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A single intravenous rAAV injection as late as P20 accomplishes efficacious and sustained CNS gene-therapy in a mouse model of Cananvan's disease

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Abstract

The CNS is an important target for gene therapy of neurological disorders. Recombinant adeno-associated virus (rAAVs) holds the promise for therapeutic gene transfer to treat a variety of diseases including the CNS diseases. Recent discovery of some novel primate rAAVs that can cross the blood-brain-barrier and achieve wide spread CNS gene transfer, after intravascular delivery, remarkably expanded potentials of rAAV in treating neurodegenerative disorders. Canavan's disease (CD) is a fatal pediatric leukodystrophy caused by autosomal recessive mutations in aspartoacylase (AspA) gene. CD is characterized by dysmyelination, hydrocephalus, progressive central nervous system vacuolation and psychomotor retardation. Currently there is no effective treatment for CD. Here, we studied progressive neuropathology and gene therapy in short-lived (≤1 month) AspA-/- mice, a bona-fide animal model for the severest forms of CD. Single intravenous injections of several primate-derived novel rAAVs as late as postnatal day 20 (P20) completely rescued their early lethality and alleviated the major disease symptoms, extending survival to as long as 2 years for rAAV9 and rAAVrh.8 injected groups thus far. We successfully used microRNA-mediated post-transcriptional detargeting for the first time to restrict therapeutic rAAV expression in the CNS and minimize potentially deleterious effects of transgene overexpression in peripheral tissues. rAAV treatment globally improved CNS myelination, although some abnormalities persisted in the content and distribution of myelin-specific and-enriched lipids. We demonstrate that systemically delivered and CNS-restricted rAAVs can serve as efficacious and sustained gene therapeutics in a model of a severe neurodegenerative disorder even when administered as late as P20.

Biography

Guangping Gao, Ph.D., is the Director of the Gene Therapy Center and Penelope Booth Rockwell Professor in Biomedical Research, UMass Medical School. He received his Bachelor Degree in Medicine from Sichuan University, China, and his Ph.D. in molecular genetics at Florida International University with his work on discovering the human aspartoacylase gene and the genetic mutations responsible for Canavan disease. Dr. Gao joined the Institute for Human Gene Therapy (IHGT) at University of Pennsylvania in 1994 and served as the Director of Vector Program of IHGT to oversee the vector discovery, process development, vector manufacturing and QC testing. One of his most important contributions to the field of gene therapy is the discovery of a novel family highly efficient and safe AAV vectors. His primary research interests include molecular mechanisms of AAV evolution, microRNA functional genomics in adult mammals, biology and clinical application of miRNA therapeutics, and gene therapy of CNS disorders using rAAVs to cross BBB for global CNS gene transfer. He has published more than 135 papers in peer-reviewed journals and has 26 patented inventions. Dr. Gao served on several international committees for gene therapy. He is the senior editor of the Book Series on Gene and Cell Therapy publishing by ASGCT and Springer Publisher and serves on Advisory Board of Advances in Experimental Medicine and Biology.