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Poster title: AAV Transgene Silencing at the Blood-Brain Barrier is Mediated by Innate Immune Sensors DNA-PK and TLR9

Abstract: Adeno-associated virus (AAV)–mediated gene therapy enables efficient delivery of therapeutic genes across tissues such as the liver and CNS, producing strong initial expression and functional benefit. However, a major limitation is the loss of durable transgene expression over time. Studies in nonhuman primates reveal a disconnect between vector persistence and function: despite long-term retention of vector DNA after systemic delivery, transgene RNA and protein decline significantly, indicating transcriptional silencing rather than vector loss. Similar patterns are observed in human retinal gene therapy, where initial improvements in visual sensitivity peak and subsequently decline. These findings suggest that intrinsic host responses to AAV genomes, including sensing of vector DNA by pathways may contribute to transgene silencing. We set out to better understand this silencing by asking whether we could first detect AAV silencing in mouse brains. Here, we measure AAV transgene expression over weeks in endothelial cells lining the blood–brain barrier (BBB) and in-vitro to characterize how transgene kinetics change post-delivery. We further evaluate innate immune sensors in modulating transgene expression with important implications for AAV gene therapy.