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Widespread Transduction of the Central Nervous System Following Systemic Delivery of AAVHSC7, AAVHSC15 and AAVHSC17 in Non-Human Primates

Laura Smith, Hillard Rubin, Jacinthe Gingras, Albert Seymour, Pablo Morales, Elizabeth Chlipala, Michael O'Callaghan, and Jeff Ellsworth

Homology Medicines, Inc., Bedford, MA, USA; The Mannheimer Foundation, Inc., Homestead, FL; Premier Laboratory, LLC, Longmont, CO, USA

Adeno-associated viruses derived from human hematopoietic stem cells (AAVHSCs) are a group of viruses that map to the AAV9-containing Clade F. AAV9 has the unique ability to cross the blood brain barrier after intravenous (IV) administration. We investigated the HSC-derived AAVHSC7, AAVHSC15 and AAVHSC17 biodistribution, ability to cross the blood brain barrier, and tropism to the central nervous system (CNS) in non-human primates. Biodistribution of the three novel AAVHSCs, AAVHSC7, 15 and 17, were compared to AAV9 in 3- to 4-month old male cynomolgus macaques (Macaca fascicularis). Animals were pre-screened for anti-AAVHSC7, -AAVHSC15, -AAVHSC17 and -AAV9 neutralizing antibodies (Nab). Nab negative animals (n = 2/group) received a single IV injection [0.7 x 1013 or 1 x 1014 vg/kg] of recombinant AAVHSC7, AAVHSC15, AAVHSC17 or AAV9 self-complementary green fluorescent protein (scGFP) vector. Animals were euthanized and perfused on day 14 and collected tissues were fixed in 4% PFA. Biodistribution was assessed by GFP immunohistochemistry on 40 □m frozen sections of CNS tissue and on 4 □m sections of paraffin-embedded non-CNS tissues. IV administration of all four Clade F viruses, AAV9, AAVHSC7, AAVHSC15 and AAVHSC17, produced widespread distribution of GFP expression in astrocytes throughout the brain, with highest levels seen in the pons and lateral geniculate nuclei. GFP positive neurons were also observed throughout different regions of the brain. GFP expression was evident in sensory neurons within the dorsal root ganglia and large motor and sensory neurons in the spinal cord. Widespread GFP expression in non-CNS tissues was observed in all animals with prominent staining in hepatocytes, skeletal- and cardio-myocytes. These data demonstrate that AAVHSC7, AAVHSC15 and AAVHSC17 were able to effectively cross the blood brain barrier following systemic delivery in non-human primates, making AAVHSCs amenable for potential therapeutic applications in treating CNS-related human genetic diseases.