Society for Neuroscience
Session 610 - Molecular, Biochemical, and Genetic Techniques: Molecular Techniques II
November 6, 2018
1:00 p.m. PT
SDCC Halls B-H

Biodistribution of AAVHSCs in the Central Nervous System of Non-Human Primates

Jacinthe Gingras, Kevin Oliveri, Thia St-Martin, Nicole Zapata, Laura Smith, Hillard Rubin, Nancy Avila, Omar Francone, Jeff L. Ellsworth and Albert Seymour

Homology Medicines, Inc., Bedford, MA

Adeno-associated viruses (AAVs) have emerged as key viral-based delivery vehicles for gene therapy in the nervous system due to their stable transgene expression in post-mitotic cells, neuronal tropism, lower risk of insertional mutagenesis and diminished immune response. We have recently reported the identification of novel AAVs derived from human hematopoietic stem cells (AAVHSCs). These novel AAVHSCs map to AAV Clade F alongside AAV9, which has been demonstrated to successfully cross the blood-brain-barrier (BBB) following systemic administrations. We set out to characterize the AAVHSCs to: 1) determine whether crossing the BBB was a generalized trait of Clade F AAVs and 2) assess whether the AAVHSCs could be attractive viral-vehicle candidates for gene therapy applications in the central nervous system (CNS). Herein, we report the biodistribution of AAVHSC7, AAVHSC15 and AAVHSC17 in the nervous system of 4- to 5-month old male cynomolgus macaques (*Macaca fascicularis*). Animals pre-screened for anti-AAVHSC neutralizing antibodies received a single intravenous (IV; 0.7-1E14 vg/kg) injection of recombinant AAVs packaging a self-complementary enhanced green fluorescent protein (sc-eGFP) transgene driven by the chicken beta actin (CBA) promoter. Biodistribution of AAVHSCs was assessed by anti-eGFP immunohistochemistry (IHC). All three AAVHSCs showed anti-eGFP immunoreactivity in the brain following IV administration. Furthermore, the three AAVHSCs displayed a distinct rostro-caudal distribution of anti-eGFP expression with the highest levels seen in the mesencephalon and myelencephalon. The largest cellular population displaying anti-eGFP were of glial origin, but anti-eGFP-positive neurons were also observed throughout different regions of the brain. Both neuronal cell bodies, dendrites and axons/axonal tracts were detected. These data demonstrate that AAVHSCs effectively cross the BBB following intravenous delivery in non-human primates, creating the potential for therapeutic applications in treating human genetic diseases of the CNS, such as metachromatic leukodystrophy (MLD).

MLD is an inherited disorder characterized by various mutations in the hARSA gene resulting in an accumulation of sulfatides in cells of the nervous system that produce myelin. The observed NHP biodistribution observed renders MLD amenable for gene therapy in the CNS with the goal of correcting hARSA enzymatic activity to levels known to be clinically relevant. Biodistribution studies of 12 additional AAVHSCs is underway in NHP, as is further efforts to identify new AAVHSCs.