Penn Medicine
Orphan Disease Center

CDKL5 Program of Excellence
Pilot Grant Program

Application Title: Brain Rho GTPases: in search of innovative therapeutic targets for CDKL5 deficiency disorder

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CDKL5 is a protein particularly abundant in the brain that plays a crucial role in the regulation of the central nervous system. Mutations in the gene which produces this protein cause a distinct neurodevelopmental disorder characterized by severe developmental delay, early-onset seizures, severe mental disability and motor dysfunction. No cure is currently available for patients affected by this rare genetic syndrome. The association between CDKL5 protein and another group of proteins called Rho GTPases, which play a fundamental role in the plasticity of the brain, has been proposed to be involved in the development of the complex symptomatology associated with CDKL5 deficiency disorders. In the present project, we propose to study the significance of the association between CDKL5 and Rho GTPases. Given the inaccessibility of brain tissue, we will take advantage of the availability of two preclinical models of the CDKL5-associated diseases: a mouse model carrying mutations in the CDKL5 gene and a human neuronal cellular model obtained from patients fibroblasts through a technique called “genetic reprogramming”. The potential therapeutic value of drugs targeting the Rho GTPases molecular signaling will be also assessed in these models. The proposed studies are expected to shed further light on the neurobiological mechanisms underlying CDKL5 deficiency disorder and allow the identification of innovative therapeutic strategies for this severe and untreatable disorders.