CDKL5 Program of Excellence
2020 Pilot Grant Program

Project Title: "Structural/functional characterization of full-length hCDKL5 isoform 1 produced in recombinant marine bacteria and use of pharmacological chaperones to stabilize hCDKL5 missense mutants"

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CDKL5 Deficiency Disorder (CDD) is a severe and rare genetic disease due to mutations in the X-linked *CDKL5* human gene. Although all pathogenic at a different extent, some kind of mutations, such as nonsense, frameshift or some deletions, often ends up in the complete absence of the enzyme from the cells expressing the mutant allele. On the contrary, missense mutations drive the synthesis of *h*CDKL5 variants which differ from the healthy one for just one amino acid. One of the aims of this project is understanding how these tiny differences negatively impact on *h*CDKL5, interfering with its physiological roles in neuronal cells. This comprehension is fundamental to suggest a therapeutic approach, not yet pursued in CDD, consisting in the treatment with pharmacological chaperones. These are chemical compounds that can bind the missense sick enzyme and compensate or restore its perfect functionality. Although quite simple in principle, this approach to CDD treatment was never suggested before because it requires the availability, in the form of pure enzyme, of either the healthy *h*CDKL5 or the missense mutated enzymes reproducing the exact mutations found in CDD patients. This achievement will allow our multidisciplinary team to better describe *h*CDKL5, and to study if the correct function of *h*CDKL5 missense mutants can be restored upon their binding with some selected molecules.