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Nuclease-Free Genome Editing by AAVHSC Vectors Leads to *In Vivo* Genome Correction and Amelioration of Disease Phenotype in a Mouse Model of Phenylketonuria (PKU)

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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) and has shown high efficiency nuclease-free gene editing as well as gene transfer capabilities. Here we explore the potential of AAVHSCs for *in vivo* gene editing. AAVHSC vectors containing a promoter-less 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 promoter-less 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 phenotypes were 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.