# Directed Evolution of an AAV5 Capsid Library Identifies a Variant with Enhanced Transduction in Non-Human Primate and Rodent Brain Following Systemic Administration

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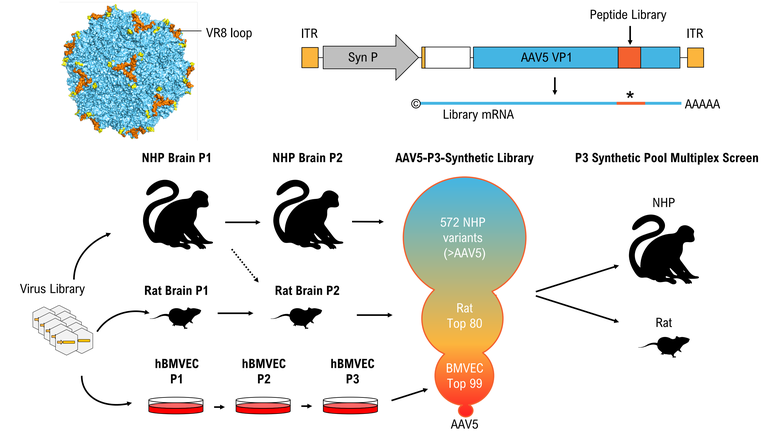
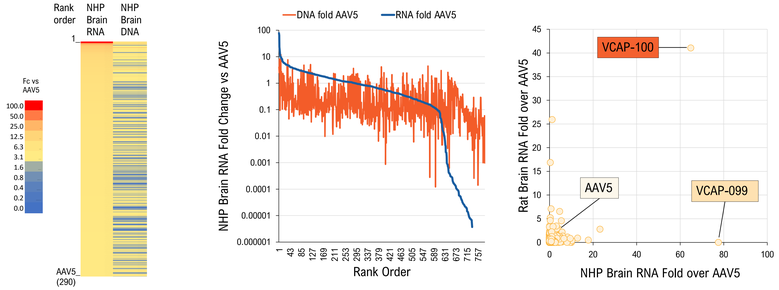
## SUMMARY

- AAV5 is a strong candidate for capsid engineering due to unique immunological properties, ease of manufacturing and clinical safety profile
- We applied Voyager proprietary TRACER™ platform to perform directed evolution of an AAV5 peptide display library in non-human primates (NHPs) and rodents via systemic administration
- We identified a variant, VCAP-100, with a similar gain-of-function in both rodents and non-human primates
- In NHPs, VCAP-100 showed a significant increase (>20-fold) in brain transduction relative to AAV9 benchmark following intravascular dosing
- VCAP-100 transduction was improved in multiple CNS regions and cell types, while a partial detargeting from the Dorsal Root Ganglia (~2-fold) was observed
- VCAP-100 transduction of non-CNS tissues (liver, heart) was similar to AAV9 with no detectable toxicity
- This study identifies VCAP-100 as a strong candidate for clinical development in CNS indications

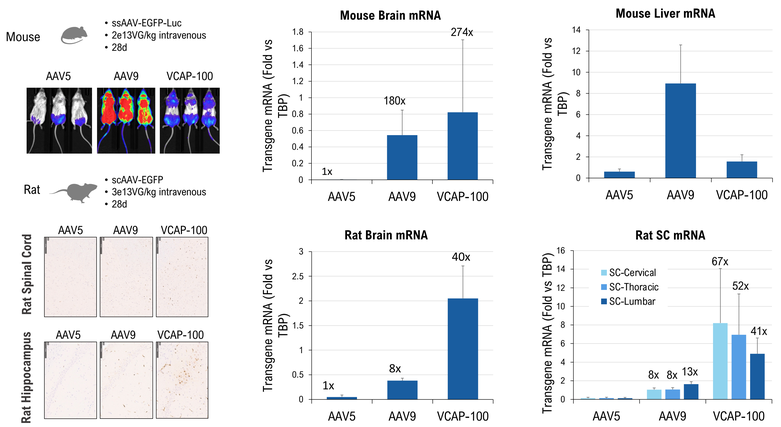
## Figure 1. TRACER Biopanning of an AAV5 Peptide Display Library



