CDKL5 Program of Excellence
2025 Pilot Grant Program

Project Title: "Preclinical Investigations of Proteasome and Lysosome Inhibitors In CDKL5-Deficient Mice"

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CDKL5 Deficiency Disorder (CDD) is caused by loss of function mutations within the CDKL5 gene. The ensuing absence of CDKL5 activity does not allow the brain to develop or function properly and causes a host of symptoms. Excitingly, recent work suggests a related family member of CDKL5, named CDKL2, might be able to compensate for the absence of CDKL5 if its actions could be effectively harnessed. Our lab recently identified two ways in which CDKL2 expression can be increased within the brains of CDKL5-deficient mice. In this project, we will test whether either mechanism will rescue the CDD-like behavioral phenotypes of CDKL5-deficient mice and/or reduce their seizure sensitivity by increasing CDKL2 levels. Importantly, each strategy will use clinically approved drugs, increasing the likelihood they could be repurposed for patient use if positive results emerge from the studies. The first drug is Ixazomib, a proteasome inhibitor, and the second is Chloroquine, a lysosome inhibitor. Encouragingly, pilot data obtained using a patient-specific CDD mouse model supports this possibility, as phenotypic improvements were seen in mice treated with each drug. This project is designed to not only identify new mechanisms for how the absence of CDKL5 affects the brain, but also to provide key information needed to guide the translation of our findings into clinical use.