Stepwise Evolution of the AAV5-Derived Capsid VCAP-100 Identifies Novel Variants with Improved CNS Transduction and Liver Detargeting Following Systemic Injection

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SUMMARY

- Current AAV gene therapies are limited by target tissue transduction and liver-associated toxicity when administered systemically
- AAV capsid engineering for CNS application has mostly focused on AAV9, but alternative serotypes such as AAV5 could offer unique features in terms of tropism, tissue specificity, manufacturability or immunogenicity
- We previously reported VCAP-100, an AAV5-derived capsid with improved CNS tropism in NHP & rodents following systemic injection
- Here, we aimed at 1) further improving VCAP-100's CNS transduction, and 2) reducing liver transduction to improve AAV safety profile
- We further evolved various surface regions of VCAP-100 & AAV5 using our RNA-driven TRACER capsid evolution platform, and identified several capsid families based on sequence homology and tropism phenotype
- One family of VCAP-100 derivatives displayed up to 300-fold liver detargeting and 6-fold improved brain transduction in NHP over the parental sequence
- One family of AAV5 derivatives included variants with 800-fold improved brain transduction in NHP and 45-fold in Rodent, as well as 60-fold & 30-fold improved heart & muscle transduction in NHP while displaying a slight liver detargeting over the AAV5 serotype
- These novel capsid candidates identified from pooled library assays will be further validated individually to determine cellular tropism

Figure 1. VCAP-100 was previously identified through our TRACER platform as a cross-species CNS capsid

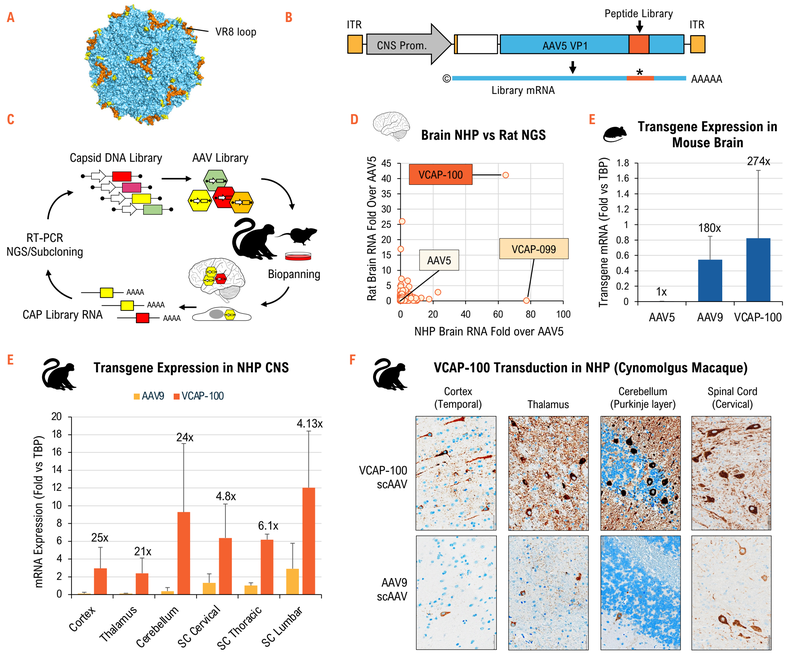


Figure 2. TRACER Biopanning strategy of a VCAP-100 & AAV5 local affinity maturation library

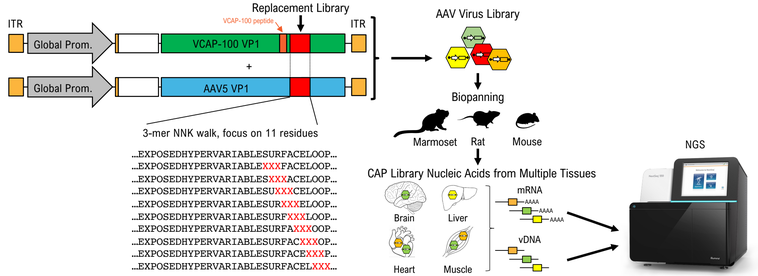


Figure 3. Identification of capsid variants with improved CNS transduction across multiple species

