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CNS Biodistribution of AAVHSCs and their Gene Therapy Application for Targeting Metachromatic Leukodystrophy (MLD)

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Adeno-associated viruses (AAV) have emerged as key viral-based delivery vehicles for gene therapy. We identified 15 novel, naturally occurring AAVs derived from human hematopoietic stem cells (AAVHSCs), which map to AAV Clade F. These AAVHSCs can cross the blood-brain-barrier (BBB) in non-human primates (NHPs) following single intravenous (IV) delivery, thus creating the potential for therapeutic applications in treating human genetic diseases of the central nervous system (CNS). Herein, we report (1) the CNS biodistribution of AAVHSC7, AAVHSC15 and AAVHSC17 in cynomolgus macaques (Macaca fascicularis) and (2) murine preclinical data in support of the therapeutic application of AAVHSCs for the treatment of metachromatic leukodystrophy (MLD).

NHPs pre-screened for anti-AAVHSC neutralizing antibodies received a single IV injection of recombinant AAVHSC packaging a self-complementary enhanced green fluorescent protein (sc-eGFP) transgene. All three AAVHSCs evaluated showed a rich, common caudo-rostral gradient of anti-eGFP immunoreactivity in addition to regional variations in expression levels in key neuronal pathways and cellular subtypes. The largest eGFP-positive cellular population in the brain was of glial origin. However, immunoreactive neuronal cell bodies, proximal dendrites and axons/axonal tracts were also observed throughout the brain. These data demonstrate that with a single IV injection, AAVHSCs effectively cross the BBB in NHPs and distribute widely across the nervous system to a large variety of cellular profiles.

MLD is a fatal lysosomal storage disorder with a great unmet medical need. This neurodegenerative disease occurs in three forms - late infantile, juvenile and adult - and is due to a deficiency in the lysosomal enzyme arylsulfatase-A (ARSA), most commonly caused by mutations in the *ARSA* gene. The lack of this enzyme leads to a large accumulation of lipids (sulfatides) in the brain, spinal cord and peripheral organs, which results in severe damage of myelin, the main protective layer of the nerve fibers. In dose- range finding studies, a single IV dose of AAVHSC15 human *ARSA* (hARSA) administered to a murine model of MLD achieved ~40-145% of normal hARSA enzymatic activity that significantly exceeded the established human therapeutic target of 10-15% of normal levels, with no observed negative impact. AAVHSC15-hARSA expression patterns were detected in key regions of the brain and spinal cord in therapeutically relevant cellular profiles. Taken together, these results led to the nomination of our development candidate, HMI-202, and initiation of IND-enabling studies as a potential MLD treatment.