

RNA-driven Evolution of AAV Capsid Libraries Identifies Variants with High Transduction Efficiency in Non-Human Primate Central Nervous System

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ASGCT 2021

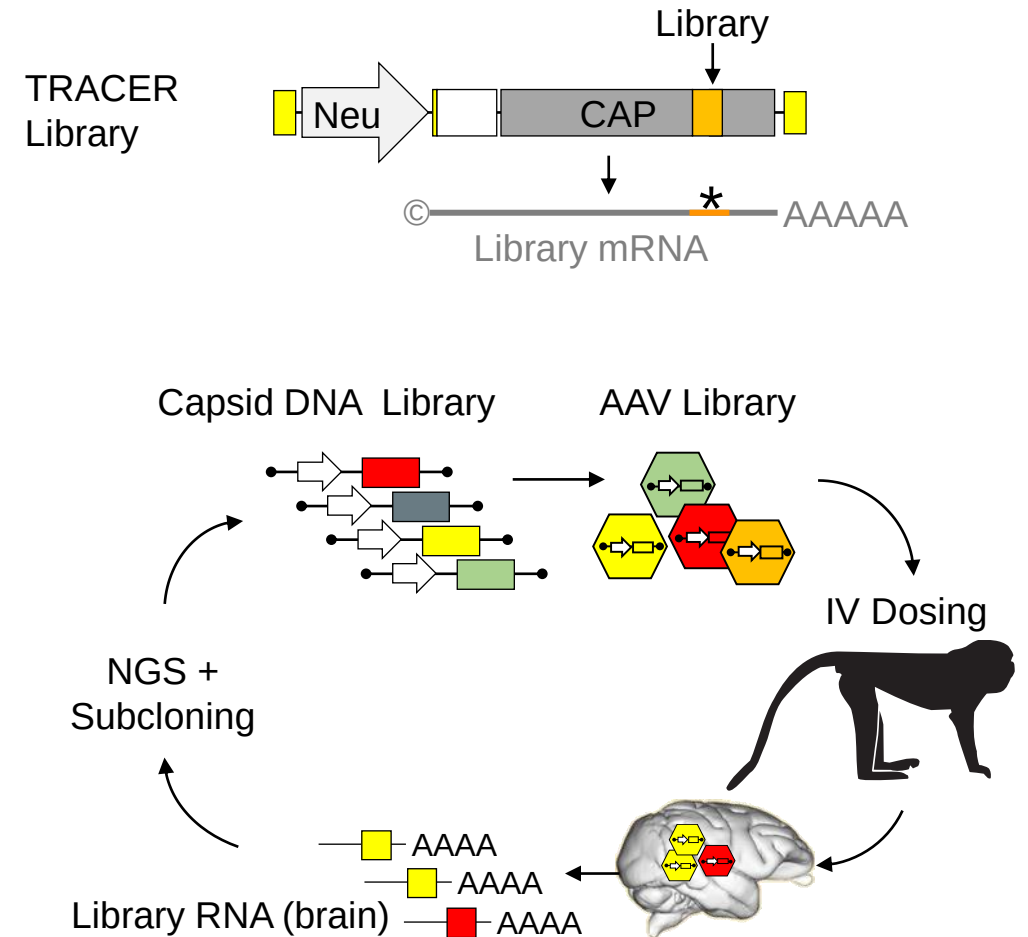


Disclosure

- Mathieu Nonnenmacher is a full-time employee of Voyager Therapeutics, Cambridge, MA

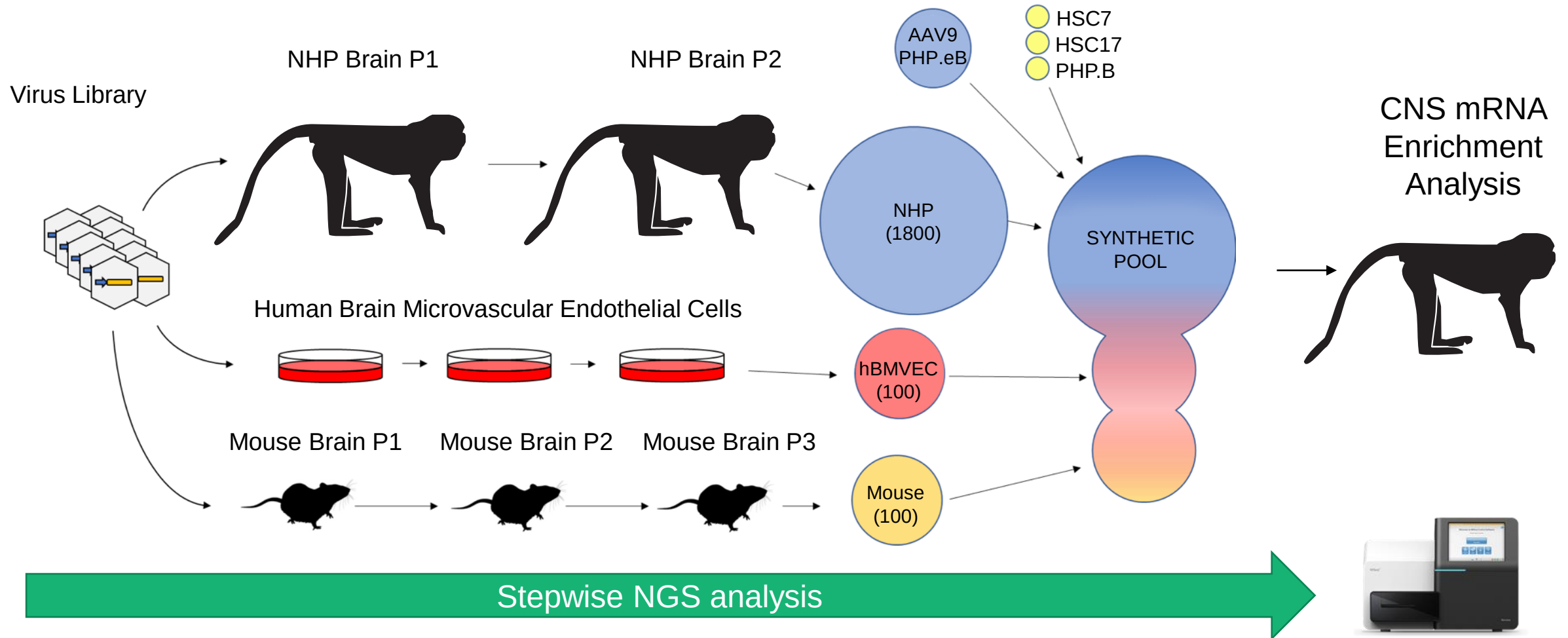
TRACER-NHP Directed Evolution for Neurotrophic AAV Capsids

- **Challenges with widespread CNS gene delivery**
- Current best-in-class, AAV9, achieves only limited CNS transduction from IV route
- Local delivery can unlock some indications, but may not achieve sufficient distribution for others
- Functional evolution of AAV in mice identified BBB-penetrant AAV capsids but failed to translate to primates (Deverman, 2016; Hordeaux et al., 2018)
- TRACER platform validated in rodents (Nonnenmacher et al., 2020) for functional biopanning
- **Voyager strategy: apply TRACER platform for RNA-driven AAV9 evolution in primate brain**



