**XVIIth International Parvovirus Workshop**
**Poster Session**
**June 11 – 13, 2018**

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

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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 5-month-old male cynomolgus macaques (Macaca fascicularis). Animals were pre-screened for anti-AAVHSC7, -AAVHSC15, -AAVHSC17 and -AAV9 neutralizing antibodies (Nabs). Nab negative animals (n = 2/group) received a single IV injection [$0.7 \times 10^{13}$ or $1 \times 10^{14}$ 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 post-fixed in 4% PFA. Biodistribution was assessed by anti-GFP immunohistochemistry on frozen sections of CNS tissue and on 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 glial cells throughout the brain, with highest levels seen in the pons and lateral geniculate nuclei. Anti-GFP immunoreactive neurons were also observed throughout different regions of the brain. GFP expression was also evident in the spinal tissue. Dorsally, sensory nerve terminals (confirmed by dorsal root ganglia IHC) were detected, as well as large ventral neurons, most likely of motor origin. 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.