

# *The Neuroscience Graduate Program*

*presents:*

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**ADVISOR:**

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*IN A THESIS PROPOSAL*

*TUESDAY, 1 SEPTEMBER 2015*

*1:00PM IN AUDITORIUM K-207 (2-6408)*

## ***Role of lung-brain coupling in neutrophil priming and reperfusion injury following global cerebral ischemia***

Neurologic recovery after cardiac arrest is complicated by a constellation of organ dysfunction and systemic inflammation known as Post Cardiac Arrest Syndrome (PCAS). After return of spontaneous circulation, reperfusion of the brain is accompanied by the migration of “primed,” neurotoxic neutrophils (PMNs) that cause blood-brain-barrier dysfunction and damage to local tissue with the release of degradative enzymes, cytokines, and reactive oxygen species. Recent work in the fields of pulmonary and critical care suggests that priming is reversible and mediated at the PMN-pulmonary endothelium interface.

Our lab has found that targeted expression of extracellular superoxide dismutase (SOD3, an antioxidant enzyme) in the lung alters PMN kinetics and neuronal injury after ischemia-reperfusion. In this proposal we investigate the link between lung inflammation, PMN activation, and cerebral ischemia-reperfusion injury in a mouse model of PCAS that combines the effects of global cerebral ischemia-reperfusion and systemic inflammation. We hypothesize that PCAS induces PMN priming, and that the level of SOD3 activity and inflammation in the lung in turn modulates their histotoxic effects of as they traverse the post-ischemic cerebrovasculature. The experiments proposed will test the effects of manipulating SOD3 activity on: 1) the spatiotemporal trafficking of PMNs and degree of ischemic injury to the CNS observed, 2) PMN neurotoxicity *in vitro*, and 3) whether the lung can effectively “de-prime” PMNs exposed to priming stimuli *ex vivo* and reintroduced to the systemic circulation by transfusion.

These studies highlight the potential role of lung-brain coupling in ischemia-reperfusion injury and focus on the PMN priming circuit as a potential target for therapeutic intervention. Given its salient role in modulating the inflammatory response to ischemia-reperfusion injury, the lung is an easily accessible target in which putative neuroprotective strategies may be tested.