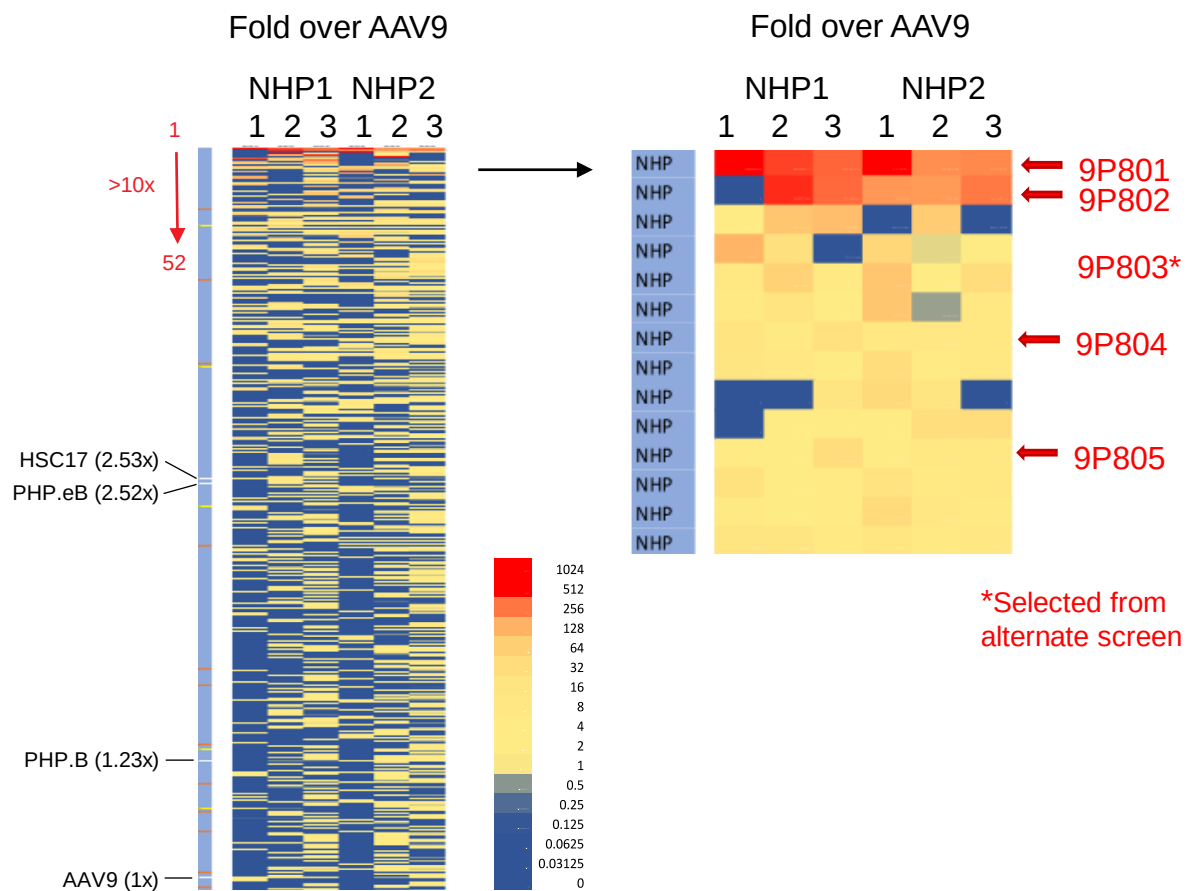
Adapted from
Nonnenmacher et al., *Mol Ther Methods Clin Dev.* 2020

Cross-Species TRACER Evolution



Validation of Top TRACER Candidates in NHP

Pooled Brain RNA Enrichment Screen



Individual Validation (5 candidates)

