

CDKL5 Program of Excellence Pilot Grant Program

Application Title: Therapeutic potential of pregnenolone and its synthetic non-metabolized derivative for CDKL5 disorder

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CDKL5 deficiency is generally discovered in infants early after birth due to the manifestation of severe and often drug-resistant seizures. Additional prominent features include severe intellectual disability, hypotonia, gross motor dysfunctions, and sleep disturbances. At the moment, no curative solutions exist for patients with CDKL5 deficiency and drug-based therapies still represent the most immediate strategy. The development of pharmacologic therapies against CDKL5 disorder can be significantly accelerated by increased knowledge of CDKL5 functions. Our recent identification of the IQGAP/CLIP170 complex as a novel target of CDKL5 led us to consider the neurosteroid pregnenolone (P5) and its synthetic derivative pregenenolone-methyl-ether (PME) as interesting candidates for CDKL5 disorder. These two compounds are currently considered as innovative therapeutics against disorders that include impaired learning and memory and depression. We have already confirmed the capacity of the two compounds to cause a robust rescue of neuronal defects linked to CDKL5. We therefore believe that time is mature to push forward P5 and PME to preclinical studies in *Cdkl5-null* mice aimed at evaluating their therapeutic potential *in vivo*. In this project we shall therefore through behavioral tests evaluate whether P5 or PME is capable of restoring cognitive and locomotor defects in *Cdkl5-null* mice. Moreover, brains from treated animals will be subjected to biochemical and histological analyses aimed at correlating any treatment efficacy with restoration of morphological and molecular defects linked to loss of Cdkl5.

In case of positive results, we believe that our studies will be of high impact for patients with CDKL5 disorder since both drugs hold a strong translational promise. Indeed, P5 was well tolerated with a positive safety profile in clinical studies of psychiatric disorders in humans, suggesting that it can relatively easy be brought to the bedside of patients.