CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Mechanisms and treatment of paradoxical hyperexcitability in CDKL5 Deficiency Syndrome

PI: Timothy Benke, MD, PhD
Institution: University of Colorado

CDKL5 deficiency disorder results in medically refractory epilepsy beginning in the first year of life. In our experience, epilepsy begins as early as 2 weeks of age and is medically refractory in nearly all patients. Coupled with the burden of severe global developmental delays, this creates great challenges for patients and families. These findings strongly support the role of CDKL5 as a key player in the development of excitatory synapses, the connections that transfer information through the brain. This is also evidenced in experimental models where CDKL5 deficiency results in the loss of excitatory synapses. This could explain the global developmental delays; however, the presence of epilepsy suggests that excitatory synapses are hyperactive. This is a paradox that needs to be addressed in order to understand CDKL5 function. We address the possibility that the remaining excitatory synapses are themselves hyperactive using rat neuronal cultures and a rat model of CDKL5 deficiency. We determine whether or not a novel compound corrects this hyperactivity. Additionally, our data suggest that the epilepsy may add insult to injury that could be ameliorated by this compound. These data are key for development of larger proposals using this compound in vivo that will allow us to address the interactive role of epilepsy with the global developmental delays associated with CDKL5 deficiency. These future studies are necessary as potential CDKL5 replacement strategies may not be sufficient to fully correct the developmental challenges our patients and families face. We will share the novel compound with the community as we are hopeful that this class of compounds can be quickly moved towards clinical trials.