

# *The Neuroscience Graduate Program*

*presents:*

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***IN A PHD THESIS DEFENSE***

***MONDAY, 10 APRIL 2017***

***9:00 AM IN WHIPPLE AUDITORIUM (2-6424)***

## ***LUNG-BRAIN IMMUNOLOGICAL COUPLING MEDIATES NEUTROPHIL DE-PRIMING AND NEUROPROTECTION FOLLOWING CEREBRAL ISCHEMIA-REPERFUSION***

Systemic inflammation and multi-organ failure represent two hallmarks of the Post Cardiac Arrest Syndrome (PCAS), and when present, are associated with severe neurological injury and often mortality. With the return of spontaneous circulation, 'primed,' neurotoxic neutrophils (PMNs) release degradative products that cause blood-brain-barrier dysfunction, tissue injury, and further PMN activation. In pilot studies, we noted that remote cerebral ischemia-reperfusion triggered the activation and accumulation PMNs in the lung. These observations led us to propose the existence of immunological coupling between the lung and brain and to investigate whether systemic inflammation impairs this protective influence in the setting of ischemia-reperfusion.

To test this, we developed a model of PCAS in mice by pairing transient global cerebral ischemia (achieved by three-vessel occlusion, 3VO) with the exposure to the prototypical endotoxin lipopolysaccharide (LPS) upon reperfusion. Studies have shown that targeted expression of the antioxidant extracellular superoxide dismutase (SOD3) from type II pneumocytes is sufficient to reduce oxidant-induced lung injury and inflammation in mice. To test whether focal manipulation of lung redox biology could exert similar effects in our model, we examined the effects of 3VO/LPS treatment in the Tg(SOD3) model. Our results indicate that increased SOD3 expression in the lung was protective against 3VO/LPS-induced lung edema, pulmonary PMN accumulation, microglial activation, cortical damage, and hippocampal apoptosis.

Our work highlights the importance of lung-brain coupling in ischemia-reperfusion injury and suggests that interventions targeting both PMN priming and redox changes that occur in the lung after ischemia-reperfusion may be valuable. These findings are particularly salient given the increased risk of stroke in patients with underlying lung disease and endothelial damage caused by smoking and other cardiovascular risk factors. Given its accessibility to pharmacological manipulation, our work suggests that targeting the lung with inhaled pharmacological agents could produce maximal benefit by short-circuiting systemic immune priming in patients following cardiac arrest or focal stroke revascularization.