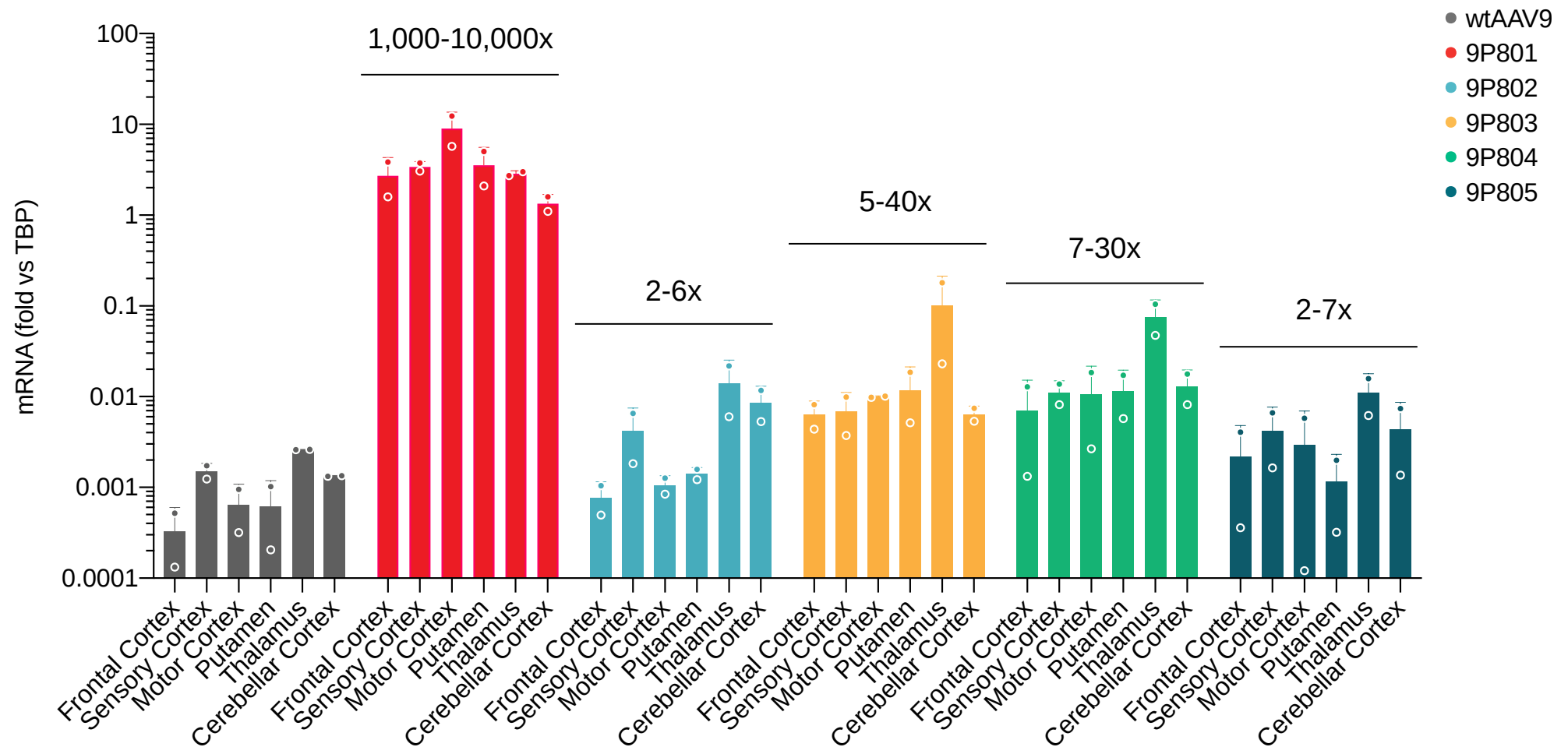
ssAAV CBA-TG- HA_{tag}



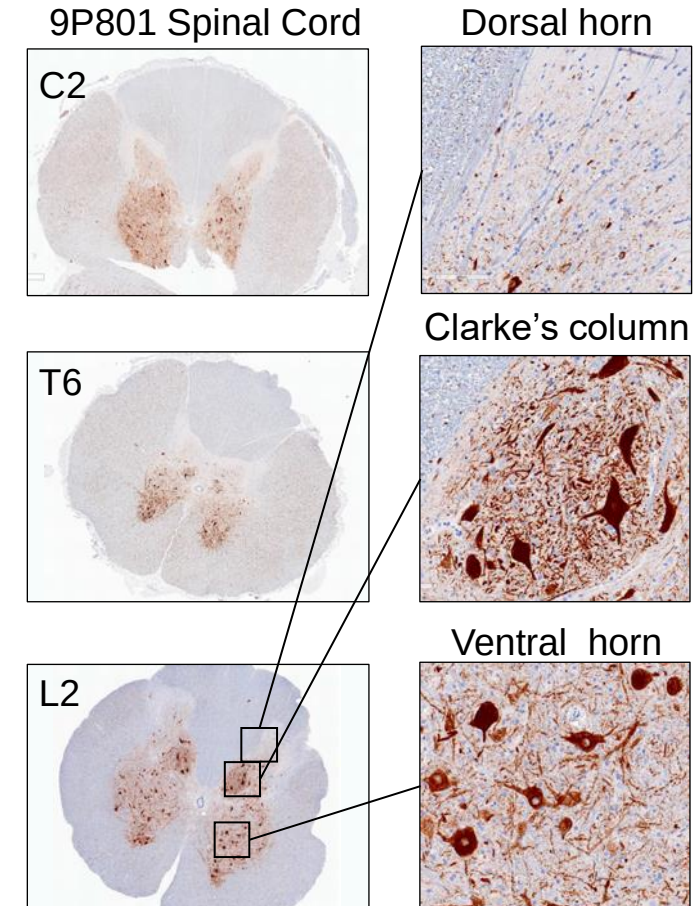
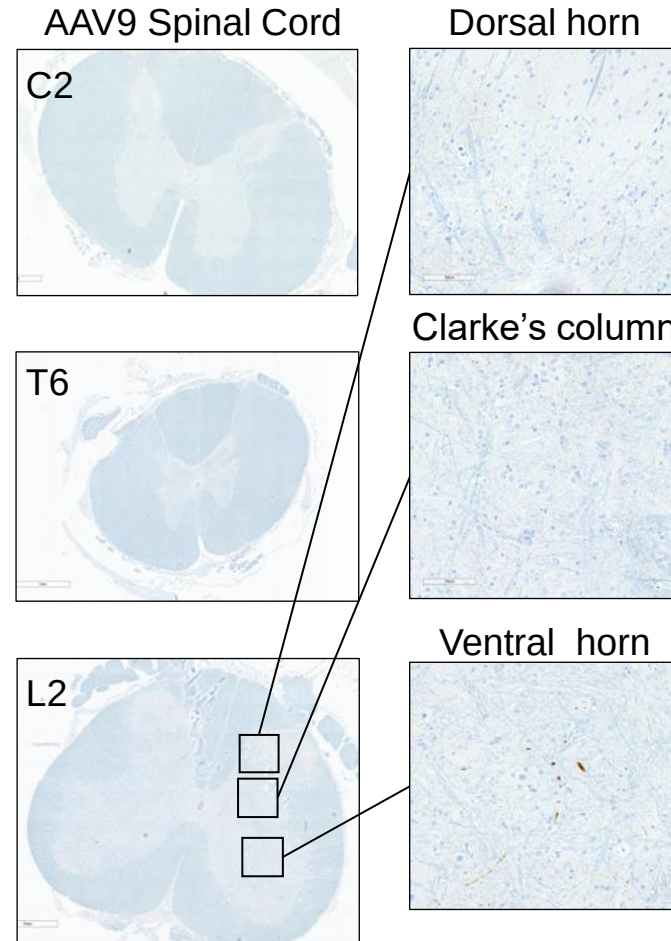
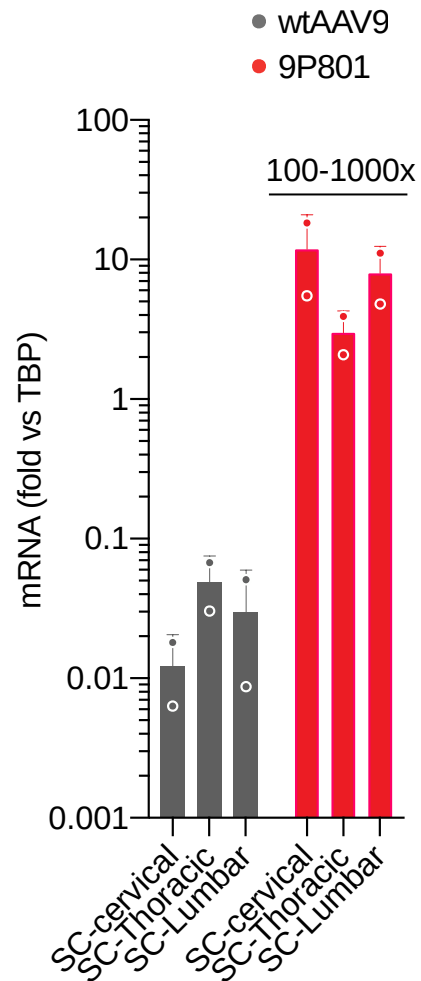
Adult cyno Macaques (n=2)

- Intravenous dosing
- 2e13 vg/kg (low dose)
- 14 days in-life
- Transgene Expression

