Penn Medicine

the orphan disease center

CDKL5 Program of Excellence
2018 Pilot Grant Program

Project Title: "Evaluating a Novel Strategy to Stimulate mTORC1 in Two Mouse Models of CDKL5 Deficiency Disorder"

PI: James Eubanks, PhD

Institution: University of Toronto

To help better understand how specific mutations of CDKL5 affect brain function and cause CDKL5-Deficiency Disorder (CDD), we generated a new line of experimental mice that have a small deletion in the tail end of their CDKL5 gene. This mutation is known to cause CDD, but it affects a region of the CDKL5 protein we know little about. This new tool will allow us to investigate whether the mechanisms causing CDD from these types of CDKL5 mutations differ from those that occur due to a complete loss of CDKL5. The outcomes could impact future personalized medicine strategies to treat specific CDD patients. Towards this goal of treating CDD, recent results suggest the absence of CDKL5 affects how the brain uses its energy supplies. One system, named mTOR, is a key rheostat that governs the metabolic rate of cells. In CDD, there is too little mTOR activity. As part of our ongoing work, we identified a new system named TRPM2 whose function inhibits mTOR, and excitingly, decreasing TRPM2 leads to increased mTOR activity in the brain. In this study we will test whether decreasing TRPM2 in CDKL5-deficient mice will reverse their impaired mTOR activity, and improve their CDD-like behavioral and biochemical phenotypes.