Penn Medicine

the orphan disease center

CDKL5 Program of Excellence
2019 Pilot Grant Program

Project Title: "Identifying the brain-wide, synapse-to-circuit functional abnormalities upon the loss of CDKL5 kinase activity in ubiquitous/excitatory/inhibitory-neuron-specific Cdkl5 kinase-dead knock-in mice and human patients"

PI: Teruyuki Tanaka, PhD

Institution: University of Tokyo

Our group has previously generated Cdkl5 knock-out (KO) mice, and identified the postsynaptic NMDA receptor (NMDAR) abnormalities in the hippocampus and altered emotional behavior and memory. However, functional mechanisms underlying these phenotypes remain unknown, and the KO mice did not fully recapitulate the major symptoms of human patients. My ultimate goal is to help enable the patients to talk to the parents, walk with the families, and smile from the heart. To this end, understanding the brain-wide, synapse-to-circuit functional alteration upon the loss- of-function (LOF) of CDKL5 is absolutely necessary, and animal models that better represent the LOF and enable the evaluation of therapeutic effects are in urgent need. Aiming to solve these issues, I have generated kinase activity-deficient (kinase-dead) Cdkl5 knock-in (KI) mice, hypothesizing that (1) kinase-dead KI mice exhibit CDKL5 LOF effects that escape functional compensation by other proteins, and thus represent more sensitive mouse models of CDD; (2) the loss of CDKL5 kinase activity disrupts the brain-wide, functional connectivity by generating excitatory/inhibitory (E/I) imbalance. I will test these hypotheses by the following aims: (1) determine the brain-wide, synapse-to-circuit dysfunction upon the loss of CDKL5 kinase activity in hemizygous and heterozygous conditions, applying the in vivo Ca+2 imaging and real-time identification of the genotype of neurons in the heterozygotes; (2) determine the neuron-type- specific role of CDKL5 kinase activity by generating excitatory-/inhibitory-neuron-specific Cdkl5 kinase-dead KI mice; (3) determine if and to what extent postnatally-restoring the Cdkl5 gene in the kinase-dead KI mice rescues the LOF phenotypes by generating kinase-dead KI mouse that is Cre-dependently reversible to the wild-type (WT) equivalent; (4) identify functional connectivity alteration of CDD patients by the resting state (rs)-fMRI. This proposal enables to determine the correlation of altered functional connectivity upon the LOF of CDKL5 between mice and humans, and provide underlying mechanism of CDD and the foundation for the gene therapy.