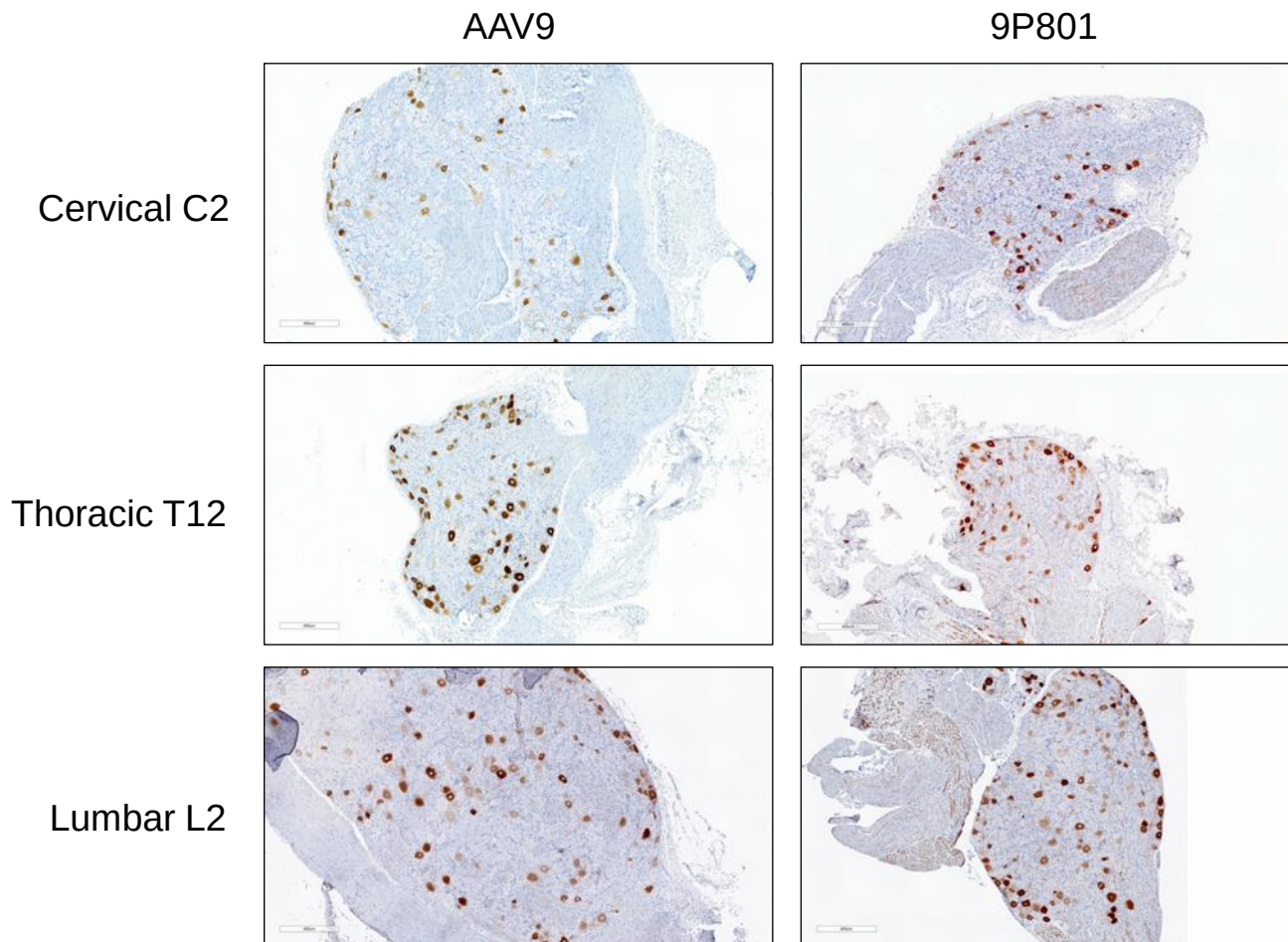
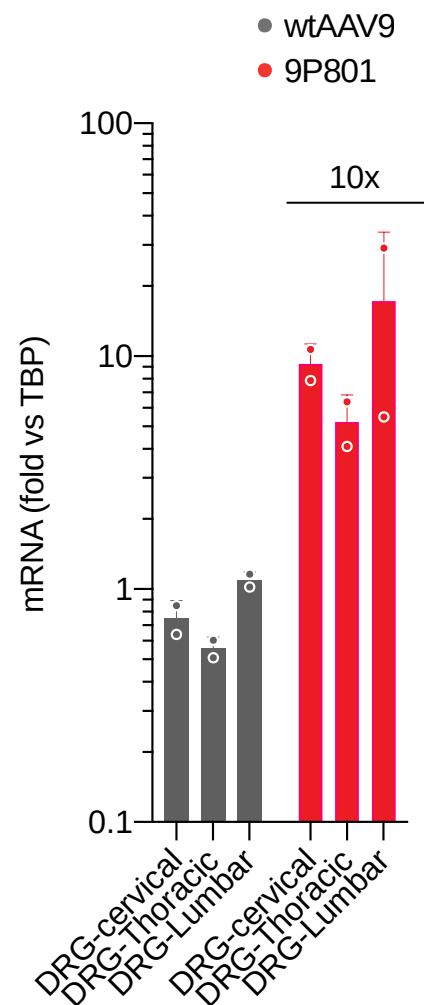
TRACER-NHP Capsids Show Increased Transgene mRNA Expression in the Brain



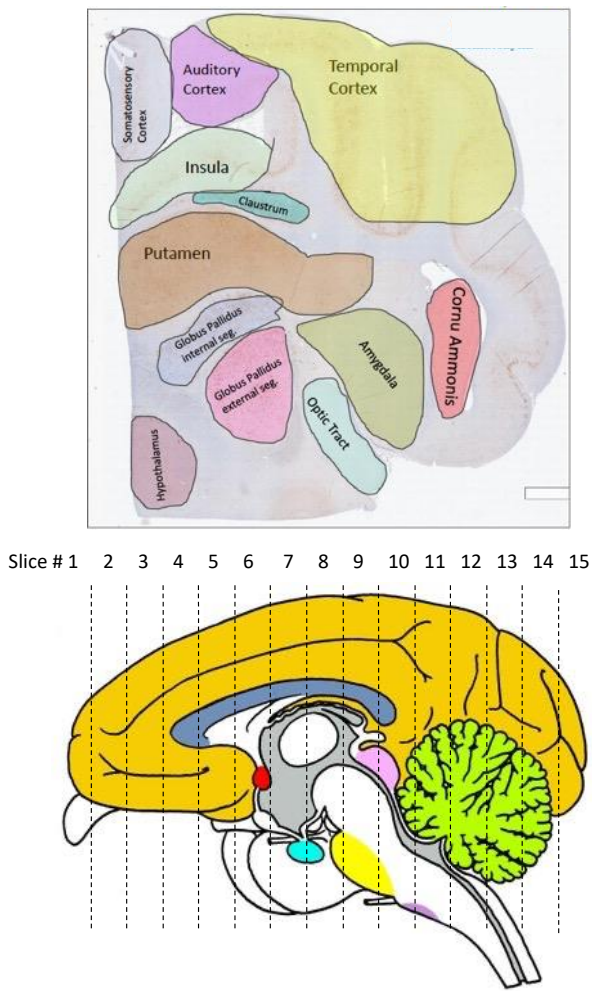
Capsid 9P801 Mediates Strong Transduction in the Spinal Cord



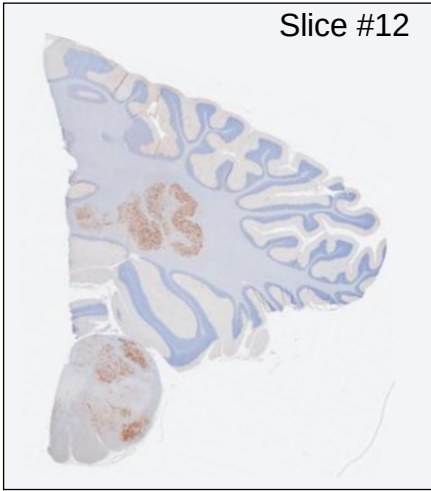
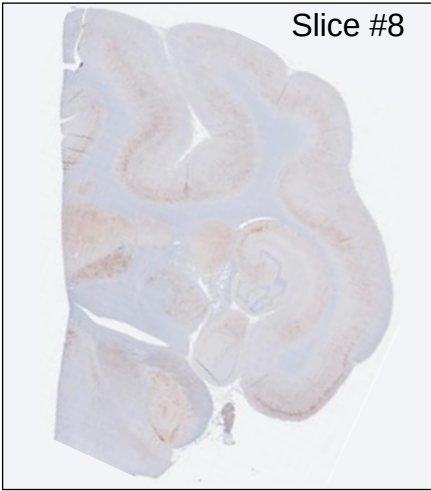
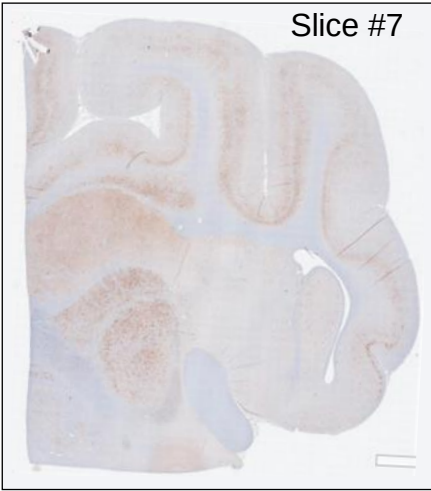
Transduction by AAV9 and 9P801 in the DRG



