American Society of Gene & Cell Therapy (ASGCT) Annual Meeting
Poster Session II
Thursday, May 17, 2018
5:15pm – 7:15pm
Stevens Salon C & D

486. AAVHSC Nuclease-Free Genome Editing Leads to *In Vivo* Genome Correction and a Significant Reduction in Disease Phenotype in a Mouse Model of Phenylketonuria

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The direct correction of pathogenic variants has great potential for the treatment of genetic disorders. A novel group of Clade F adeno-associated viruses has been isolated from normal human CD34+ hematopoietic stem cells (AAVHSCs). Here we explore the potential of AAVHSCs for *in vivo* gene editing. AAVHSC vectors containing a promoterless luciferase cassette flanked by sequences homologous to intron 6 of the mouse F8 gene were administered into NOD/SCID mice and resulted in liver-specific expression of luciferase for up to 9 weeks. Analysis of liver DNA display a significant proportion of successfully edited F8 with no detection of insertion or deletion mutations. To correct a disease phenotype, an AAVHSC correction vector containing a promoterless cDNA encoding human phenylalanine hydroxylase (PAH) flanked by sequences homologous to exon 1 of the murine *Pah* gene was administered into a mouse model of the disease phenylketonuria (PKU). Treatment with AAVHSC vectors led to a significant correction in serum Phe levels relative to baseline. Reduction in disease phenotype was maintained over 21 weeks post injection, and liver DNA displayed efficient gene editing and expression. In total, these data establish that the AAVHSCs are a viable platform for precise *in vivo* gene editing and correction.