CDKL5 Program of Excellence
2023 Pilot Grant Program

Project Title: "Therapeutic potential of Cav2.3 inhibitors in CDD mouse and human models"

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CDKL5 deficiency disorder (CDD, DEE2) is one of the most common types of genetic childhood epilepsy, affecting an estimated 1:40-60k people. In most CDD cases, early-onset epileptic spasms evolve into generalized, treatment-resistant seizures that can occur several times per day. Additional symptoms include severe global developmental delay, motor, visual and autonomic impairments. CDD patients carry de novo mutations in the CDKL5 gene leading to loss of function of this protein kinase and reduced phosphorylation of its downstream targets. The identification of molecular players affected by CDKL5 loss is critical to understand the pathological mechanisms at play in CDD and the design of effective therapies. Using CDKL5-deficient mice, our lab has recently discovered that CDKL5 targets a protein that participates in the regulation of neuronal excitability, the voltage-gated Ca2+ channel Cav2.3. Loss of Cav2.3 phosphorylation by CDKL5 causes over-activity of the channel and abnormal Ca2+ currents. Interfering with Cav2.3 phosphorylation by CDKL5 in mice results in motor and cognitive deficits and neuronal hyperactivity. Moreover, another form of genetic childhood epilepsy (DEE69) is directly linked to mutations in the Cav2.3 gene that cause similar gain-of-function in the ion channel, suggesting a shared mechanism between CDD and DEE69. Altogether, our results raise the possibility that Cav2.3 dysfunction contributes to seizure generation in CDD (as in DEE69) and that suppression of its activity could be beneficial. Lario Therapeutics have recently developed novel selective inhibitors of Cav2.3. We propose to test the efficacy of these compounds using established mouse and human CDD disease models.