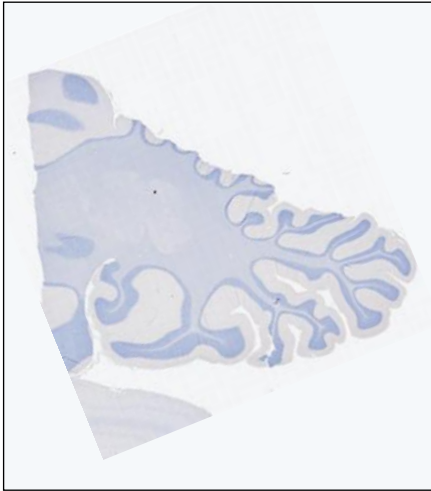
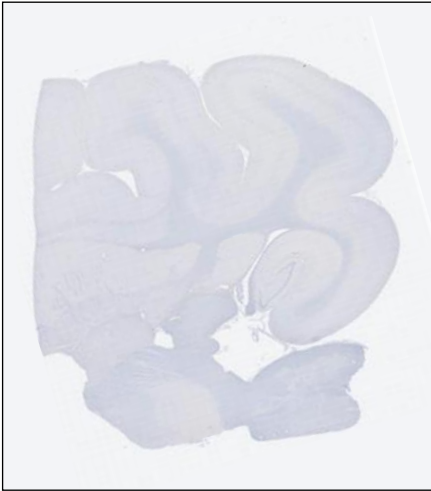
9P801 Mediates Widespread Transgene Expression in NHP Brain



