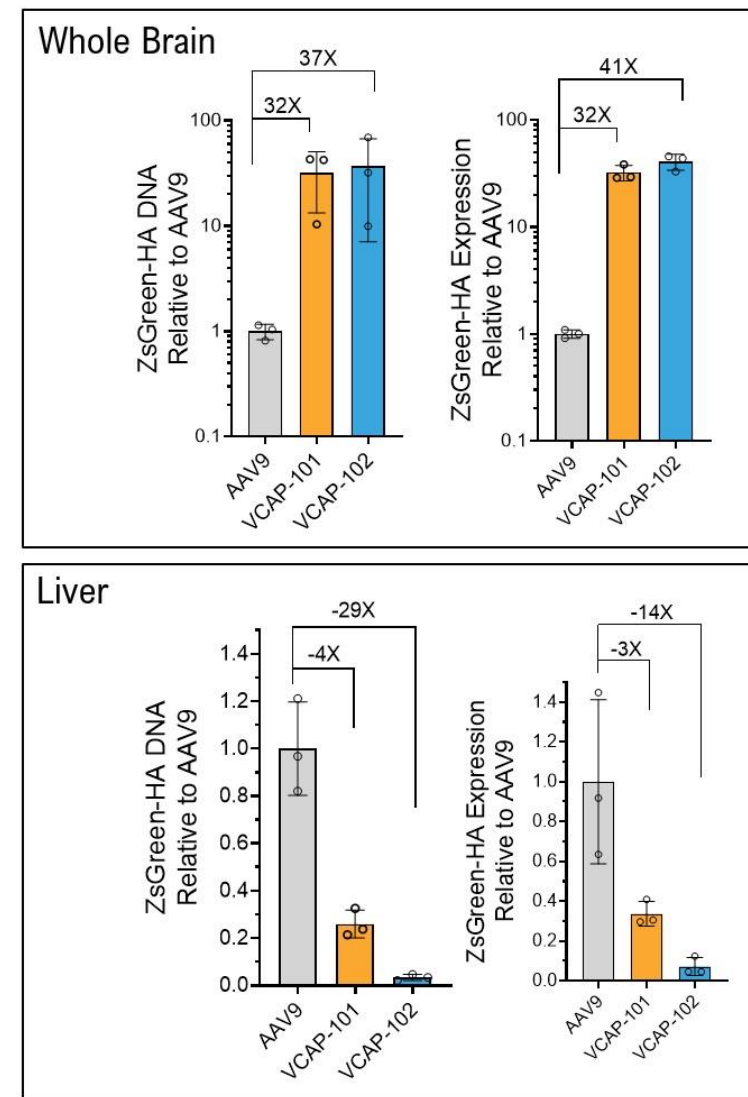
Network Clustering of Hits with FC/wtAAV9 > 10:



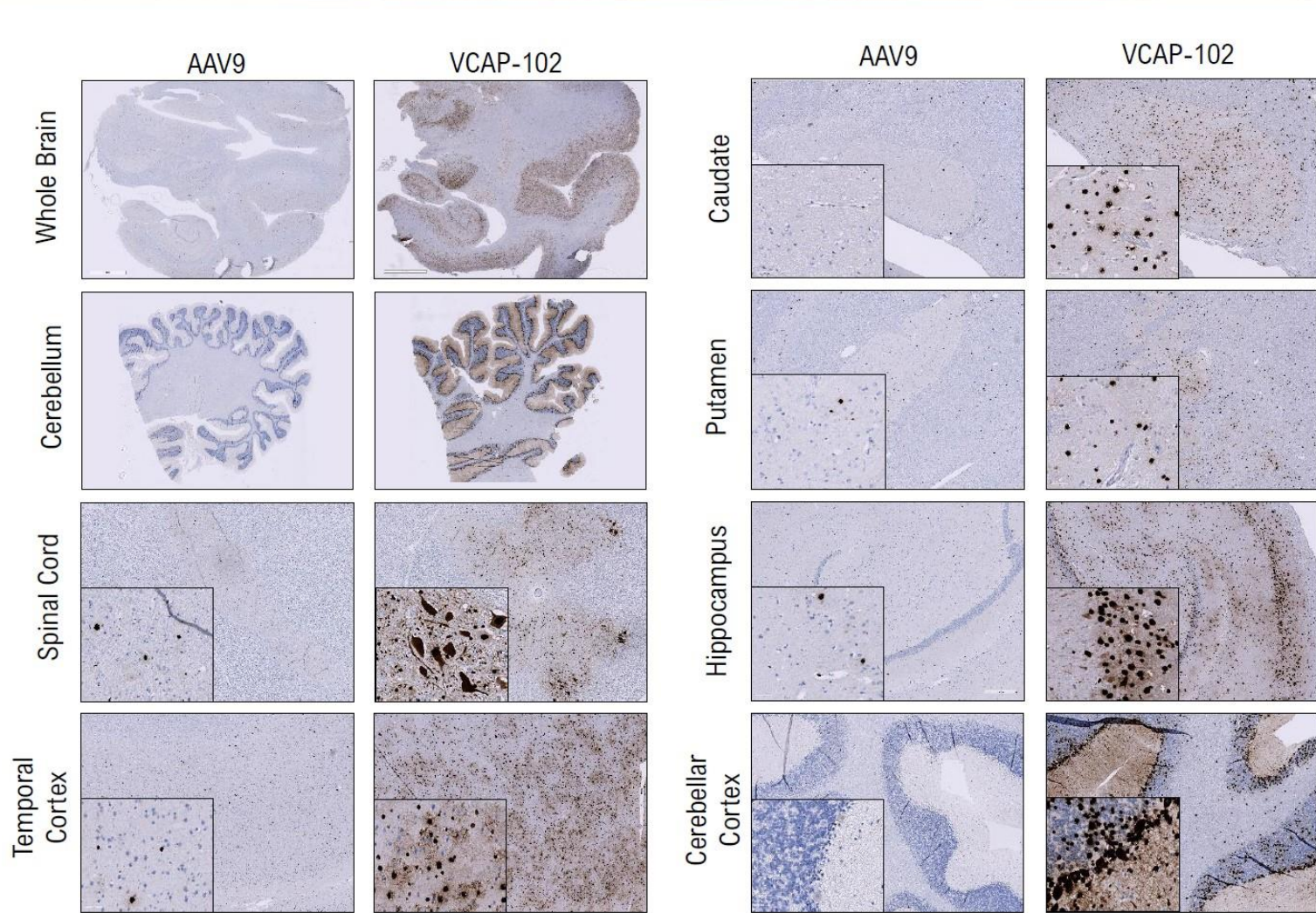
VCAP-102 Demonstrates Increased CNS Tropism and Liver Detargeting in Mice



