

725 - Assessment of CSF Route for Gene Delivery in Sandhoff Mice Using AAV9 Expressing an Hexosaminidase Isoenzyme.

○ Add To Itinerary

📅 May 7, 2016, 11:15 - 11:30 AM



Keywords

AAV Vectors, Gene Correction/Modification/Targeting, Animal Models

Authors

Patrick Thompson¹, Karlaina Osmon¹, Evan Woodley¹, Subha Karumuthil-Meethil², Steven J. Gray³, **Jagdeep S. Walia**⁴

¹Medical Genetics/Departments of Pediatrics and Pathology and Molecular Medicine, Queen's University, Kingston, ON, Canada, ²Gene Therapy Center, University of North Carolina, Chapel Hill, NC, ³Gene Therapy Center, Department of Ophthalmology, University of North Carolina, Chapel Hill, NC, ⁴Medical Genetics/Departments of Pediatrics and Pathology and Molecular Medicine, Department of Biome, Queen's University, Kingston, ON, Canada

Disclosures

J.S. Walia: None.

Abstract

GM₂ gangliosidosis is a group of neurodegenerative disorders, characterized by the malfunctioning Hexosaminidase A (HexA) enzyme. HexA is formed by heterodimerization of two subunits, α and β . Hex A, in interaction with GM2 activator protein (GM2AP), is the main isoenzyme able to hydrolyze GM2 gangliosides. HexA deficiencies result in Tay-Sachs (α -subunit deficiency) or Sandhoff disease (SD, β -subunit deficiency). In the recent work by Tropak et al. (Mol Ther Methods Clin Dev, *in press*), a hybrid human α -subunit, named " μ " and coded by *HEXM*, was created (patent pending) by incorporating the dimer stabilization and GM2AP binding sites of the β -subunit while maintaining the catalytic properties of the α -subunit. The μ -subunit is able to homodimerize to form a stable and functional enzyme, named HexM, which can interact with the human GM2AP and effectively hydrolyse GM₂ gangliosides. Another advantage of this subunit (~1.6 kb) is that it can be packaged in a self-complementary adeno-associated virus (scAAV/*HEXM*). An intravenous route of scAAV administration has been shown to be successful, but brings with it translational issues including large scale viral preparation and relatively high vector uptake by liver. We tested the cerebrospinal fluid (CSF) route, as an alternative, for delivering scAAV9/*HEXM*. We injected 2.5E+11 vector genomes per mouse of scAAV9/*HEXM* via the *cisterna magna* at 6 weeks of age (n=13). Our controls include treatment with scAAV9/*GFP* (n=3) and vehicle (n=8). One additional cohort received an IV injection of 25% mannitol (2g/kg) post-AAV9 injection (n=10). We sacrificed part of the cohorts (n=4 each group) at 16 weeks of age (humane end-point of untreated SD mice) for tissue analysis. The remainder are being monitored for long-term survival. The parameters for analyses are survival benefit, locomotor behaviour, Hexosaminidase activity, GM2 ganglioside accumulation, and vector genome biodistribution. The preliminary results from this ongoing study show a significant survival advantage to the humane endpoint in HexM treated (average 28 weeks to date) as compared to negative controls (~16 weeks). The behaviour tests showed improved locomotor activity in HexM-treated mice as compared to negative controls. Results were similar when mannitol was administered in conjunction with scAAV9/*HEXM*. These preliminary results indicate that the intra-CSF route of administration of AAV9/*HEXM* is a tractable translatable approach for SD worth further exploration. Additional studies are focused on increased dosage and methods to improve distribution.

