

**European Society of Human Genetics Conference**  
**Oral Presentation**  
**June 17, 2019**

**AAVHSC15 Packaging Human Phenylalanine Hydroxylase Results in Sustained *in vivo* Correction of Phenylketonuria Following a Single IV Administration in the Murine Model**

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Phenylketonuria (PKU) is a rare hepatic metabolic disease caused by mutations in the phenylalanine hydroxylase (*PAH*) gene causing elevated levels of phenylalanine that lead to neurocognitive defects. Current treatments do not address the underlying genetic defect. A suite of Clade F adeno-associated viruses was isolated from human peripheral blood CD34+ hematopoietic stem cells (AAVHSCs) and show high hepatic affinity and potential for gene therapy. Here we describe the ability of AAVHSC-mediated gene therapy to durably correct the disease phenotype in the *Pah*<sup>enu2</sup> mouse model of severe PKU.

Gene therapy vectors containing a human *PAH* transgene driven by ubiquitous or liver-specific promoters packaged in AAVHSC15 were tested in *Pah*<sup>enu2</sup> mice. Vectors were administered in a single intravenous dose followed by periodic assessment of serum phenylalanine and tyrosine (byproduct of phenylalanine metabolism). At study termination, livers were processed to measure vector genomes, mRNA and PAH enzyme activity.

One week post-dose of an initial research vector using an ubiquitous promoter, phenylalanine levels decreased from 2000 $\mu$ M to <150 $\mu$ M ( $p < 0.0001$ ) and were sustained out to >28 weeks ( $p < 0.0001$ ). To enhance long-term durability with decreased doses, vector sequences in AAVHSC15-PAH were optimized using different liver-specific promoters. We selected a vector, HMI-102, that decreased serum phenylalanine and increased serum tyrosine at ten-fold lower doses compared to the initial research vector. A durable response was seen out to 48 weeks, consistent with the model's lifespan. These data demonstrate that a single dose of HMI-102 resulted in long-term correction of PKU in *Pah*<sup>enu2</sup> mice on protein-containing chow.