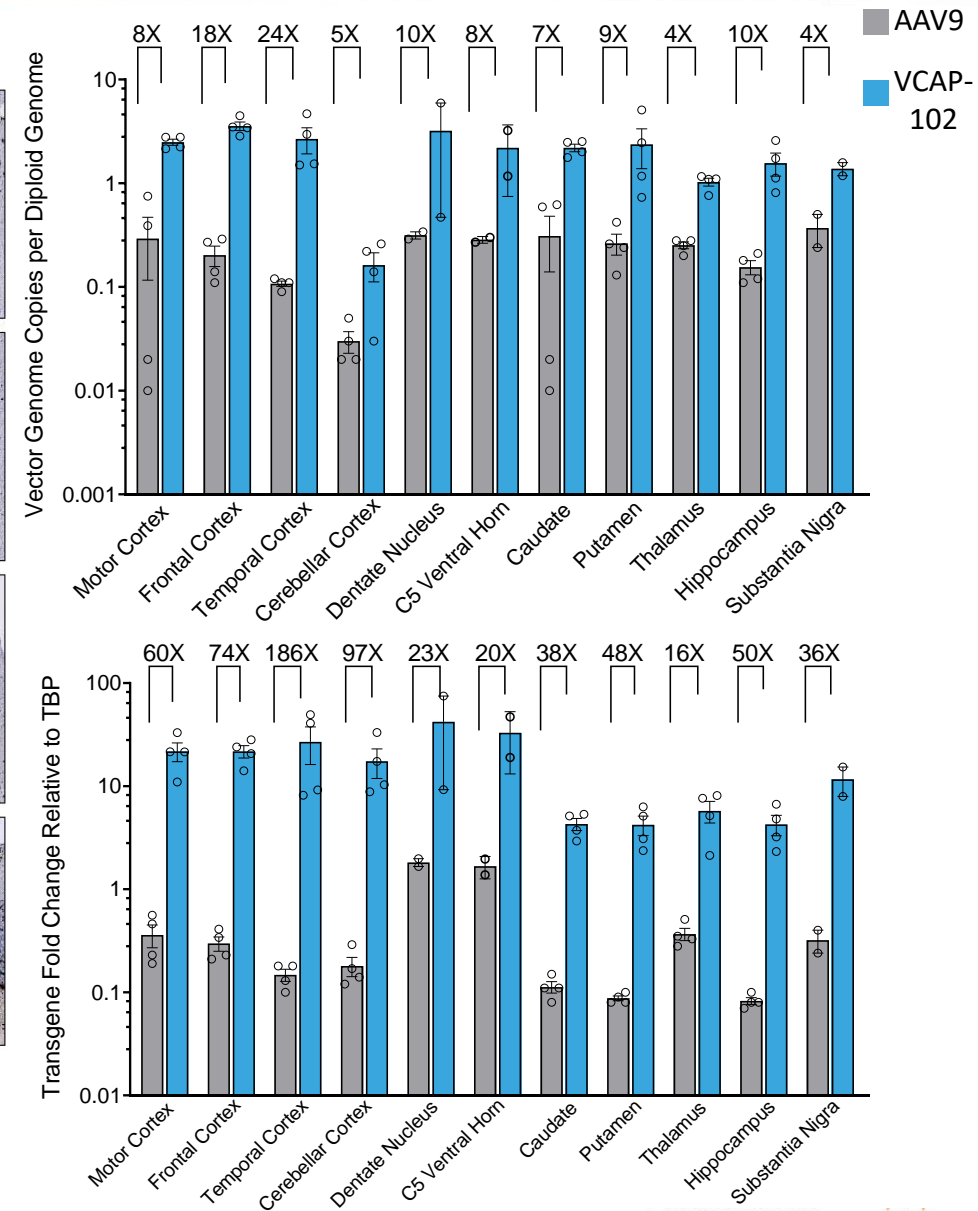
Dosings were at 1E13 VG/kg of scCBA-ZsGreen-HA; intravenous; 28 days in-life; n=3 6-8 week old female Balb/c