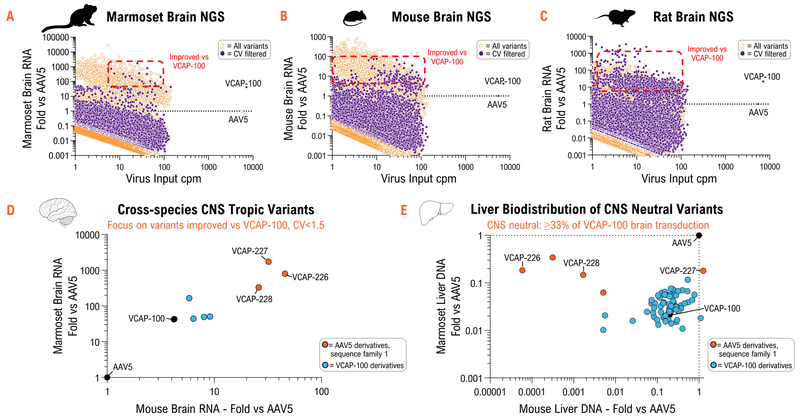


Figure 4. Identification of capsid variants with improved Muscle & Heart transduction

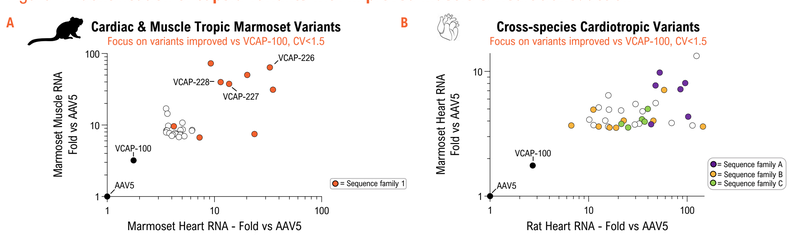


Figure 5. TRACER Biopanning strategy of a VCAP-100 distal affinity maturation library

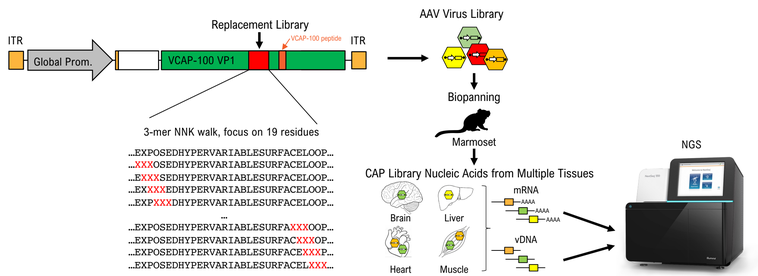
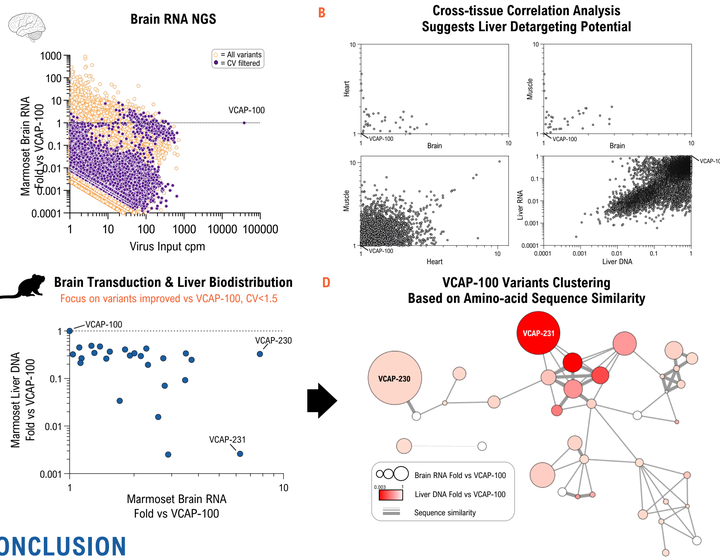


Figure 6. Identification of capsid variants with improved CNS transduction & liver detargeting



CONCLUSION

- Identification of novel VCAP-100 & AAV5 variants with improved cross-species tropism using our TRACER platform
- Interestingly, a small number of substitutions appears to significantly improve capsid tropism
- These variants will be validated individually *in vivo* to determine cellular tropism
- Capsid variants with 100+ fold liver detargeting were identified
- Capsids showing reduced liver targeting may have improved safety profiles