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transgene expression between ACE-502, wild-type AAV serotypes (AAV5, AAV9), and published engineered capsids. (b) Representative images of motor cortex sections showing neuronal transduction efficiency. Transgene expression was evaluated by combined in situ hybridization (ISH) for GFP mRNA and neurons (immunohistochemistry (IHC) for GFP protein, with MAP2 mRNA serving as a neuronal marker. Dose: 1×10^{13} vg/kg; tissue analysis performed 21 days post-administration.

2029 Integrated Randomized and Cell Surface-Informed Peptide Libraries Enable Tissue-Tropic AAV Capsid Evolution

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Introduction Directed evolution of capsid is critical for optimizing adeno-associated virus (AAV) vectors for gene therapy. A common strategy involves inserting randomized peptides into specific capsid variable regions (VRs) to evolve variants with enhanced tissue tropism. More recently, libraries derived from proteins known to interact with cell surface receptors have emerged as a complementary approach. We developed PEARS (Peptide-driven Evolution of AAV via Randomized and Surface-informed libraries) to combine the advantages of both strategies. PEARS integrates a fully randomized peptide library with a surface-informed library derived from diverse cell surface-interacting proteins. By combining optimized capsid library production with RNA-Seq-based in vivo screening, PEARS enables rapid, high-throughput directed evolution of AAV variants across multiple organs.

Methods Peptide libraries were inserted into the VR VIII region of AAV9, a site compatible with capsid assembly and surface display. Two complementary libraries were generated. The randomized library included fully randomized 7-mer and 10-mer sequences. The surface-informed library comprised approximately 4 million unique 7-mer and 10-mer sequences derived from ~15,000 cell surface-interacting proteins from human, other mammals, and microbial proteomes. Both libraries were cloned into a common CAG promoter-driven vector backbone. Libraries were packaged in suspension HEK293 cells following transfection optimization, yielding approximately 2.65×10^{13} vector genomes per liter. Pooled capsid libraries were administered intravenously to mice. Three weeks post-injection, viral mRNA was enriched from multiple tissues and analyzed by RNA-Seq. Three iterative rounds of in vivo screening were performed to identify high-confidence variants enriched in different tissues.

Results Approximately 1,000 high-confidence capsid variants were identified across eight tissue types. Overall transgene expression mediated by these variants was highest in the brain and lung, strong in the kidney, moderate in the heart and skeletal muscle, and lowest in the liver, bone, and adipose tissue. Randomized variants exhibited superior performance in the brain and lung, whereas surface-informed variants performed better in the liver, adipose tissue, and kidney. Heart and skeletal muscle showed mixed enrichment profiles. Peptide length influenced tissue tropism. 10-mer peptides showed superior performance in

the brain, lung, and kidney, while 7-mer peptides were preferentially enriched in the heart, skeletal muscle, and bone, especially variants containing the RGD motif. Top-performing variants for the brain, lung, and kidney were validated using a barcoded capsid library, showing strong concordance with initial screening results. Brain-targeting variants achieved up to 150-fold higher expression than AAV9, lung-targeting variants up to 50-fold higher, and kidney-targeting variants up to 10-fold higher. Individual characterization identified BY168 as a highly CNS-tropic capsid, achieving up to 105-fold and 149-fold higher mRNA expression in the brain and spinal cord, respectively, compared with AAV9, with minimal liver transduction.

Conclusion

PEARS revealed that capsid performance is shaped by library design, peptide length, and target tissue, highlighting the advantage of combining randomized and surface-informed peptide libraries. In vivo validation demonstrated the platform's ability to efficiently isolate potent organ-tropic capsids, exemplified by the CNS-targeting variant BY168, which achieved robust brain and spinal cord transduction while maintaining minimal liver expression.

2030 Microglia-targeted gene therapy using receptor-based rAAV delivery

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Introduction

Microglia are the resident immune cells of the central nervous system (CNS) and are essential for neuronal maintenance and for the development and progression of many neurological disorders. However, dissecting microglial molecular mechanisms remains challenging because standard viral gene delivery approaches, especially recombinant adeno-associated virus (rAAV) transduce microglia inefficiently and often produce unstable transgene expression in vitro and in vivo. Existing AAV strategies, including microglia-selective promoters and engineered capsids, have not consistently overcome these barriers, largely due to an incomplete understanding of the cellular and molecular restrictions that limit AAV entry and expression in microglia. Improving AAV compatibility with microglia would enable more effective microglia-targeted gene delivery for mechanistic studies and therapeutic development.

Methods