9P801

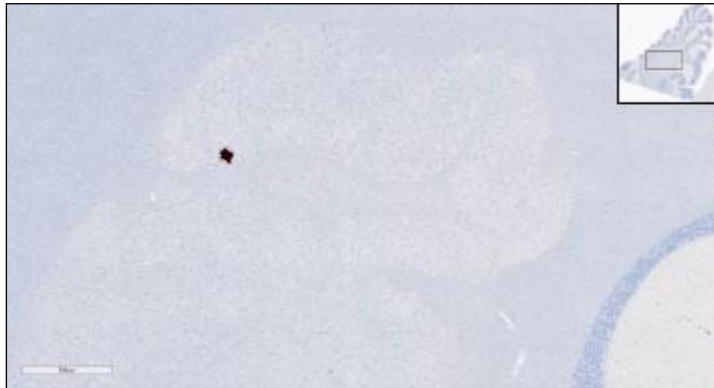


AAV9

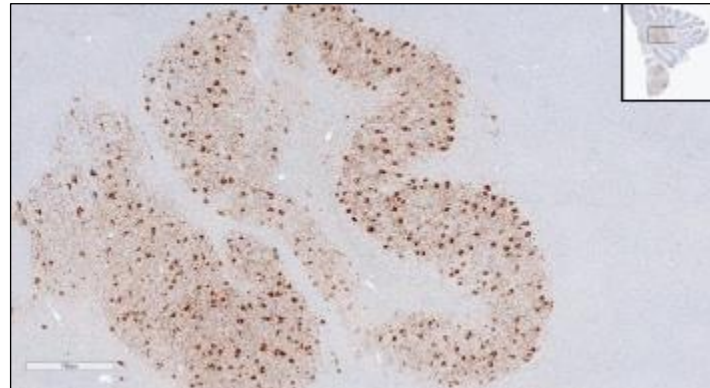


9P801 Displays a Predominantly Neuronal Tropism in Deep Cerebellar Nuclei

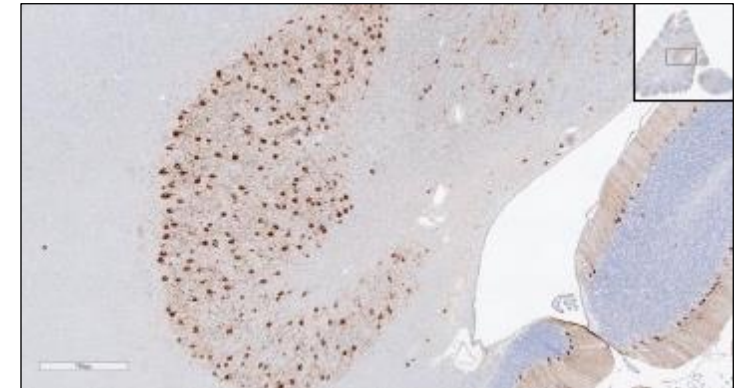
AAV9– NHP#1



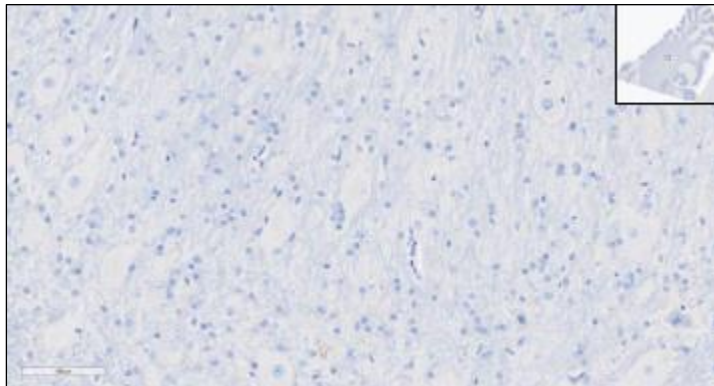
9P801– NHP#1



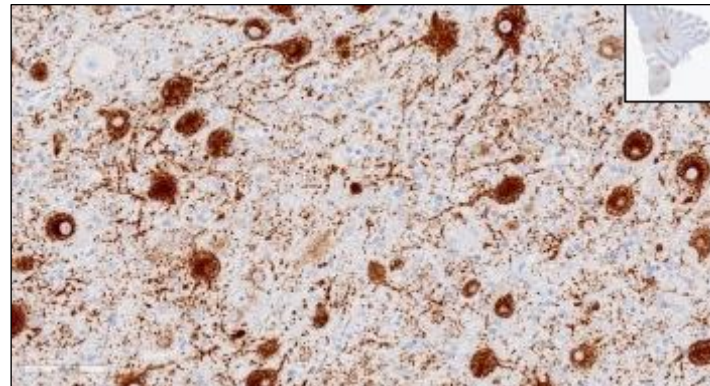
9P801– NHP#2



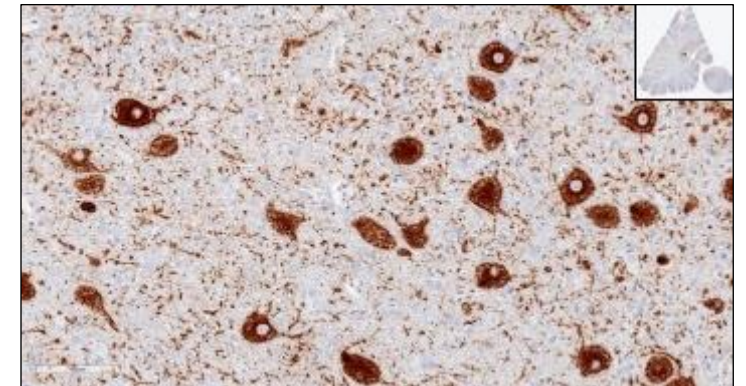
AAV9– NHP#1



9P801 – NHP#1

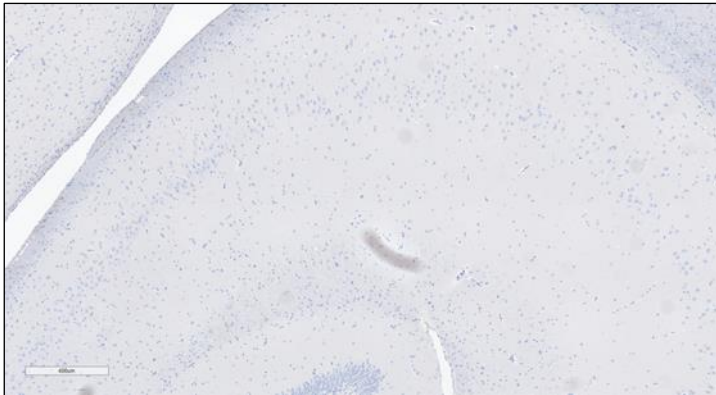


9P801 – NHP#2

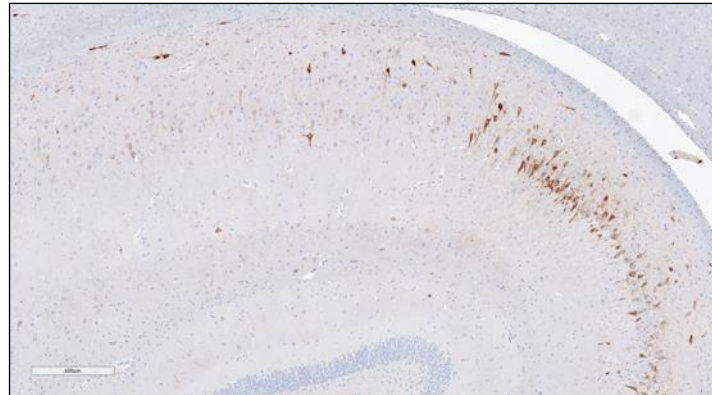


9P801 Displays a Predominantly Neuronal Tropism in the Hippocampus

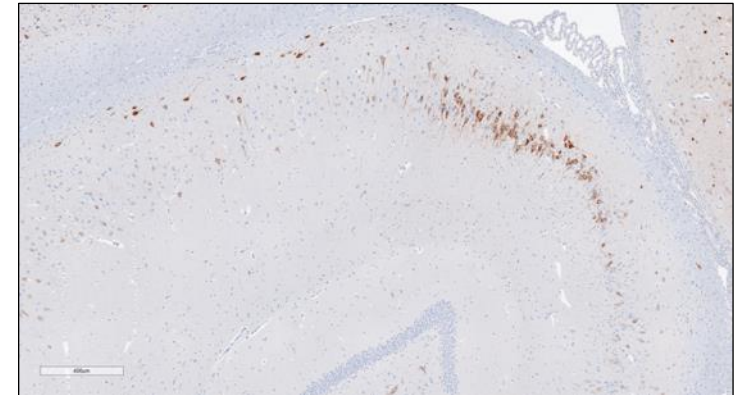
AAV9– NHP#1



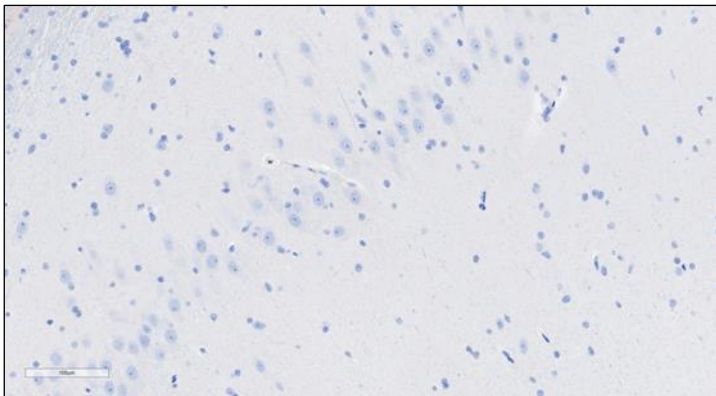
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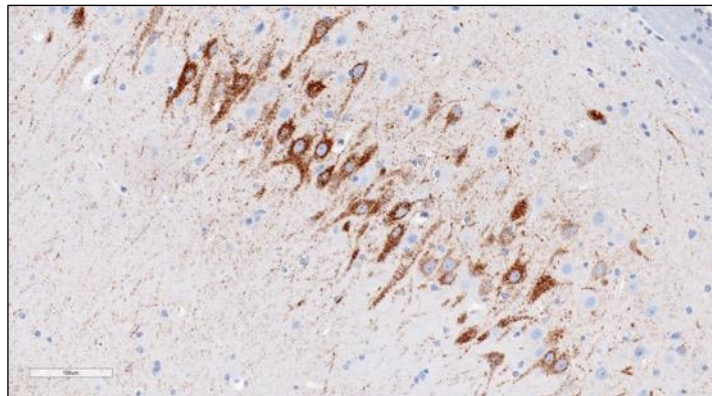
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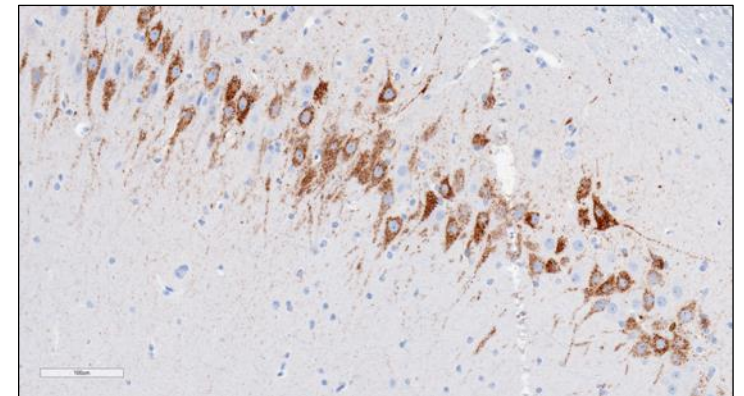
AAV9– NHP#1



9P801 – NHP#1

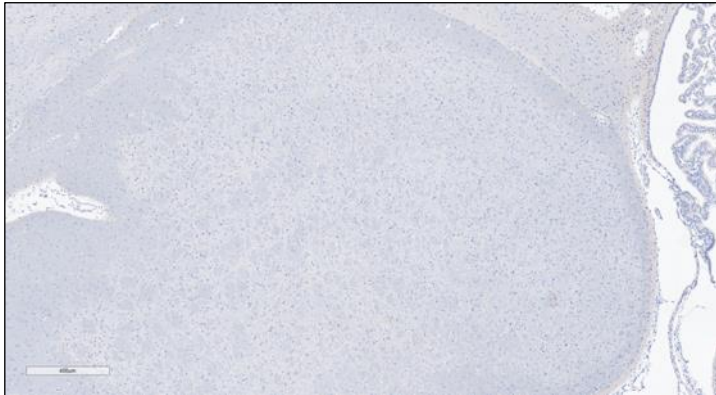


9P801 – NHP#2

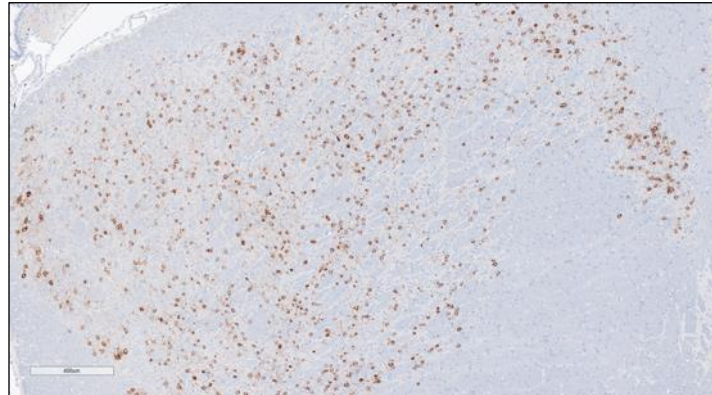


9P801 Displays a Predominantly Neuronal Tropism in the Thalamus (Lateral Geniculate Nucleus)

