ADMINISTRATION OF AAV VECTORS TO *Pcca*−/−(A138T) MICE ELICITS LONG TERM CORRECTION OF DISEASE MARKERS

Adam J. Guenzel[1], Sean E. Hofherr[2], Matthew Hillestad[3,4], Mary Barry[3], Jan P. Kraus[5], Dietrich Matern[2,6], and Michael A. Barry[3,7]

[1]*Virology and Gene Therapy Graduate Program*
[2]*Department of Laboratory Medicine and Pathology, USA*
[3]*Department of Internal Medicine, Division of Infectious Diseases*
[4]*Nephrology Training Program, USA*
[5]*University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA*
[6]*Department of Medical Genetics and Department of Pediatric and Adolescent Medicine*
[7]*Department of Immunology and Department of Molecular Medicine, Mayo Clinic, Rochester, MN, USA*

Background: The development of new therapies for propionic acidemia (PA) is limited by the lack of an adult model of the disease. We generated a hypomorphic mouse model of PA using a transgene bearing an A138T mutant of the human PCCA protein in *Pcca*−/− null mice. *Pcca*−/−(A138T) mice have 2% of wild-type PCC activity, survive to adulthood, and have significant elevations in many biomarkers including propionyl-carnitine (C3), methylcitrate, glycine, and ammonia, as well as cardiac defects.

Methods and Results: *Pcca*−/−(A138T) mice were given a single dose of 5×10^{11} viral genomes of AAV8-hPCCAco by intravenous administration. Subsets of these animals were then analyzed at time points including 10 days, 25 days and 1.5 years post administration. This single injection mediated decreases in propionyl carnitine and methyl citrate at all time points. Additionally, enzyme activity levels were significantly higher as early as ten days post injection and remained at levels ten times that of untreated *Pcca*−/−(A138T) animals for over 1.5 years post injection and no instances of hyperammonemia have been observed to date in these treated animals. Additional AAV vectors designed to restrict expression to specific tissues including muscle and liver have also offered insight into optimal treatment methods for PA.

Conclusions: This study provides further evidence that AAV-based vectors may offer a viable long-term alternative to liver transplantation in PA patients. Even at 1.5 years after single dose administration *Pcca*−/−(A138T) mice are deriving a disease-mediating benefit from the AAV treatment. Additionally the use of modified AAV vectors allows us to study the effect that treatment of specific tissues has on organ-specific pathology, particularly the heart.