CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Therapeutic drug discovery for CDKL5 deficiency disorder using random shRNA selection

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Mutations in the CDKL5 gene causes CDKL5 deficiency disorder, a distinct neurogenetic disorder characterized by intractable epilepsy and severe neurodevelopmental delay. CDKL5 is important for the development and function of neurons. Although more highly expressed in neurons, CDKL5 is ubiquitously expressed and is apparently multifunctional. The exact functions of CDKL5, and the targets and downstream signaling pathways it impacts, are not yet fully elucidated. There are currently no approved treatments for CDKL5 deficiency. We have developed a novel technology, based on very small RNA molecules called shRNAs, that allows us to screen up to 3 million bioactive molecules in a single dish using cell-culture disease models. Our screening is based on improved cell function and is unbiased: after introduction of random shRNAs into cells, we let the cells tell us which shRNAs work best. Hit shRNAs can be optimized by creating variants and re-screening. Bioinformatic analyses of hit shRNAs reveal relevant biochemical pathways, potential drug target pathways, and potential therapeutics. For this project we will apply our approach to screening to cell-culture models of CDKL5 deficiency disorder. The overall goal is to identify drugs and drug target pathways for the treatment of CDKL5 deficiency disorder.