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Structural characterization of a novel human adeno-associated virus capsid with neurotropic properties

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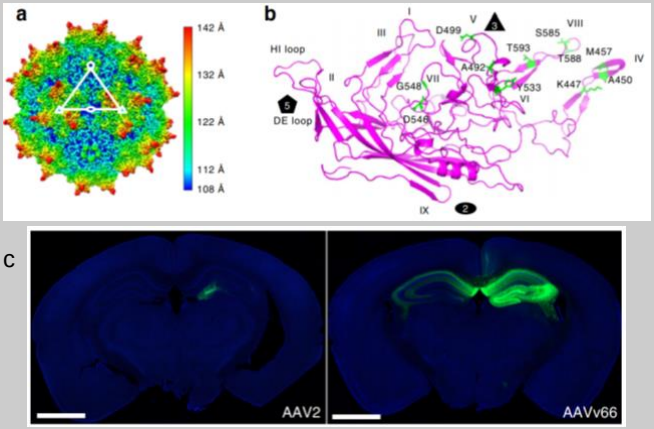
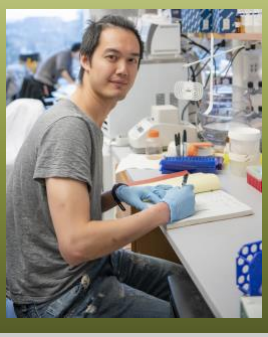


a. Density map of AAVv66. Color scheme demarcates the topological distance from the center (Å). **b**. Ribbon structure of the refined AAVv66 capsid monomer. Amino acids differing from AAV2 highlighted in green. AAVv66 exhibits a better vector yield and is more thermostable than prototypical AAV2. **c**. AAVv66 has a better distribution spread within brain tissue when administrated by intracranial and systemic injections.

Recombinant adeno-associated viruses (rAAV) vectors have emerged as promising and attractive tools for in vivo gene therapy. Unfortunately, the current library of discovered and engineered AAV capsids falls short for certain clinical applications that require targeting of specific tissues or cell types. Furthermore, patients may have pre-existing immunity to the vector via neutralizing antibodies (NAbs) that would limit therapeutic efficacy. In addition, certain capsids are known to be problematic under standard production schemes for generating high-yield titers needed to meet therapeutic doses. In response to these shortcomings, there is a need to discover and develop capsids that exhibit better vector yields, can escape innate immunity, and possess unique tropism profiles. Nevertheless, in 2019, a novel protein was discovered in the cap gene which was named membrane-associated accessory protein, MAAP. The current understanding is that MAAP protein plays role in virus egress, which might be related to increasing virus yield.



Hung-Lun Hsu, PhD

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I received my Ph.D. in chemical and biomolecular engineering at Cornell University. My doctoral studies were focused on using supported lipid bilayer to influenza virus entry and investigating lipid physics of various materials. I'm currently working in Horae Gene Therapy Center (HGTC), and I exploring vector engineering strategies and vector biology of novel adeno associated virus (AAV) serotypes. My studies on elucidating the properties and function of a novel Membrane Attached Accessory Protein (MAAP) are supported by the HGTC Postdoctoral Grant.

rAAVs are currently considered the safest and most reliable gene delivery vehicles for human gene therapy. Three serotype capsids, AAV1, AAV2, and AAV9, have been approved for commercial use in patients, but they may not be suitable for all therapeutic contexts. Here, we describe a novel capsid - AAVv66 - identified in a human clinical sample by high-throughput, long-read sequencing. The capsid shares high sequence similarity with AAV2. AAVv66 exhibits enhanced production yields, virion stability, and CNS transduction as compared to AAV2. Unique structural properties of AAVv66 visualized by cryo-EM at 2.5-Å resolution suggest that critical residues at the three-fold protrusion and at the interface of the five-fold axis of symmetry likely contribute to the beneficial characteristics of AAVv66. Our findings underscore the potential of AAVv66 as a gene therapy vector. Additionally, there are still various unsolved questions in AAV virology, e.g. the role of MAAP. Some of our initial experiments demonstrate that MAAP is related to AAV egress via exosome/microvesicles pathway. We are seeking to shed light on the function of MAAP and believe that MAAP has the potential to increase virus production yield and make AAV production a cheaper and more efficient process.