Session AAV Vectors III

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568 - Widespread Transduction of the Central Nervous System Following Systemic Delivery of AAVHSC17 in Non-Human Primates

May 12, 2017, 5:45 - 7:45 PM | Exhibit Hall A & B South

Keywords
AAV
Vectors,Pharmacology/Toxicology,Neurological
Disorders

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Disclosures
J.L. Ellsworth: 1; Commercial Interest ***i.e. Company X***; Homology Medicines, Inc.. 1; What was received? ***i.e. Honorarium***; Salary, stock options. 1; For what role? ***i.e. Speaker***; employment.

Abstract
Adeno-associated viruses derived from hematopoietic stem cells (AAVHSC) have been identified and cloned from normal human peripheral blood CD34+ cells. Sequence analysis of these novel AAVHSCs map to AAV Clade F, of which AAV9 is a representative member. Clade F AAVs are emerging as successful gene therapy vectors, particularly for transduction of the central nervous system (CNS) after systemic delivery. In the current study, the bio-distribution of a novel Clade F AAV, AAVHSC17, was compared to that of AAV9 in 3- to 4-month old male cynomolgus macaques (***Macaca fascicularis)***. Recombinant AAVHSC17 and AAV9, each packaging a self-complementary green fluorescent protein (scGFP) transgene driven by the chicken beta actin (CBA) promoter, were prepared by triple transfection in HEK293 cells and purified by double banding in cesium chloride density gradients. Animals were pre-screened for anti-AAVHSC17 and -AAV9 neutralizing antibodies (Nab). Nab negative animals (n = 2/group) received a single intravenous (IV) [1 x 10^{13} or 1 x 10^{14} vg/kg] or intrathecal (IT) [1 x 10^{13} vg/kg] injection of AAVHSC17 or AAV9. On Day 14 animals were euthanized and perfused with saline followed by 4% paraformaldehyde (PFA) in phosphate-buffered saline (PBS). Tissues were collected and fixed for 48h in 4% PFA in PBS. Bio-distribution of AAVHSC17 and AAV9 was assessed by GFP immunohistochemistry (IHC) on 40 µm frozen sections of the brain and spinal cord and on 4 µm sections of paraffin-embedded non-CNS tissues. IV administration of AAVHSC17 or AAV9 produced widespread distribution of GFP expression in astrocytes throughout the brain with the highest levels seen in the pons and in the lateral geniculate nuclei. GFP positive neurons were also observed throughout different regions of the brain. GFP expression was evident in axons of the lateral dorsal white matter tracts in the rostral spinal cord and axons and neurons in the dorsal and ventral gray matter of the rostral and caudal spinal cord. Compared to IV-treated animals, IT injections of AAVHSC17 produced less GFP expression in the brain but more pronounced staining of axons and neurons in the ventral horn of the caudal spinal cord. Widespread GFP expression in non-CNS tissues was observed in animals receiving IV AAVHSC17 or AAV9 with prominent staining in hepatocytes, skeletal- and cardio-myocytes. GFP expression in CNS and non-CNS tissues was dependent on dose of AAVHSC17 administered. These data demonstrate that AAVHSC17 has a broad tissue tropism and is able to effectively cross the blood brain barrier following systemic delivery in non-human primates, making it amenable for potential therapeutic applications in treating human genetic diseases.