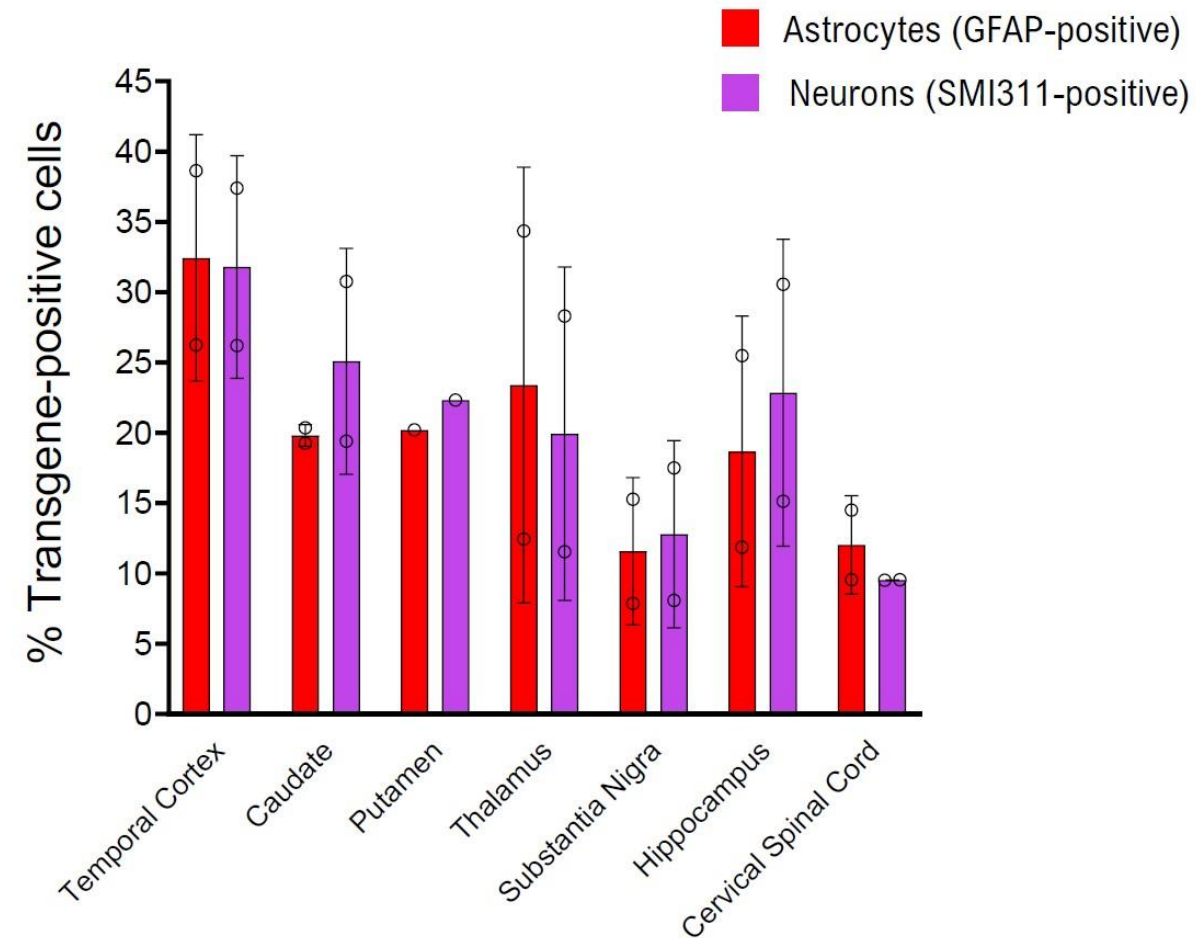
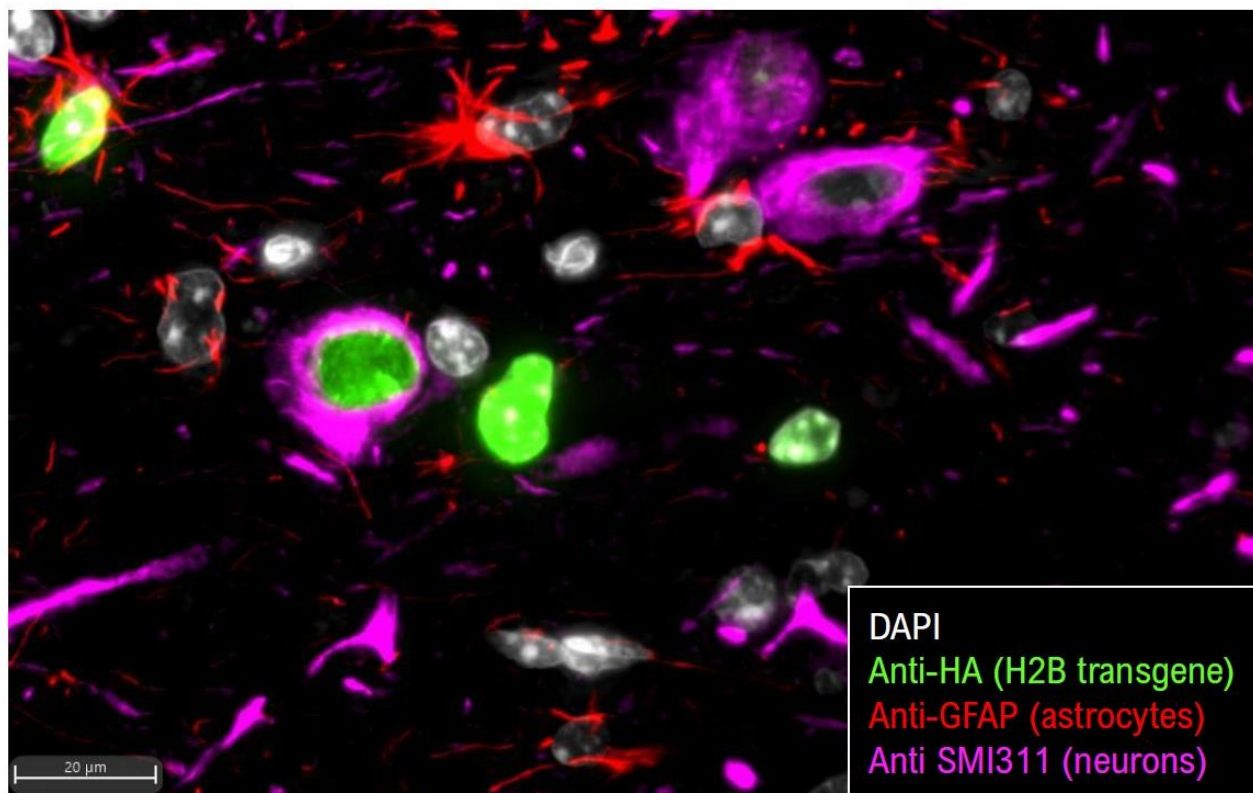
VCAP-102 Displays Increased Transduction Across Diverse Brain Regions in African Green Monkeys



Dosings were at 1E13 VG/kg of scCBA-cynoH2B-HA; intravenous; 28 days in-life; n=2 adult female *Chlorocebus sabaeus*.

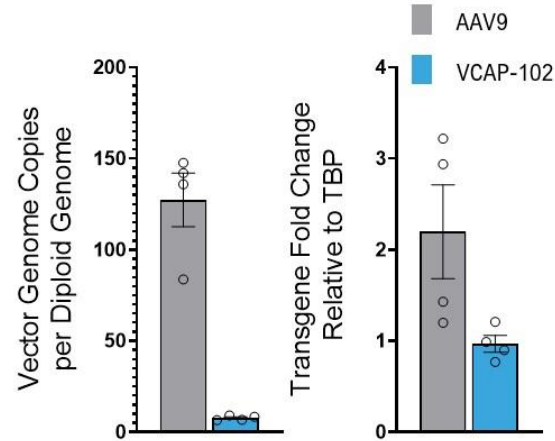
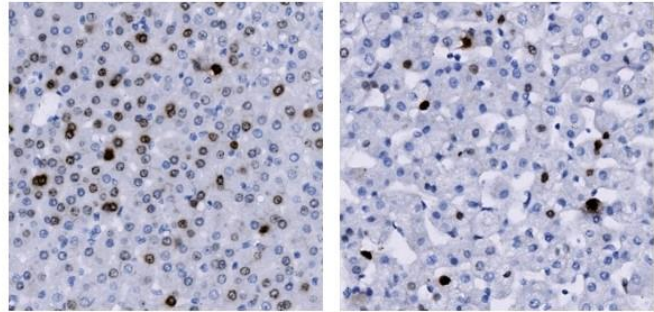


VCAP-102 Transduces Both Neurons and Astrocytes to a Similar Degree Across Diverse CNS Regions in African Green Monkeys

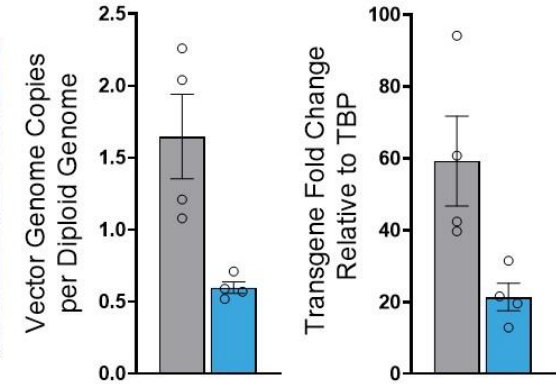
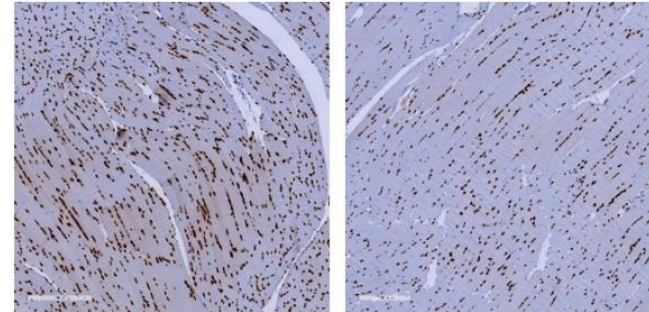


