Computational Modeling and Design of rAAV Capsid Variants Based on Brain-wide Transgene Expression

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At present, recombinant adeno-assonated-virus (rAAV) are used as vectors for delivering therapeutic transgenes in a variety of human applications. Their advantages include long-term persistence in infected cells, low immunogenicity, low pathogenicity, stable expression in vivo, and strong clinical safety record in general. Various routes of administrating these viral vectors to the central nervous system (CNS) have been explored, as means to bypass the blood–brain barrier (BBB). However, they tend to also target non-CNS tissues, notably the liver, at high levels. Therefore, our goal is to develop and generate synthetic selection methodology aimed to identify AAV capsids with specific and broad tropisms, aimed to cross the BBB, and affect various brain tissue types with distinct tropism from other tissues. Thus, based on the exiting large-scale brain-wide transgene expression information, we developed a novel method to systematically design and engineer rAAV libraries, and generated sequence variants both highly enriched in the CNS and targeted away from varying peripheral organs, such as the liver. This was done by manipulating the AAV capsid protein sequence. Specifically, we built a reference AAV capsid variable region (ACVR) set from all the possible amino acid sequences. Following, we developed a tissue-specific differential score that find sequences with high enrichment in brain tissues, and lower enrichment in non-brain tissues. Preliminary results show various sets of variants enriched in brain-specific tissues, and depleted in non-brain tissues. This proposed method has an appealing potential in various biotechnological applications such as a bloodstream delivery system.