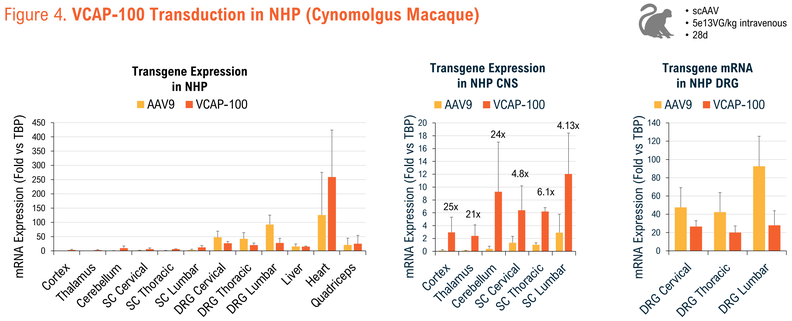

## Figure 2. Identification of VCAP-100 by Cross-Species RNA Enrichment Screen



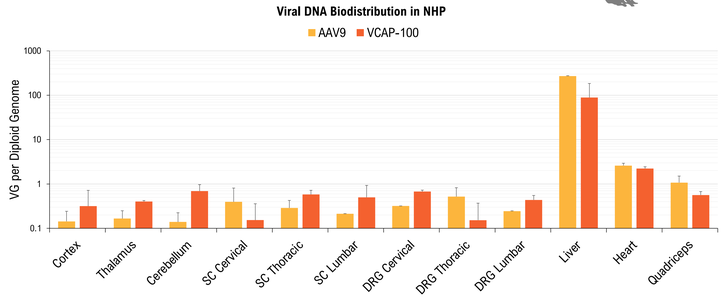

## Figure 3. Characterization of VCAP-100 in Rodents



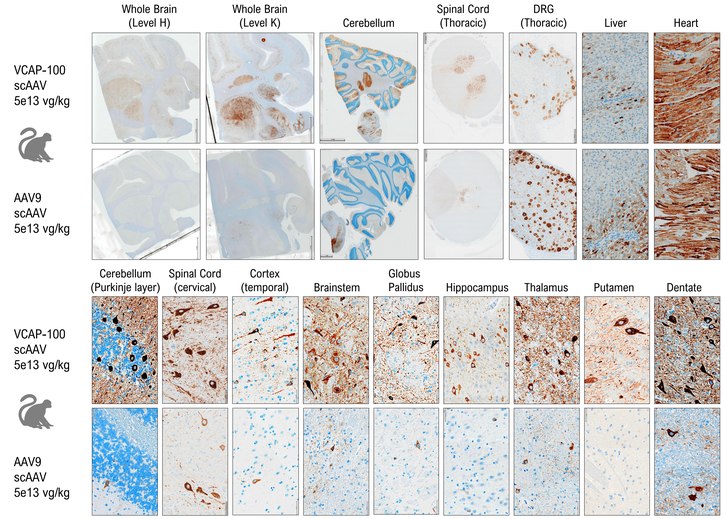

## Figure 4. VCAP-100 Transduction in NHP (Cynomolgus Macaque)



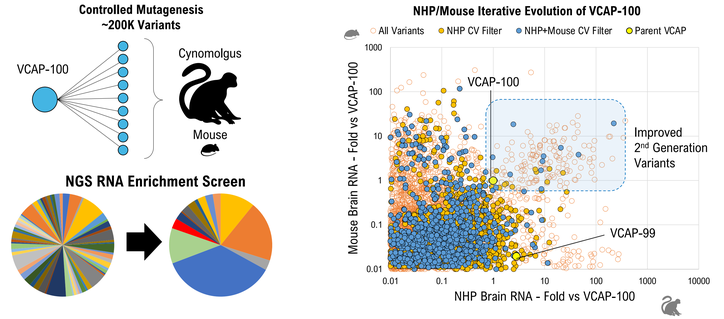

## Figure 5. VCAP-100 Biodistribution in NHP (Cynomolgus Macaque)




## Figure 6. VCAP-100 Transduction in NHP (Cynomolgus Macaque)




## Figure 7. Iterative Evolution of VCAP-100 Across Species




## CONCLUSIONS

- The AAV5 variant VCAP-100 displays a strongly enhanced tropism for NHP brain in comparison to the AAV9 benchmark
- VCAP-100 gain of function is conserved in rodents, although with a lower activity than in primates
- VCAP-100 allows high levels of transduction in multiple brain regions and cell types following systemic delivery in adult primates
- In adult primates, VCAP-100 shows a peripheral tissue transduction similar to AAV9, and a lower transduction of DRG
- Histopathology of NHP samples showed no signs of toxicity in macaques dosed with VCAP-100 at 5e13 VG/kg with a self-complementary transgene (not shown)
- Engineering of VCAP-100 by iterative evolution identified 2nd generation capsids with enhanced properties across species

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