VCAP-102 Displays Liver Detargeting in African Green Monkeys

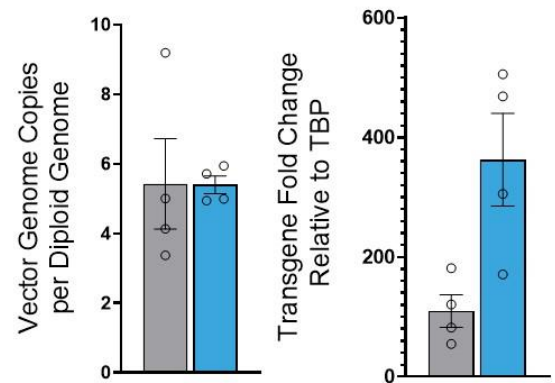
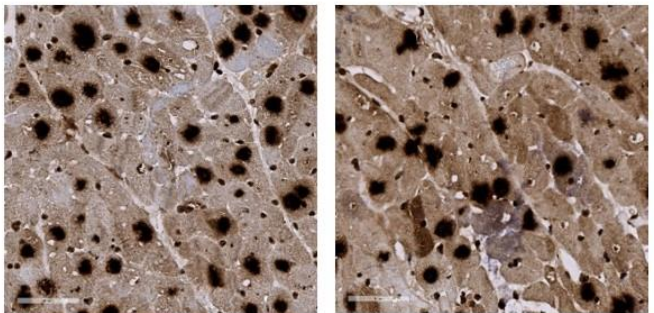
Liver



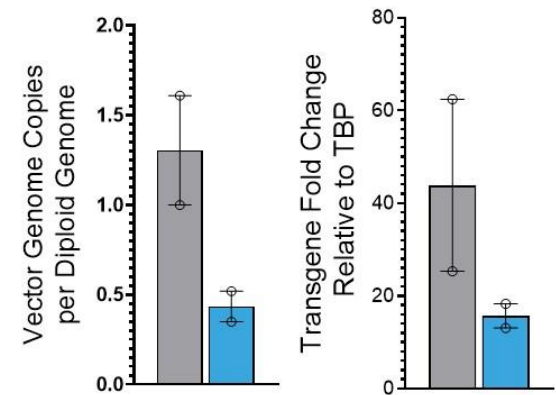
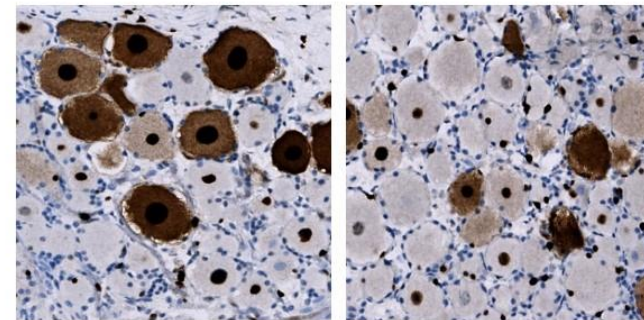
Quadricep



Heart

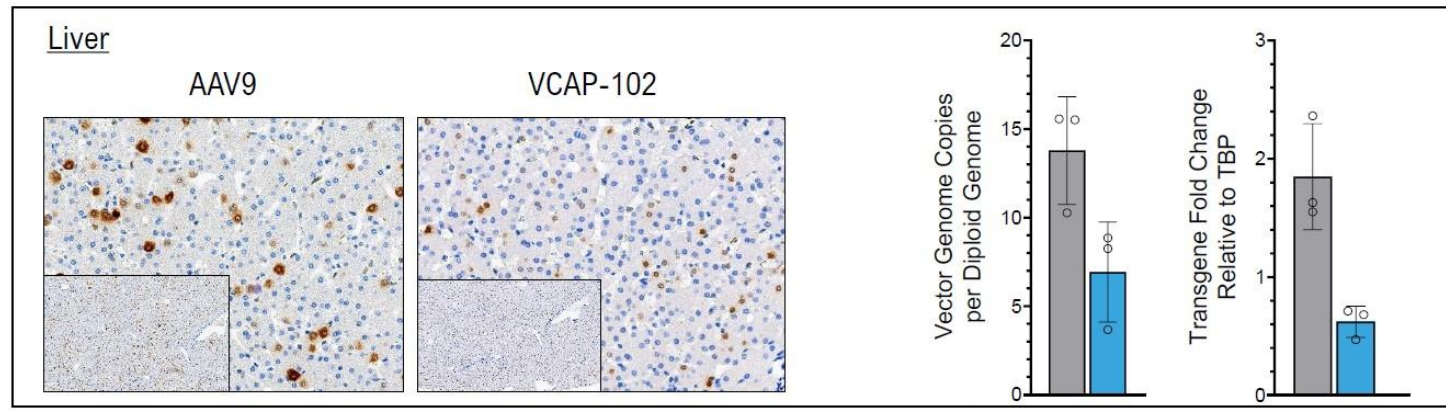
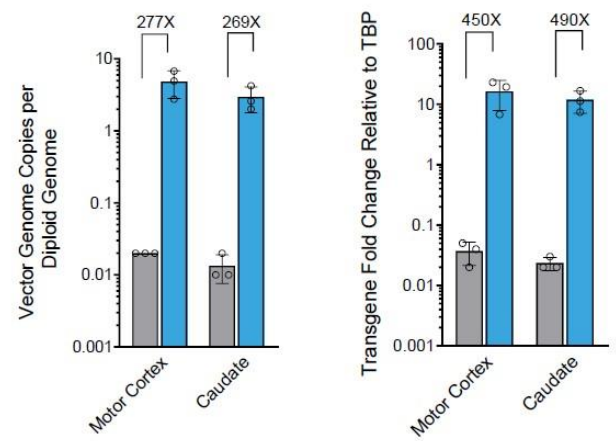
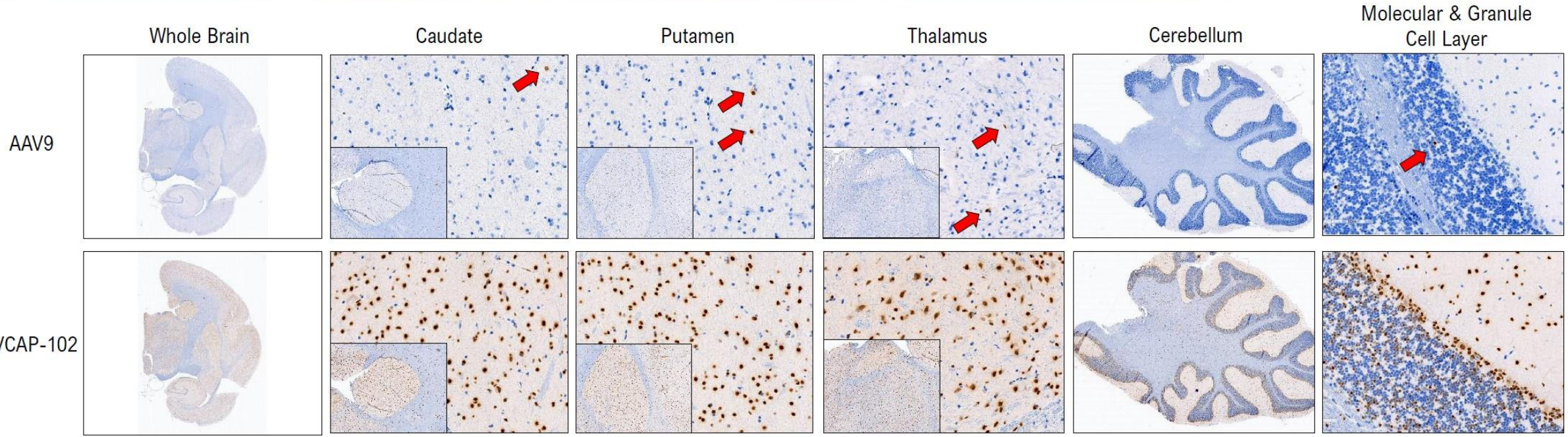


