Title: Investigating the mechanistic and temporal regulation of inhibitory synapse elimination during cerebral ischemia.

Abstract: Inhibitory synapses are crucial for maintaining correct neuronal excitability, which is important for efficient circuitry and proper brain function. Inhibitory $GABA_A$ receptors ($GABA_ARs$) mediate the majority of fast synaptic inhibition in the brain. Thus, the number of postsynaptic $GABA_ARs$ influences inhibitory strength. Shifts in neuronal excitability have been implicated in a variety of neurological disorders, including ischemia. The oxygen and glucose deprivation (OGD) observed during ischemic insult in hippocampal regions leads to synaptic depression through $GABA_AR$ and gephyrin loss from synaptic sites. However, mechanisms that regulate $GABA_AR$ declustering and gephyrin elimination following an ischemic insult remain undefined. In this project, I propose that $GABA_AR$ declustering is mediated by calcineurin activity and this is the first step in facilitating synapse elimination. Furthermore, I speculate a role of the cystine protease, Calpain, in mediating gephyrin loss during OGD. Based on this, I plan to investigate (i) mechanisms of synaptic $GABA_AR$ declustering and gephyrin elimination in hippocampal pyramidal neurons following OGD (ii) probe the temporal regulation to determine the sequential flow of events promoting $GABA_AR$ and gephyrin loss and (iii) use an in vivo model of cerebral ischemia to compare cell-type specific mechanisms in the CA1 hippocampus.