Ms. Sheila Hayes
Keith B Hayes Foundation
07/08/2020

Dear Ms. Hayes.

Last year I have proposed to start working on an AAV mediated RBCK1 cDNA delivery system to treat patients with RBCK1 mutation. With the funds I have received, I started making the AAV vector. However, my efforts have been halted due to COVID-19. I am planning to continue the project in August and test the construct in human tissue culture cells. Successful completion of this test will be followed by mouse experiments.

I will update you when I start working on the project again. Thank you for your patience and funding this project.

Sincerely

H. Orhan Akman, PhD

Grant Application to the Keith Hayes Foundation Principal Investigator: Hasan O. Akman, PhD630 W 168th street Room 4-431 New York, NY 10032Phone: 551 265 5401Email: hoa2101@cumc.columbia.eduTitle: Developing gene therapy for RBCK1 deficiency.

Background

A group of clinical investigators from the US and three European countries (Sweden, Germany, and France) have identified mutations in a novel gene in ten patients from eight families. All had childhood-onset myopathy and eight also showed rapidly progressive cardiomyopathy requiring heart transplant in four. The patients (5 women and 5 men) had abundant accumulation of polyglucosan (an abnormal amylopectin-like polysaccharide with excessive number of poorly branched glucosyl chains) both in skeletal muscle and in the heart. [1].The patients were homozygous or compound heterozygous for mutations in the heme-oxidized IRP2ubiquitin ligase 1 (HOIL-1, HGNC Approved Gene Symbol: RBCK1).Interestingly, a report by Boisson et al. (2012)[2] described two young siblings and one unrelated child with failure to thrive, chronic auto inflammation, and recurrent episodes of sepsis associated with loss-of-function mutations in RBCK1. Two of the children died from sepsis at ages 8 and 3.5 years and one child, who had allogeneic bone marrow transplantation at 13 months of age, died from sudden respiratory distress at 4 years of age. Similar to our patients, inclusions of polyglucosan were identified in skeletal muscle, heart and liver. The finding of mutations in a ubiquitin ligase instead of a “canonical” glycogen metabolism enzyme came as a surprise, but – on second thought – there is a precedent for this situation. One of the two main mutated proteins in Lafora disease, devastating myoclonic epilepsy of young adults, is an ubiquitin ligase called malin, and the pathological hallmark of Lafora disease, the Lafora bodies, are composed of polyglucosan (PG).The central question has been raised by malin deficiency in Lafora disease and by the new myopathy cardiomyopathy with mutations in RBCK1 is how a dysfunction of the ubiquination system affects glycogen metabolism and results in PG accumulation. To develop therapeutic strategies is of course the ultimate goal of translational research, especially for a

monogenic disease that can be rescued by a gene therapy that helps patients affected by crippling myopathy and often fatal cardiomyopathy