Studying neurotransmission of normal and diseased human ES cell-derived neurons in vivo

Grant Award Details

Studying neurotransmission of normal and diseased human ES cell-derived neurons in vivo

Grant Type: Basic Biology III

Grant Number: RB3-02129

Project Objective: The project objective is to develop a human-into-rat xenograft model for studying human neurological disease, with Rett syndrome (RTT) as a proof-of-principle. hESC- and hiPSC-derived neurons will be genetically modified to allow optical stimulation and transplanted in utero to allow integration during development and postnatal study in vivo and in vitro (in brain slices).

Investigator:

Name:	Yi Sun
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Autism, Neurological Disorders, Pediatrics, Rett's Syndrome

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $1,382,400

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Studying neurotransmission of normal and diseased human ES cell-derived neurons in vivo

Public Abstract: Stem cells, including human embryonic stem cells, provide extraordinary new opportunities to model human diseases and may serve as platforms for drug screening and validation. Especially with the ever-improving effective and safe methodologies to produce genetically identical human induced pluripotent stem cells (iPSCs), increasing number of patient-specific iPSCs will be generated, which will enormously facilitate the disease modeling process. Also given the advancement in human genetics in defining human genetic mutations for various disorders, it is becoming possible that one can quickly start with discovery of disease-related genetic mutations to produce patient-specific iPSCs, which can then be differentiated into the right cell type to model for the disease in vitro, followed by setting up the drug screening paradigms using such disease highly relevant cells. In the context of neurological disorders, both synaptic transmission and gene expression can be combined for phenotyping and phenotypic reversal screening and in vitro functional (synaptic transmission) reversal validation. The missing gap for starting with the genetic mutation to pave the way to drug discovery and development is in vivo validation-related preclinical studies. In order to fill this gap, in this application we are proposing to use Rett syndrome as a proof of principle, to establish human cell xenografting paradigm and perform optogenetics and in vivo recording or functional MRI (fMRI), to study the neurotransmission/connectivity characteristics of normal and diseased human neurons. Our approach will be applicable to many other human neurological disease models and will allow for a combination of pharmacokinetic, and in vivo toxicology work together with the in vivo disease phenotypic reversal studies, bridging the gap between cell culture based disease modeling and drug screening to in vivo validation of drug candidates to complete the cycle of preclinical studies, paving the way to clinical trials. A success of this proposed study will have enormous implications to complete the path of using human pluripotent stem cells to build novel paradigms for a complete drug development process.

Statement of Benefit to California: Rett Syndrome (RTT) is a progressive neurodevelopmental disorder caused by primarily loss-of-function mutations in the X-linked MeCP2 gene. It mainly affects females with an incidence of about 1 in 10,000 births. After up to 18 months of apparently normal development, children with RTT develop severe neurological symptoms including motor defects, mental retardation, autistic traits, seizures and anxiety. RTT is one of the Autism Spectrum Disorders (ASDs) that affects many children in California. In this application, we propose to use our hESC-based Rett syndrome (RTT) model as a proof-of-principle case to define a set of core transcriptome that can be used for drug screenings. Human embryonic stem cells (hESCs) hold great potential for cell replacement therapy where cells are lost due to disease or injury. For the diseases of the central nervous system, hESC-derived neurons could be used for repair. This approach requires careful characterization of hESCs prior to utilizing their therapeutic potentials. Unfortunately, most of the characterization of hESCs are performed in vitro when disease models are generated using hESC-derived neurons. In this application, using RTT as a proof of principle study, we will bridge the gap and perform in vivo characterization of transplanted normal and RTT human neurons. Our findings will not only benefit RTT and other ASD patients, but also subsequently enable broad applications of this approach in drug discovery using human pluripotent stem cell-based disease models to benefit the citizens of California in a broader spectrum.