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Canavan's disease as a model for development of efficacious, sustainable and safe rAAV gene therapeutics for CNS disorders

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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. Capability of some novel primate rAAVs to cross the blood-brain-barrier and achieve wide spread CNS gene transfer remarkably expanded potentials of rAAV in treating CNS disorders. Canavan's disease (CD) is a fatal pediatric and currently untreatable leukodystrophy caused by genetic mutations in aspartoacylase (AspA), serving as a good model for developing efficacious, sustained and safe gene therapeutics to treat widespread lethal neuropathology in CNS diseases. Thus, we investigated two different routes of vector administration for the efficacy and sustainability of rAAV gene therapeutics in CD mice which authentically recapitulate the severest clinical phenotypes of CD with a uniform lethality at 4 weeks. We first achieved a complete rescue of lethality, extending the lifespan to up to 2 years and restoring growth even with treatment as late as postnatal day 20 by single intravenous (IV) injections. To minimize potential systemic vector toxicity and reduce vector manufacturing burdens, we also demonstrated that single intracerebroventricular (ICV) injections of different serotypes of rAAV hAspa at 100-fold lower doses extended survival up to 2 years, normalized growth, and improved motor function and clinical symptoms. However ICV injections were less effective than IV in improving motor functions, suggesting the importance of peripheral AspA gene transfer. In summary, we achieved complete rescue of lethality and effective alleviation of hydrocephalus and motor dysfunction by novel rAAV gene therapy irrespective of administration route or time of intervention. Our study emphasizes the potential to further refine approaches for CD gene therapy using novel rAAVs and opens up newer vistas for the effective treatment of other currently untreatable monogenic CNS disorders.

Biography

Guangping Gao, PhD, is the Director of the Gene Therapy Center and Penelope Booth Rockwell Professor in Biomedical Research, UMass Medical School. He is also a scientific Founder of Voyager Therapeutics. He received his Bachelor Degree in Medicine from Sichuan University, China, and PhD in Molecular Genetics at Florida International University with his work on discovering the human aspartoacylase gene and the genetic mutations responsible for Canavan's disease. He joined the Institute for Human Gene Therapy (IHGT) at University of Pennsylvania in 1994 and served as the Director of Vector Program of IHGT for vector discovery, process development, vector manufacturing and QC testing. One of his most important contributions to the field of gene therapy is his discovery of a novel family of 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 applications of miRNA therapeutics, and gene therapy of CNS disorders. He has published more than 150 papers in peer-reviewed journals and has 26 patented inventions. He served on several international committees for gene therapy. He is the senior editor of the book "Series on Gene and Cell Therapy" and serves on Advisory Board of Advances in Experimental Medicine and Biology.

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