# THE HARTWELL FOUNDATION

## 2015 Individual Biomedical Research Award

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**Cracking the Autism Code by Correcting Hampered Synapses**

Autism spectrum disorder (ASD) comprises a group of brain development disorders characterized by significant deficits in social communication and social interaction. Current estimates by the U.S. Center for Disease Control suggest the incidence of the disorder at 8 years of age is an astonishing 1 in 68 children. Currently, causes are not yet clearly understood and there is no cure. It is believed that ASD represents a heterogeneous collection of disorders caused by mutation of multiple genes that function within common biochemical pathways. Recent genetic research suggests that proteins in brain synapses (specialized junctions between two nerve cells) play a key role in the pathology of ASD, where altered functionality in synapses can lead to perturbations in neural circuits, which ultimately contributes to impaired behaviors. Because of altered, duplicated, or deleted genes, lower or higher levels of specific synaptic proteins confer genetic risk. Understanding the underlying mechanism of altered synapse function could provide druggable targets for therapy, but is difficult to pursue with the limitations in how tissue samples from the brain are currently prepared. Given that the mouse brain is made up of a large number of different neuronal cell types, each with its own unique combination of proteins (proteome) and that cells are organized through billions of synaptic connections by about 70 million neurons, brain tissue extracts represent a complex mixture of proteomes. With a requirement for tissue homogenization, the interpretation of any bulk analyses is limited by "molecular averaging." While pioneering experiments by others have cataloged the near complete collection of proteins present at synapses, the precise identity of proteins present at specific neural cell synapses has not been established. To overcome this limitation, Jeff proposes a unique method of identifying proteins present at specific brain synapses in tissue samples drawn from various mouse models of ASD. His approach is to retain the organization of proteins at the synapse by proximity-based labeling *in vivo* with a chemical tag prior to tissue homogenization, which will enable the simultaneous identification of thousands of labeled proteins by high throughput quantitative mass spectrometry. By examining certain relevant regions of the brain known to be affected by ASD and profiling protein identity and abundance in specific synapses, it will be possible to determine how defined mutations manifest as remodeled synaptic proteomes. If Jeff is successful in characterizing the proteome of specific brain synapses, it will enable the identification of druggable targets for therapeutic intervention in malfunctioning synapses in neuronal circuits associated with ASD.