Dorsal Root Ganglia (T)



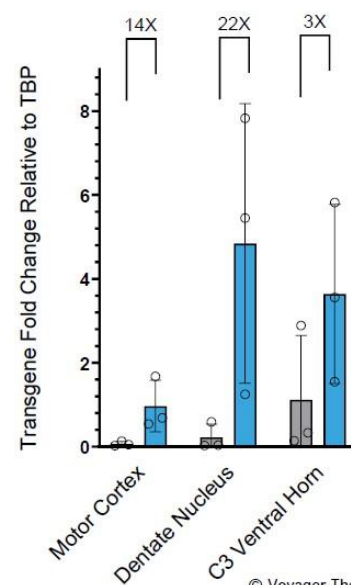
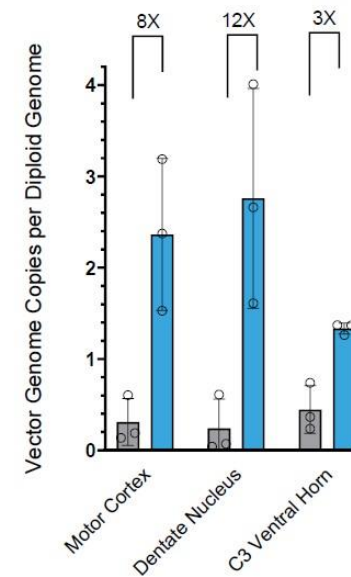
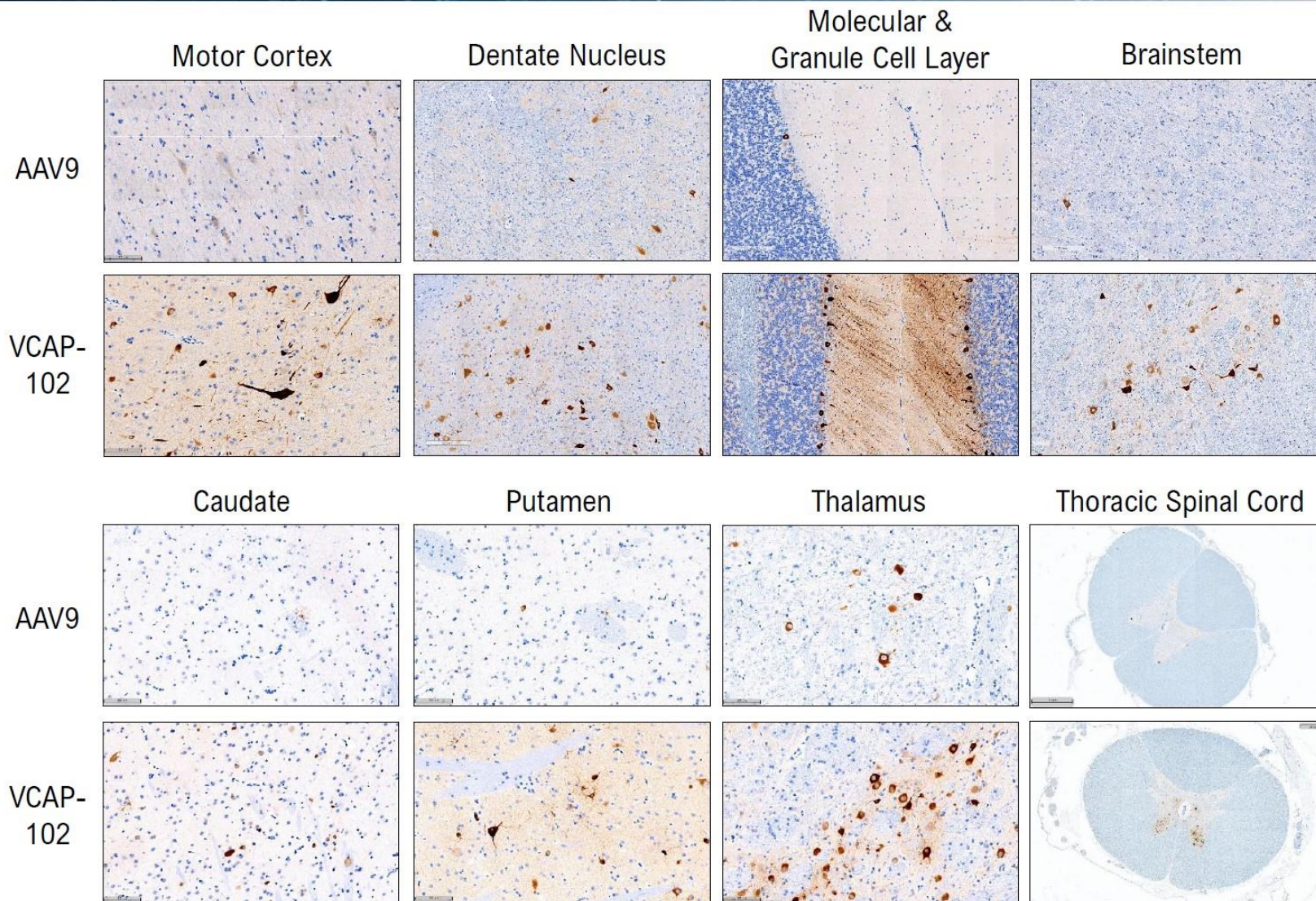
Dosings were at 1E13 VG/kg of scCBA-cynoH2B-HA; intravenous; 28 days in-life; n=2 adult female *Chlorocebus sabaeus*.

VCAP-102 Demonstrates 450X Transgene Expression in Marmoset Brain over AAV9 at 2E12 VG/kg



Dosing was at 2E12 VG/kg of scCBA-cynoH2B-HA; intravenous; 28 days in-life; n=3 adult male *Callithrix jacchus*.

