THE HARTWELL FOUNDATION

2014 Individual Biomedical Research Award

Gül Dölen, MD, Ph.D.

Assistant Professor
Department of Neuroscience

The Johns Hopkins University

Brain Circuit Photostimulation for the Treatment of Autism

Autism Spectrum Disorder (ASD) is a complex disorder of brain development characterized by dysfunctional social behaviors and communication, particularly the loss of an ability to socialize and use imagination. Diagnosis of the condition occurs typically in children around 3 years of age. Although the causes are enigmatic, these impairments appear to arise principally from disruption in two key brain functions: social reward recognition and the ability to imagine the world from another person's point of view (Theory of Mind). The U.S. Centers for Disease Control and Prevention estimate that 1 in 68 children in the United States are afflicted with ASD where, in about one quarter of cases it has been possible to identify the disrupted gene(s). Unfortunately, current therapeutic interventions for ASD are not especially effective and limited to behavioral training or drug-related treatments, leaving an immeasurable emotional toll on affected families. Bridging the knowledge gap between genetic disruption, disease symptoms, and therapeutic intervention is an unmet need in autism research. To test the consequences of gene disruptions and the efficacy of therapeutic interventions, scientists struggle with available tests to accurately identify autistic behavior in animal models. What is confounding progress in understanding the disorder is that no parallel exists in the dozens of existing animal models of ASD that takes into account social reward (i.e., Theory of Mind). In this regard, Gül has recently identified a behavioral task that can address whether social interactions are rewarding in mice. Using this task, she discovered what appears to be a novel brain circuit for social reward, which may account for Theory of Mind and be important in ASD. As a result of her discovery, Gül now proposes to develop additional behavioral assays to pinpoint this brain circuitry and its relevance to the pathology of ASD. Her approach will utilize viral mediated gene transfer to render appropriate brain circuit components responsive to light, and optogenetic probes that will enable photostimulation of specific cells. She hypothesizes that this will enable her to restore the diminished incentive value of the social information that normally elicits reward behaviors. Targeting only those neurons directly responsible for those behaviors will also provide a unique opportunity to couple the timing of stimulation to the appropriate social circumstance. If she is successful, photoactivation of specified social reward circuits in a mouse model will enable her to similarly correct social reward deficits in autism. Successful development of a Theory of Mind behavioral assay will improve strategically the validity of using animal models of ASD to test the efficacy of interventions, while also overturning the longstanding supposition that Theory of Mind is unique to humans. The implications for translation of these results into interventions for children with ASD would be groundbreaking, offering tangible hope for a cure.