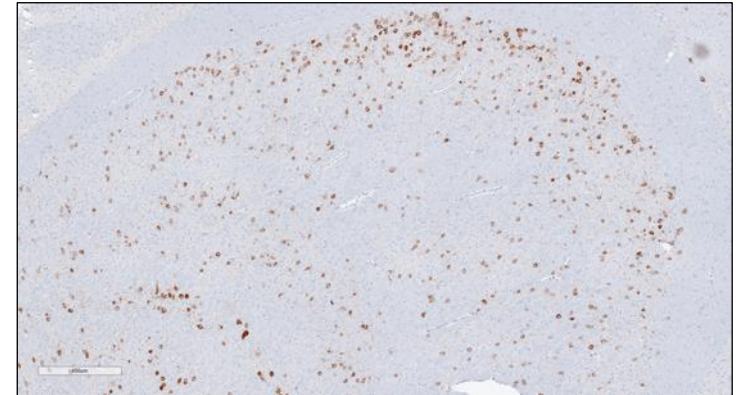
AAV9– NHP#1



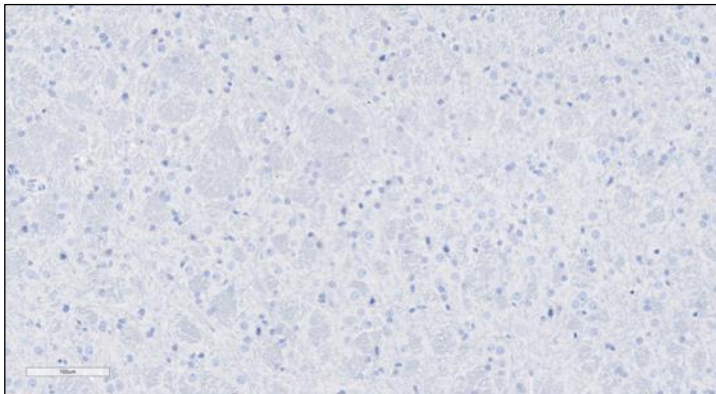
9P801– NHP#1



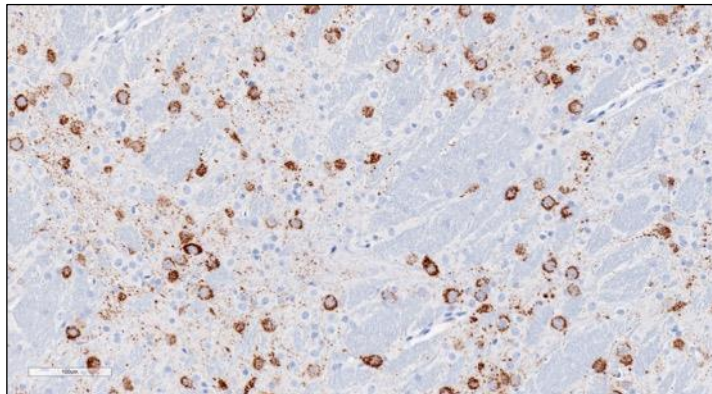
9P801– NHP#2



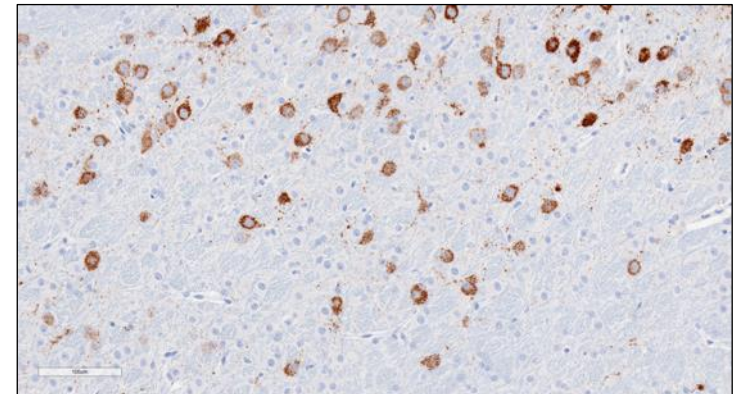
AAV9– NHP#1



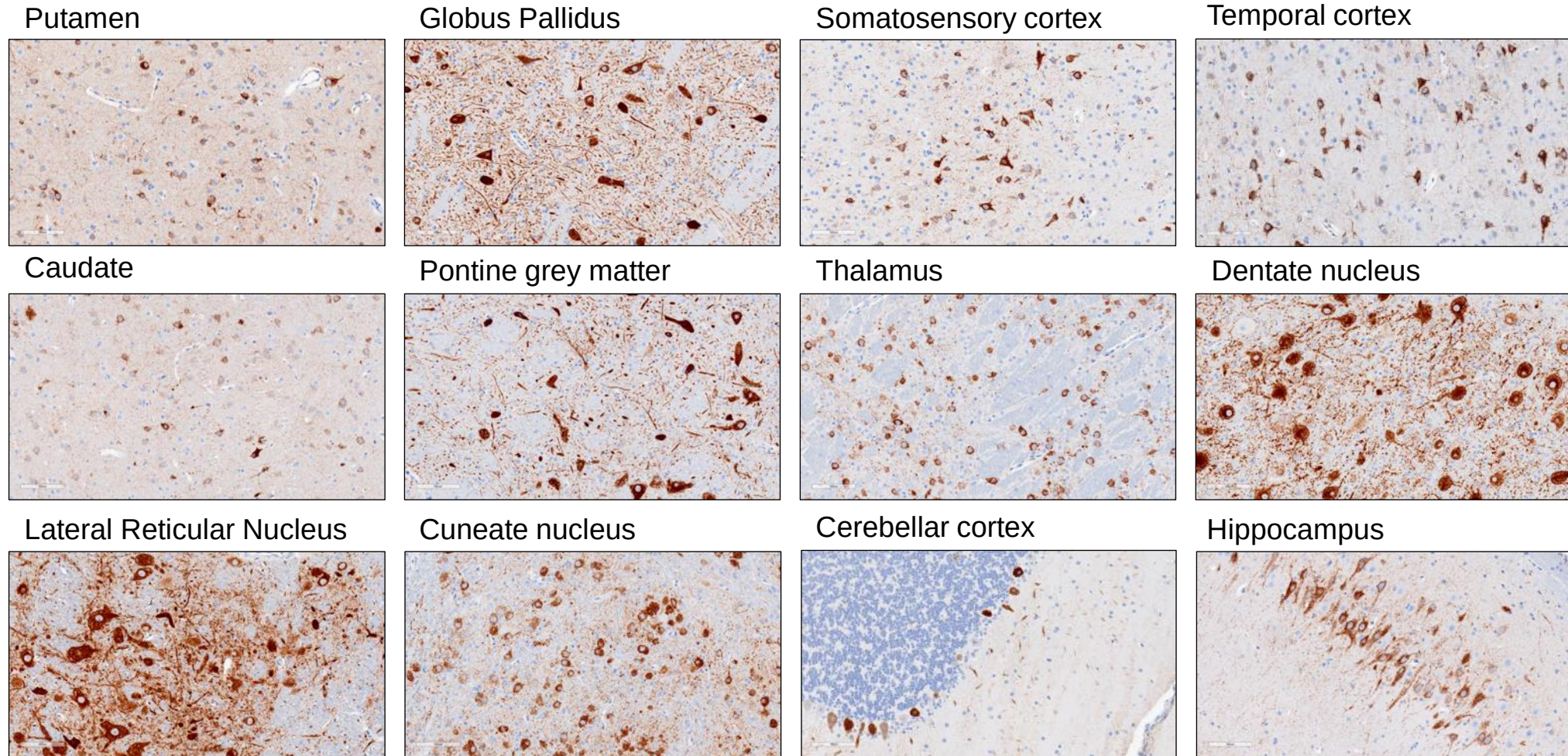
9P801 – NHP#1



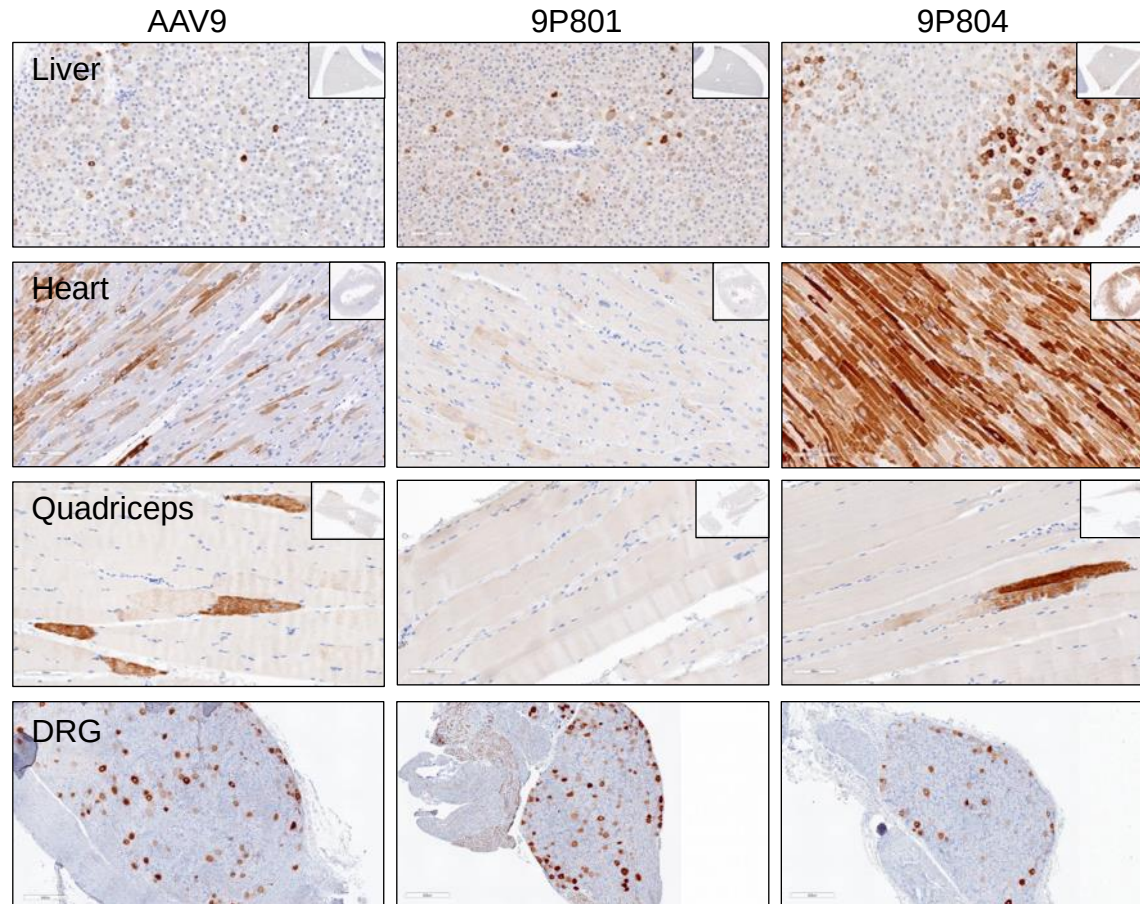
9P801 – NHP#2



Capsid 9P801 Displays Strong Transduction in Multiple CNS Regions



Transduction of Peripheral Tissues by 9P801 and 9P804

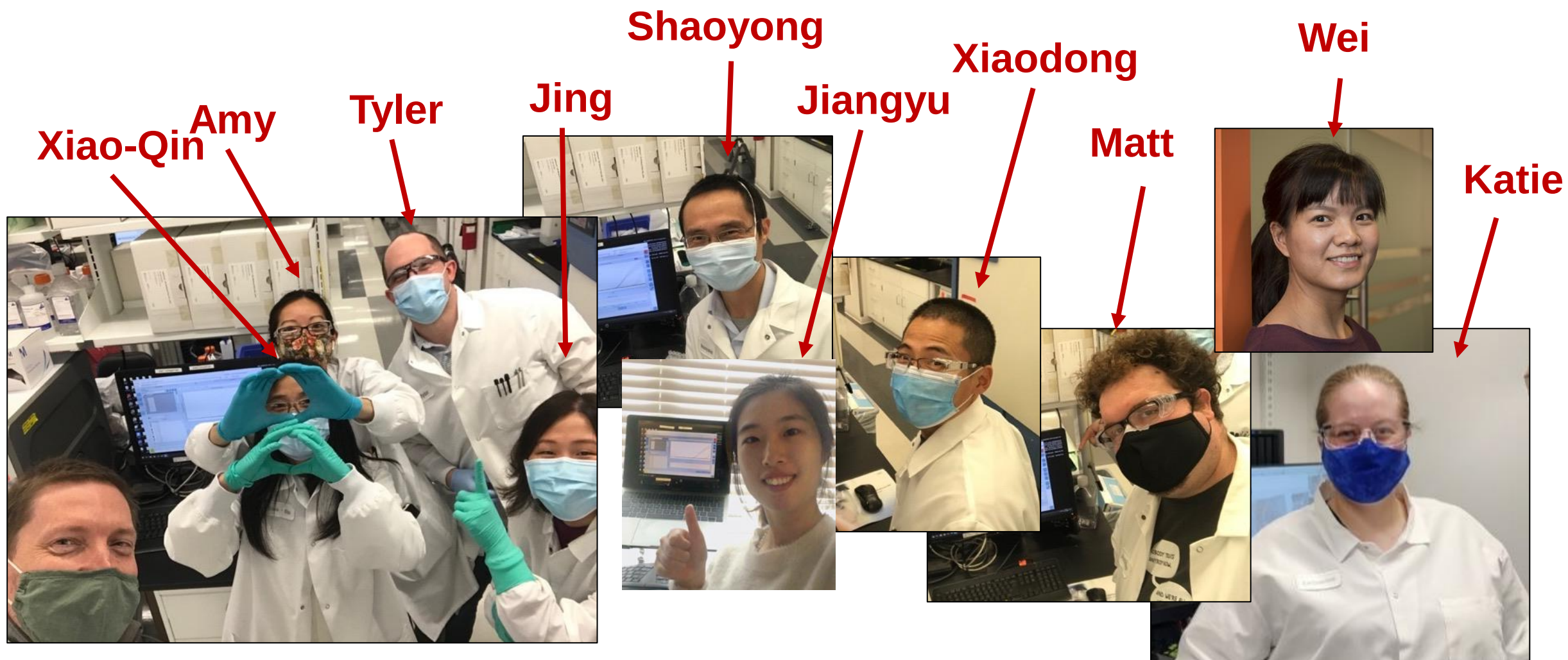


Key Takeaways

- The first run of TRACER platform in NHPs identified several BBB-penetrating capsids
- The 9P801 capsid allows unprecedented levels of primate CNS transduction by IV dosing, no toxicity was observed in the liver, spinal cord or DRG
- The 9P801 capsid showed no major difference with AAV9 in non-CNS tissue transduction, the 9P804 capsid displayed strong heart transduction and significant DRG detargeting, other candidates still under evaluation
- Nine additional NHP libraries are currently in late screening or characterization phase

The TRACER-NHP platform holds strong potential for development of enhanced capsids across multiple organisms, attributes and target tissues

Thank you



Thank you

- Nilesh Pande (IHC)
- June Deng
- Jianyu Chang
- Michael Hefferan
- Omar Khwaja
- Steve Paul
- Jay Hou

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