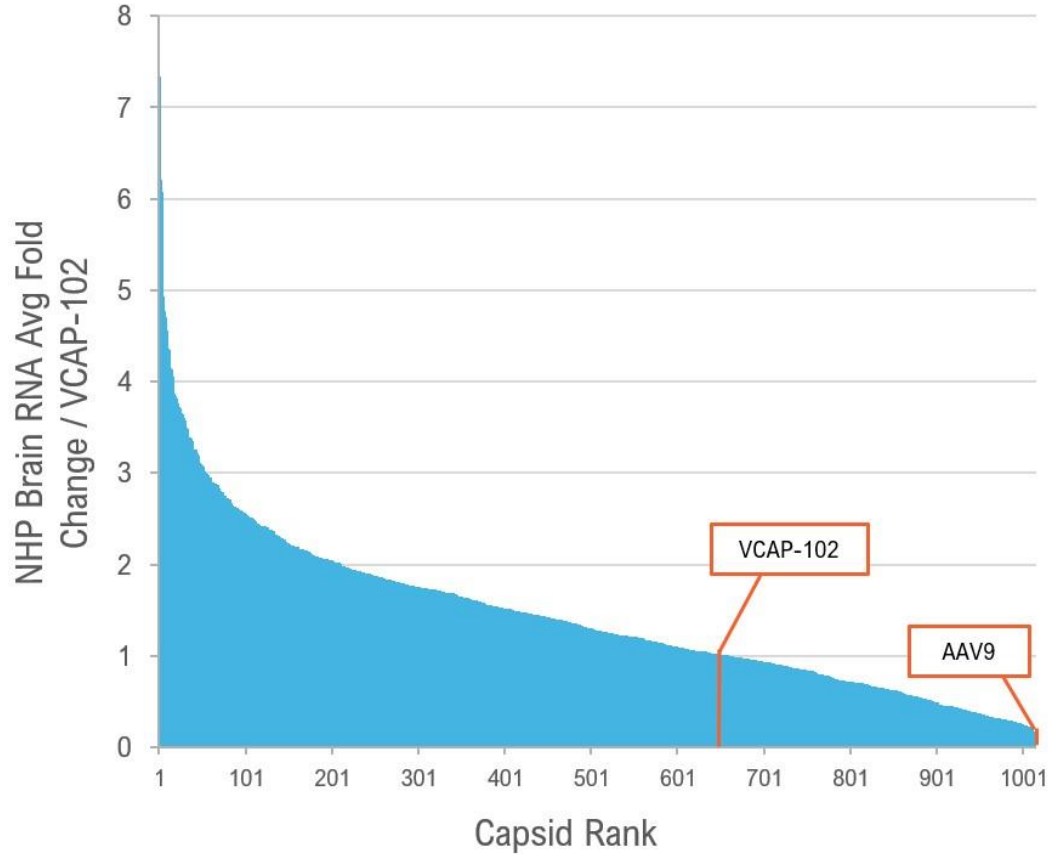
VCAP-102 Demonstrates Increased Transgene Expression Over AAV9 in Cynomolgus Macaques with a Single-Stranded Transgene



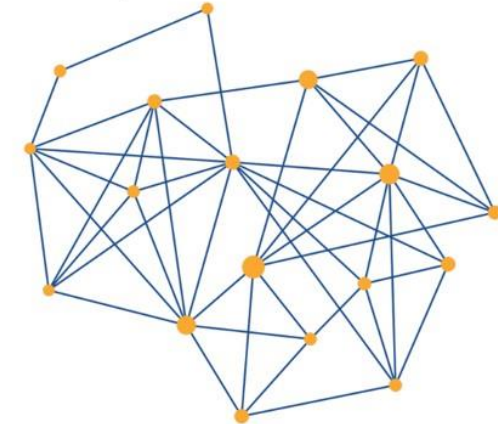
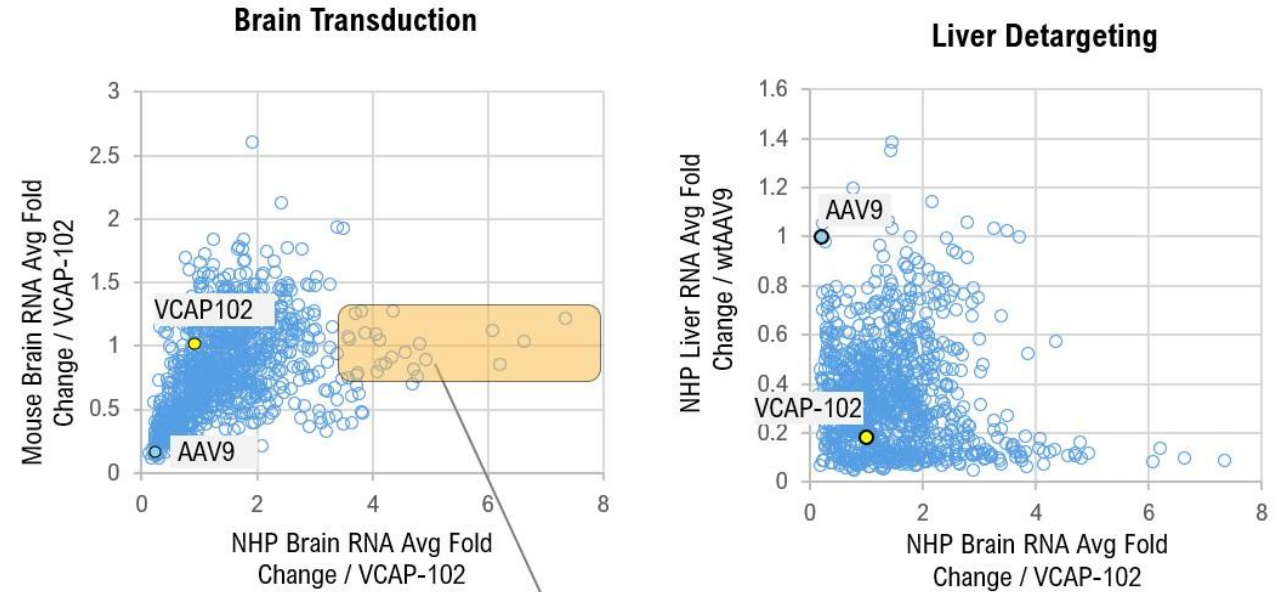
Dosings were at a mid-range dose of ssCBA-Transgene; intravenous; 27-30 days in-life; n=3 3-6yo male *Macaca fascicularis*.

