Penn Medicine
Orphan Disease Center

CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Exploiting computational biology for target identification and drug repositioning in CDKL5 disorder

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Genetic lesions of various kinds in the X-linked CDKL5 gene are responsible for a suite of disorders affecting both genders, which generally share the common feature of early drug-resistant epilepsy emerging in the first months of life. Other prominent features include severe intellectual disability (ID), hypotonia, motor impairment and the presence of certain Rett syndrome traits. No cure is currently available for CDKL5 conditions; treatment is usually based on support therapy for the comorbidities and on rehabilitation. The development of therapies for CDKL5 diseases is therefore an unmet clinical need. The development of rationally-designed therapies requires a better understanding of CDKL5 functions in brain and of the molecular consequences of its deficiency. Therefore, scientists are actively searching for molecular pathways whose correct regulation and/or activity depend on CDKL5. On this line, we will use a technique called RNA sequencing to thoroughly analyze which genes are not properly expressed in mouse brain when CDKL5 is missing. These studies will be at different phases of brain maturation in order to understand whether the protein is always relevant or if there is a time window in which its functions appear prominent. The identified deregulated genes and pathways will be analyzed through novel bioinformatics and mathematical approaches in order to identify which of the deregulated genes/pathways have a higher potential of being a relevant target for therapies. Further, we will investigate whether the identified pathways/genes might be targeted by drugs already approved for the treatment of other diseases, therefore importantly reducing the times necessary to translate successful pre-clinical studies developed in animal models into human clinical trials.
Although our studies might identify several interesting drug candidates for the treatment of *CDKL5*-opathies, with this proposal we will start validating one or two of them.