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## CDKL5 Program of Excellence 2020 Pilot Grant Program

**Project Title:** “Elucidate the mechanisms underlying sleep disturbances and the relation between seizures and sleep-wake cycle in CDKL5 Deficiency Disorder (CDD)”

**PI:** Liqin Cao, PhD

**Institution:** University of Tsukuba

CDKL5 deficiency disorder (CDD) is an X-linked severe neurodevelopmental disorder caused by pathogenic mutations in the Cyclin-dependent kinase-like 5 (*CDKL5*) gene. Early-onset refractory seizures and sleep disturbances are common features in CDD. Many patients with CDD suffer from severe sleep problems, which affect not only patients but also parents and caregivers, and impact greatly on wellbeing of the whole family. Close association between seizures and sleep-wake cycle has been observed in CDD patients. However, relatively few sleep studies using electroencephalography (EEG) and electromyography (EMG) recording have been conducted in humans and mouse models with CDD. The neural mechanisms underlying sleep disturbances and the relation between seizures and sleep-wake cycle in CD remain unknown. To address these questions, we have conducted the EEG/EMG-based sleep analysis of *Cdkl5* knock-out (KO) mice, and found sleep phenotypes similar to these observed in CDD patients. The goal of the current project is to understand the development of sleep disturbances in CDD model mice, the mechanisms underlying sleep disturbances, and the interplay between seizures and sleep-wake cycle upon loss of CDKL5 activity, in order to develop effective intervention and cure of these conditions. Recently we have generated *Cdkl5 flox* mice and *Cdkl5* kinase-dead K42R knock-in (*Cdkl5* K42R KI) mice as new CDKL5 loss-of function (LOF) models. We will perform comprehensive assessment of sleep architecture, sleep regulation, and the relation between seizures and sleep-wake cycle in the ubiquitous and conditional LOF model mice using techniques of EEG/EMG recording, optogenetics, pharmacogenetics, fiber photometry and two-photon Ca<sup>2+</sup> imaging in live mice. Moreover, we will examine sleep alterations and seizures in CDD patients by EEG recording. We believe that our studies will significantly advance the knowledge about etiology and therapy of sleep disturbance and seizures in CDD.