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Poster Presentation

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AAVHSCs and Nervous System-Targeted Gene Therapy for Lysosomal Storage Disorders

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Adeno-associated viruses (AAVs) have emerged as key viral-based delivery vehicles for gene therapy and stable transgene expression in mitotic and post-mitotic cells and broad tropism have led to their evaluation for many disorders where conventional therapies fall short. We previously reported the identification of naturally occurring AAVs derived from human hematopoietic stem cells (AAVHSCs) that have broad peripheral tropism and cross the blood-brain, -nerve and -retina barriers (BNB, BBB and BRB, respectively) following a single intravenous (I.V.) administration in non-human primates (NHPs) and murine models. Here, we evaluated the potential of utilizing AAVHSCs for inherited, monogenic lysosomal storage disorders (LSDs), which are inborn errors-of-metabolism disorders with broad clinical manifestations secondary to the progressive accumulation of undegraded macromolecules within lysosomes. Specifically, we characterized the biodistribution of 11 AAVHSCs in peripheral organs and the nervous system of NHPs dosed I.V. and outlined the tropism patterns that may allow for therapeutic applications in LSDs. LSDs are particularly amenable to gene therapy as transduced cells, in both the periphery and nervous system, can naturally secrete functional enzyme that can correct unmodified cells (e.g., short-range and long-range cross-correction) through receptor-mediated uptake. We also report the vector genome copies, transcript, active enzyme levels, enzyme distribution and/or lysosomal-burden amelioration using a single I.V. administration of constructs in murine models for Hunter syndrome (MPS II – HMI-203) and metachromatic leukodystrophy (MLD – HMI-202). Using these models, we show broad biodistribution, long-term functional enzyme secretion and direct behavioral benefits in treated mice. Moreover, we demonstrated successful transduction of the cerebral ependymal cells, indicating crossing of the blood-cerebrospinal-fluid barrier (BCSFB), in addition to the barriers listed above. Together, this data supports broad application of AAVHSCs in LSDs and the potential for AAVHSC-based gene therapies in LSDs with a peripheral and central nervous system impairment .