Enhancing KCC2 Functional Expression as a Novel Therapeutic Approach for CDKL5 Deficiency Disorder (CDD)

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CDKL5 Deficiency Disorder (CDD) is a rare genetic condition that causes severe, treatment-resistant epilepsy and developmental delays beginning in early childhood. Current therapies often fail to adequately control seizures or improve cognitive outcomes. In healthy brains, a protein called KCC2 plays a critical role in maintaining the balance between excitation and inhibition in neural circuits. In CDD, this balance is disrupted, in part due to the reduced KCC2 function, contributing to abnormal brain activity and seizures.

In this project, we will test two complementary therapeutic strategies to restore KCC2 function in CDD neurons: one that increases KCC2 production in neurons (KW-2449) and another enhances its activity (OV350). Using CDD patient-derived human brain cells grown in the lab, we will determine whether these approaches restore normal cellular function, reduce seizure-like neural network activity, and correct underlying molecular abnormalities. Our goal is to investigate a potential mechanism-based treatment for CDD, including epilepsy and broader brain function.