THE HARTWELL FOUNDATION

2012 Individual Biomedical Research Award

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Illuminating the Language of Neural Networks in Patient-iPSC Derived Brain Models with Down Syndrome

One newborn in every 700-800 live births in the U.S. is affected by Down syndrome (DS and neurological defects that originated during prenatal development. At 3-5 months of age, the anterior-to-posterior brain diameters of DS children months are shorter compared to age-matchedinfants. By the end of year one, affected infants exhibit impaired language ability and developmental delay of cognitive functions, including learning and memory. More than 90 percent of the time, DS is caused by three copies of chromosome 21 (trisomy 21). There are no therapies or drugs known to correct the common symptom of mental retardation in DS. Normally, from embryo to early childhood, the brain is developing neural networks consisting of neurons and glial cells that work together to orchestrate higher brain functions. Glial cells guide the development of neuronal networks by listening and talking to neighboring neurons. The progression of DS has long been suspected to be caused by changes in this circuitry. To understand DS, Lin hypothesizes it is important to understand the role of glial cells in forming a brain neural network and how functional interactions within the network change with progression of the disorder. To address this formidable challenge, she proposes to differentiate normal and DS patient-derived inducible pluripotent stem cells in cell culture into neurons and glial cells. Given the cells will have the same genetic backgrounds of the individual from which they were derived, she expects the neural networks formed will recapitulate normal or disrupted connectivity and function associated with the cellular phenotypes of normal and DS human brains. To mimic how abnormal logic at the network level could relate to DS in a human brain, she will use optical sensors in this model system to track calcium signaling as a measure of network dynamics and computational modeling to describe the logic of the interactions between neurons and glial cells. She will then attempt to rescue the observed network communication defects with drugs identified in a high-throughput screen of several million compounds. If Lin is successful in modeling DS brain circuitry, it will shed light not only on the way genetic identity is linked to the structure and function of neural networks, but the poorly understood nature of mental retardation in the syndrome, as well. Her innovative approach will also enable an experimental platform from which other neurocognitive diseases may be similarly examined. If she is successful in rescuing the neural communication defects in DS with target drug therapy it will have the potential to significantly improve the quality of life for affected children.