American Society of Gene & Cell Therapy (ASGCT) Annual Meeting
Poster Session
April 29, 2019

Development of a Scalable Platform for GMP Production of High Quality, Novel Clade F rAAV Vectors Following Comparison of HEK293 Mammalian and the SF9-Baculovirus Systems

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Recombinant adeno-associated virus (rAAV) is one of the leading viral vectors in the gene therapy field, attributed to its low immunogenicity and therapeutic persistence. We have identified 15 novel Clade F rAAVs derived from human hematopoietic stem cells (AAVHSCs). Multiple methods have been developed to produce rAAVs based on introduction of packaging genes by helper viruses, stable cell lines, or plasmid transfection. To determine the optimal method for manufacturing our AAVHSC vectors, the production of an AAVHSC15 encoding a human phenylalanine hydroxylase (*PAH*) gene was evaluated in Sf9-baculovirus and HEK293 triple transfection systems. Both methods showed similar virus productivity as measured by vector genome titer and percentage of full capsids; however, increased *in vitro* infectivity and *in vivo* efficacy were observed with purified triple transfection produced vectors in the Pah^{enu2} murine model of phenylketonuria (PKU). Linear scalability of our transfection-based platform was demonstrated up to 400L in a serum-free, suspension cell line system to produce our lead gene therapy candidate for PKU, HMI-102. This triple transfection platform was utilized to produce other AAVHSC capsid serotypes and package multiple different therapeutic constructs all demonstrating similar virus productivity and quality.