Generation 2 Capsids Demonstrate Increased CNS Potency and Further Liver Detargeting Over VCAP-102 in Cynomolgus Macaques

Gen2 Candidates Ranking in NHP Brain

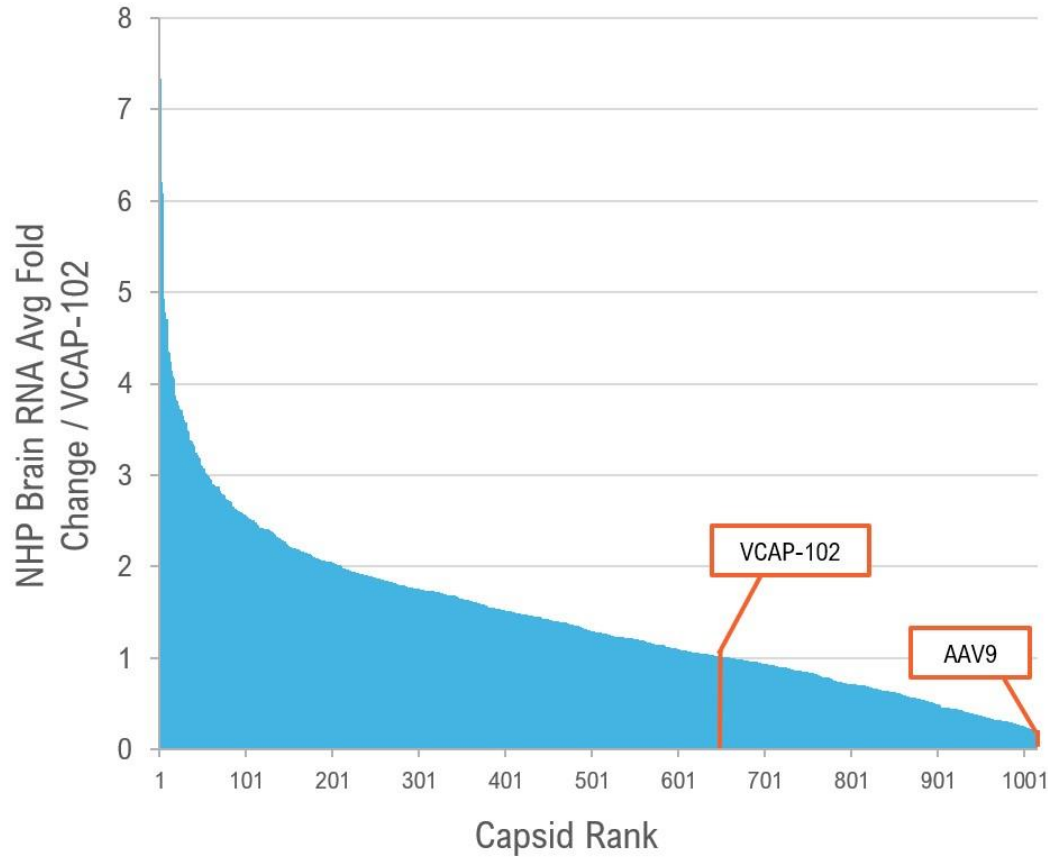


Gen2 Candidates Selection

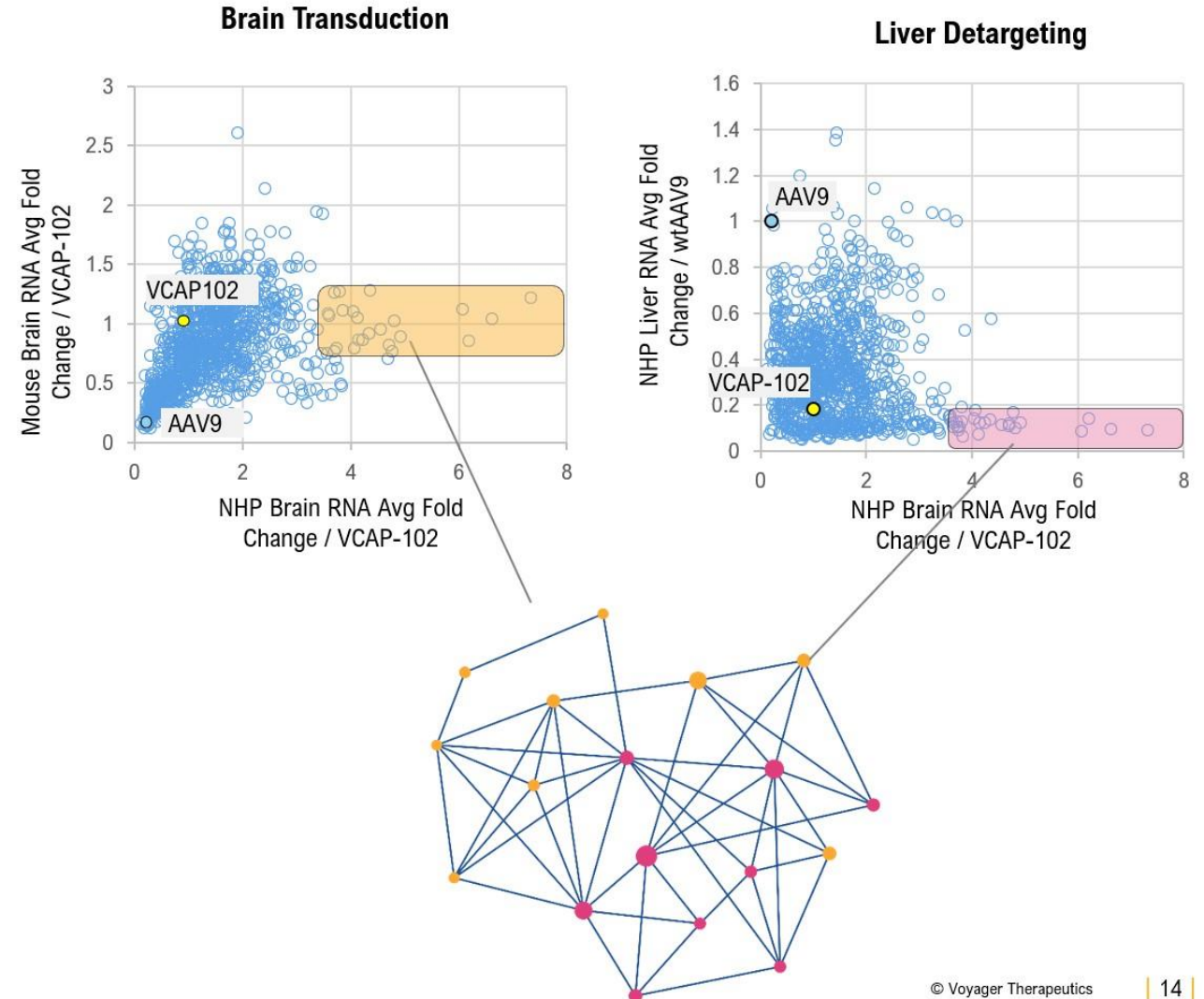


Generation 2 Capsids Demonstrate Increased CNS Potency and Further Liver Detargeting Over VCAP-102 in Cynomolgus Macaques

