Kay: Comparative NHP Study to Test New Capside Against AAV1

OVERVIEW

This grant was awarded to conduct a nonhuman primate (NHP) experiment, to evaluate the in vivo performance of improved adeno-associated virus (AAV) vectors recently developed in the Kay laboratory under a prior CAVD grant. AAV vectors are of interest as gene transduction systems for the endogenous production of anti-HIV broadly neutralizing antibodies, with the caveat that current AAV vectors have seen limited success in achieving high expression levels of secreted proteins. The improved AAV vectors from the Kay laboratory (AAV-NP22 and AAV-NP66) have been engineered to have superior human skeletal muscle tropism and, when assessed in vitro using human muscle explant models, have provided much higher transduction levels than previously possible. For pre-clinical in vivo testing of the new AAV vectors, murine models are a poor choice as they have historically been poorly predictive of the cellular tropisms and transduction efficiencies of AAV serotypes in humans. The Kay laboratory has already shown via explant models of NHP muscle tissues that the AAV-NP22 and NP66 achieve the same significant improvement in gene transduction as observed with the human tissue model, an important prelude to proceeding with the in vivo NHP evaluation.

The NHP model will establish the relative transduction efficacy of AAV-NP22 and AAV-NP66 against a standard AAV-1 vector in the skeletal muscle of non-human primates to predict future passive vaccine expression levels in human patients. Translating these high transduction levels to a clinical setting would enable lower dosing of this passive antibody vaccine while still achieving therapeutic levels of antibody expression, thereby reducing the cost of vaccine per patient and reducing the probability host T cell responses against transduced muscle fibers.

The grant is led by Mark Kay, PhD (Stanford University), and the animal model will be run at the University of California – Davis California National Primate Research Center, where the protocol will be directed by Christopher J. Miller, DVM, PhD. Phil Johnson, MD (IAVI) serves as a consultant. The award was made in September, 2016 with an anticipated duration of 18 months.

Grant at a Glance

Principal Investigator
Mark Kay, PhD

Grantee Institution
Stanford University, CA, USA

Project Title
Comparative NHP Study to Test New Capsids Against AAV1

OPPID
1154293

Grant Award
Up to $717,000, awarded in September, 2016

Collaborating Institutions
- UC Davis – California National Primate Research Center, Davis, CA USA

RESEARCH OBJECTIVES

1.) Construction and functional verification of rhesus AAV vector plasmids, with ensuing GMP-like production of 3 AAV vectors.

2.) Animal selection after excluding animals with neutralizing anti-AAV antibodies against the 3 AAV serotypes.

3.) Administration of the vectors and monitoring the animals for six months, using routine veterinary clinical laboratory assessments as well as evaluating transgene expression levels. The study will conclude with tissue analysis of the subject animals.