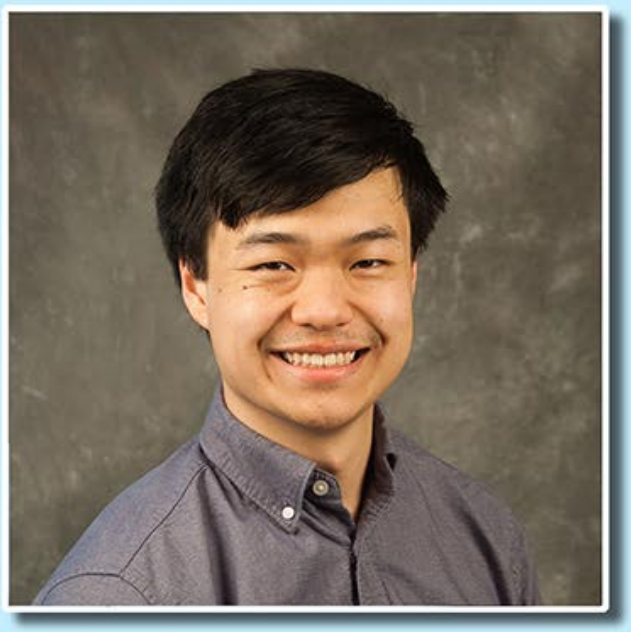

Austin Sun

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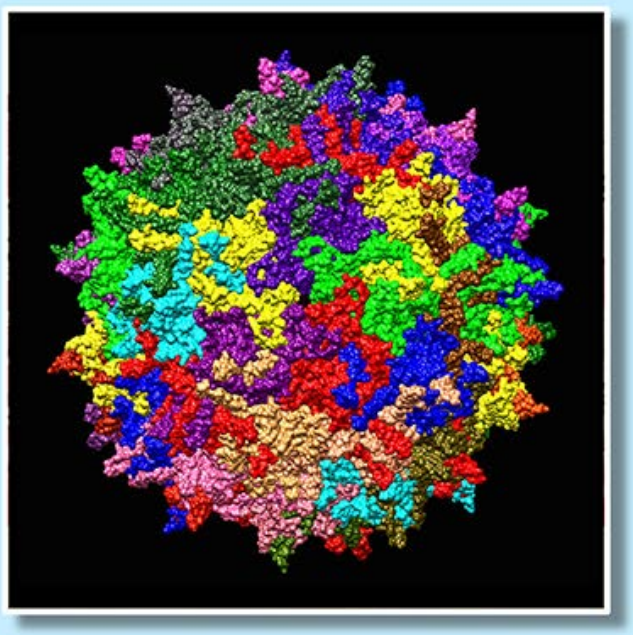

Surface View of an Adeno-associated Virus, a Vector Used for Human Gene Therapy

Disruption of Water Homeostasis Affects AAV Transport Across the Blood-Brain Barrier

Adeno-associated viruses (AAVs) have the potential to serve as delivery vectors for gene therapy treatments, since they are non-inflammatory and non-pathogenic. The aim of this study was to compare the transduction capabilities of different AAV serotypes across the blood-brain barrier, allowing for a better understanding of the mechanisms utilized by AAVs during this behavior. Aquaporin 4 acts as a water channel which assists in clearance of interstitial solutes from the CNS. Here, we examined how Aquaporin 4 (AQP4) misregulation, which occurs with aging and in neurological disease, influences the entry and gene transfer efficiency of AAVs into the brain. The blood-brain passage of AAVs was compared between B6/129 wild-type control mice and mice deficient for AQP4. We first verified that AQP4 knockout mice exhibited an increase in the permeability of the blood-brain barrier by tracking intravenously injected Hrp or Hrp tagged with histamines. Indeed, AQP4 null mice were found to have increased concentrations of Hrp in the brain, indicating a compromised blood-brain barrier. We found that AAV1 had increased access to the brains of AQP4 null versus wild-type mice. Interestingly, the accumulation of AAV9 and AAV.Rh10 in the cortex and thalamus was not significantly different between AQP4 null and B6/129 mice. In summary, our findings highlight the role of AQP4 in maintaining BBB homeostasis, which in turn affects viral transduction in the brain. The study has clinical implications that could inform CNS gene therapy trials, but also constitutes a fundamental step towards understanding the mechanisms by which certain AAV serotypes cross the BBB.