Gen2 Candidates Ranking in NHP Brain

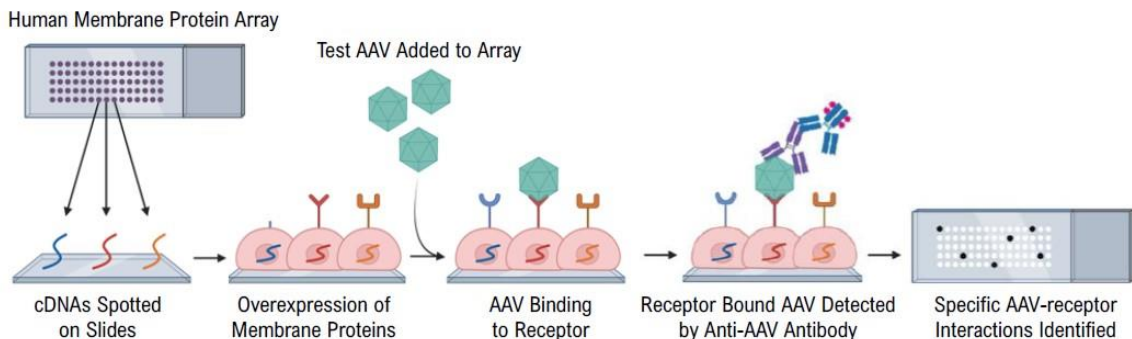


Gen2 Candidates Selection

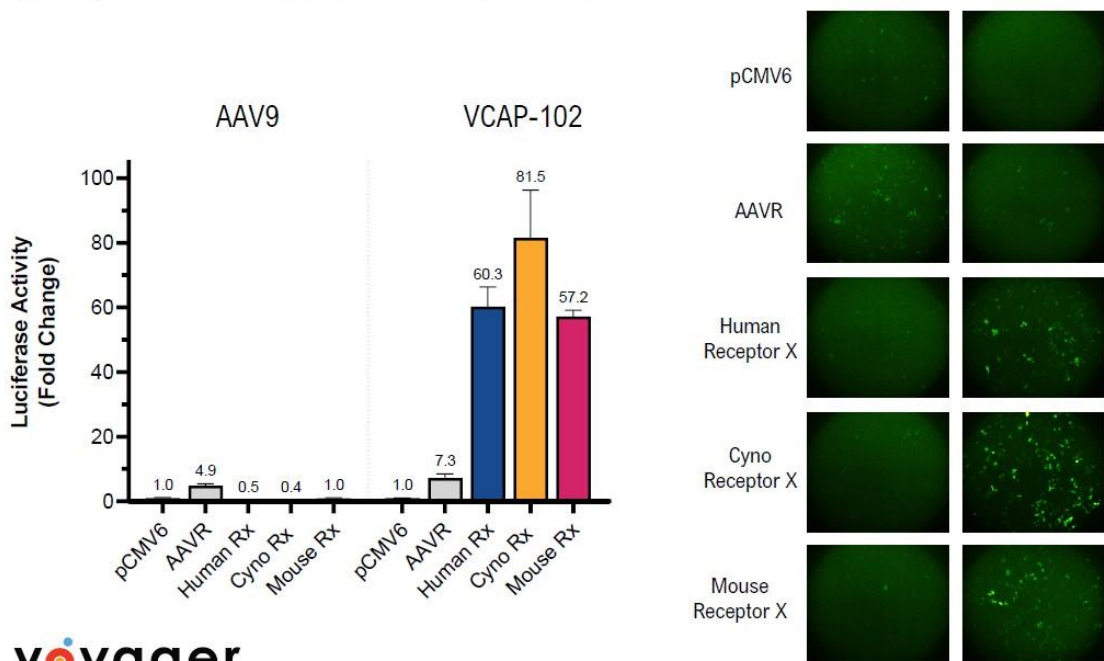


Receptor X Demonstrates Direct and Specific Binding to VCAP-102

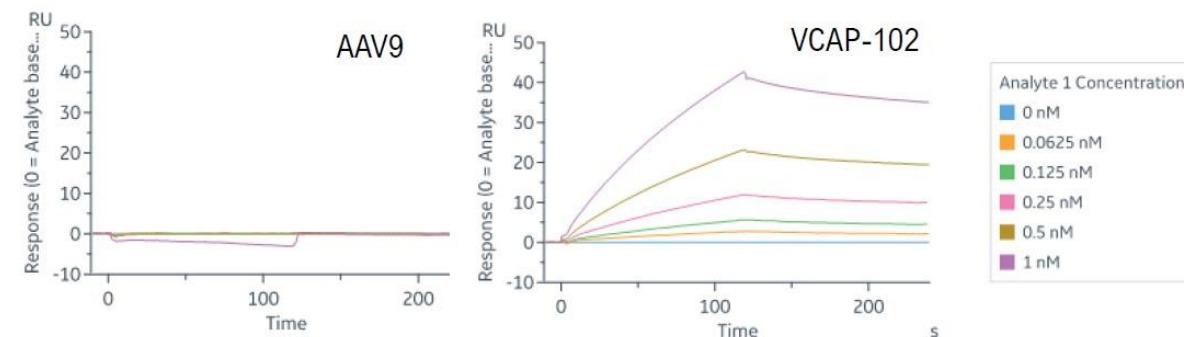
Receptor Screen



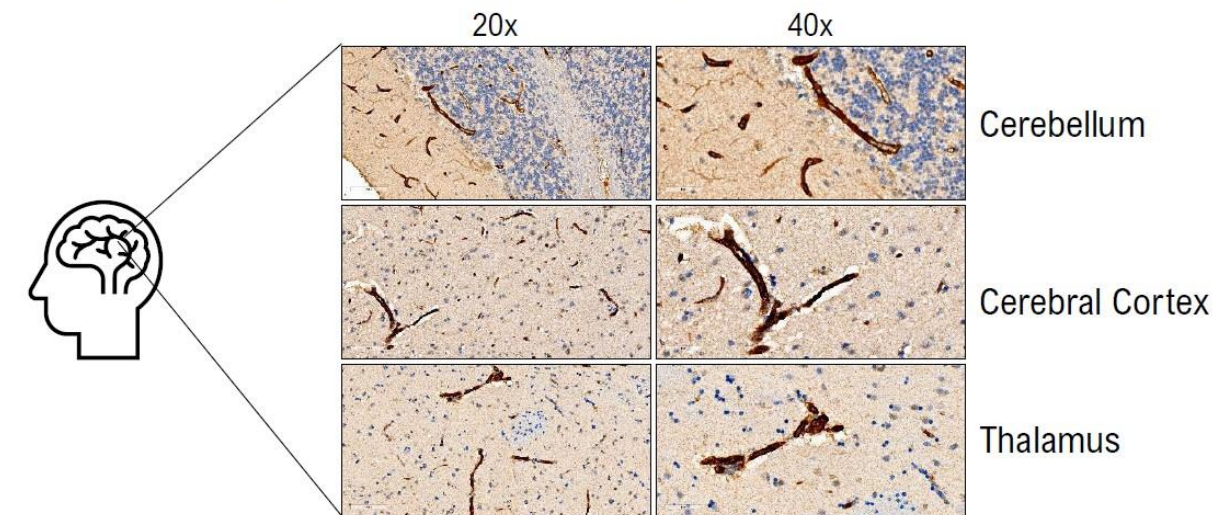
Receptor Hit Validation – “Receptor X”



VCAP-102 Demonstrates Direct Binding to Receptor X



Receptor X is Expressed on Brain Endothelial Cells



***Oral Presentation: Brett Hoffman, Ph.D.
Wednesday, May 17, 2023 8-8:25 AM**

Acknowledgements

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- Ishan Shah
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- Katherine Tyson

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- Alexis Bloedel
- Rebecca Spellman

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- Dhiral Shah
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- Dillon Kavanagh
- Jack Studer
- Jordan O'Brien
- Usman Hameedi

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QUESTIONS?

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