Developing a drug-screening system for Autism Spectrum Disorders using human neurons

Grant Award Details

Developing a drug-screening system for Autism Spectrum Disorders using human neurons

Grant Type: Early Translational II

Grant Number: TR2-01814

Project Objective: The project objective is to develop a fluorescence-based drug screening assay for autism spectrum disorders (ASD). they are using iPSC lines derived from ASD patients and have described phenotypic abnormalities in ASD patient-derived iPSC-neurons relative to controls. They are developing a platform using those phenotypes to look for drugs to revert those phenotypes.

Investigator:

Name:	Alysson Muotri
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Autism, Neurological Disorders, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,376,198

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: NCE (Year 4)

View Report

Grant Application Details

Application Title: Developing a drug-screening system for Autism Spectrum Disorders using human neurons

Public Abstract: Autism and autism spectrum disorders (ASD) are complex neurodevelopmental diseases that affect 1 in 150 children in the United States. Such diseases are mainly characterized by deficits in verbal communication, impaired social interaction, and limited and repetitive interests and behavior. Because autism is a complex spectrum of disorders, a different combination of genetic mutations is likely to play a role in each individual. One of the major impediments to ASD research is the lack of relevant human disease models. ASD animal models are limited and cannot reproduce the important language and social behavior impairment of ASD patients. Moreover, mouse models do not represent the vast human genetic variation. Reprogramming of somatic cells to a pluripotent state (induced pluripotent stem cells, iPSCs) has been accomplished using human cells. Isogenic pluripotent cells are attractive from the prospective to understanding complex diseases, such as ASD. Our preliminary data provide evidence for an unexplored developmental window in ASD wherein potential therapies could be successfully employed. The model recapitulates early stages of ASD and represents a promising cellular tool for drug screening, diagnosis and personalized treatment. By testing whether drugs have differential effects in iPSC-derived neurons from different ASD backgrounds, we can begin to unravel how genetic variation in ASD dictates responses to different drugs or modulation of different pathways. If we succeed, we may find new molecular mechanisms in ASD and new compounds that may interfere and rescue these pathways. The impact of this approach is significant, since it will help better design and anticipate results for translational medicine. Moreover, the collection and molecular/cellular characterization of these iPSCs will be an extremely valuable tool to understand the fundamental mechanism behind ASD. The current proposal uses human somatic cells converted into iPSC-derived neurons. The proposed experiments bring our analyses to real human cell models for the first time. We anticipate gaining insights into the causal molecular mechanisms of ASD and to discover potential biomarkers and specific therapeutic targets for ASD.

Statement of Benefit to California: Autism spectrum disorders, including Rett syndrome, Angelman syndrome, Timothy syndrome, Fragile X syndrome, Tuberous sclerosis, Asperger syndrome or childhood disintegrative disorder, affect many Californian children. In the absence of a functionally effective cure or early diagnostic tool, the cost of caring for patients with such pediatric diseases is high, in addition to a major personal and family impact since childhood. The strikingly high prevalence of ASD, dramatically increasing over the past years, has led to the emotional view that ASD can be traced to a single source, such as vaccine, preservatives or other environmental factors. Such perspective has a negative impact on science and society in general. Our major goal is to develop a drug-screening platform to rescue deficiencies showed from neurons derived from induced pluripotent stem cells generated from patients with ASD. If successful, our model will bring novel insights on the dentification of potential diagnostics for early detection of ASD risk, or ability to predict severity of particular symptoms. In addition, the development of this type of pharmacological therapeutic approach in California will serve as an important proof of principle and stimulate the formation of businesses that seek to develop these types of therapies (providing banks of inducible pluripotent stem cells) in California with consequent economic benefit.