Supervisor & Project Information Form

Please complete and return via email ONLY to gdip.hres@utoronto.ca by ***Monday September 30, 2019***

Supervisor Information

MUST have unrestricted SGS appointment (appointment to supervise graduate students)

Name: **Beverley A. Orser**	**Email:** beverley.orser@utoronto.ca
SGS Department: **Department of Physiology, IMS**	**Field of Research:** **Translational Neuroscience**
Research Institution affiliation (if applicable):	**Location of Work:** **Rm 3318, Medical Sciences Building**
Student contact time (number of hours per week YOU are available to the student for any concerns or to review progress:	**2 hours/week**

Project Information (will be posted on GDipHR website for student access)

TITLE:

Persistent cognitive impairment and disrupted inhibitory transmission after the double-hit of inflammation and anesthesia

DESCRIPTION (MAX 500 WORDS):

Every year, over 312 million patients undergo surgery under general anesthesia. Unfortunately, a subset of these patients experiences persistent cognitive deficits after their surgeries, a condition known as postoperative neurocognitive dysfunction (PNCD). These deficits are associated with poor long-term outcomes including loss of independence, early retirement, and increased mortality.

Clinical studies suggest that PNCD has a multifactorial origin, with a "double-hit" of preoperative inflammation (1st hit) plus the general anesthetics (2nd hit) used during surgery likely contributing to its development. Pre-clinical studies have mostly studied the underlying mechanisms for cognitive deficits after inflammation or anesthetics in isolation, but those mechanisms underlying the persistent cognition-impairing effects of the double-hit are unknown.

We have previously shown that inhibitory $GABA_A$ receptors play an important role in the cognitive deficits after inflammation or general anesthetics alone. Specifically, these are the $GABA_A$ receptors containing the $\alpha5$ subunit ($\alpha5GABA_ARs$). These "memory-blocking" receptors mediate a form of tonic inhibition in the brain, and are activated by the ambient GABA present in the brain tissue. General anesthetic drugs can increase the surface expression of $\alpha5GABA_ARs$ long after the drug has been eliminated, causing persistent cognitive deficits. Similarly, inflammation can also increase the surface expression of these receptors, leading to impaired cognition. In addition, inflammation can also increase the concentration of ambient GABA, which would lead to an even further increase in the function of $\alpha5GABA_ARs$. Given the convergence on $\alpha5GABA_ARs$, a double-hit of inflammation and anesthesia likely greatly increases tonic inhibition, leading to further cognitive impairment in the double-hit. Our preliminary data supports this notion.

Based on these findings, we are exploring the hypothesis that the double-hit of inflammation and general anesthesia causes additional cognitive impairments that are not observed with single hits alone. Further, we postulate that these impairments are due to a marked increase in inhibitory neurotransmission in the double-hit. To test this hypothesis, we are combining mouse behavioral studies with biochemical and electrophysiological approaches to characterize the sustained changes in inhibitory neurotransmission after the double-hit.

If human subjects are involved, have the appropriate Research Ethics Board approvals been obtained?

☐Yes ☒No ☐Application Submitted (Date: _____)

Do you expect this work will be published within the 20 months?

☒Yes ☐No ☐Uncertain / Other

Student Roles & Responsibilities (*please be as specific as possible****)***

Please indicate who will serve as the student's direct report for daily oversight (PI, PhD student, technician, etc…)

The student will report to and work closely with a senior PhD student in the lab, with further oversight provided by the senior research associate as well as the PI. The major responsibility of the student will be in helping with behavioral and biochemical studies. For behavior studies, the student will be heavily involved with data analysis, including scoring videos of mouse performance in various assays, compiling the data, performing statistical analyses, and generating figures. For biochemical studies, the student will aid in performing qPCR and western blot studies to investigate the expression of various $GABA_A$ receptor subunits, as well as other proteins of interest.

In addition, the student will be responsible for maintaining clear records of experiments, attending regular lab meetings, and presenting their findings to the team in both written and oral formats. Additionally, we work in a very collaborative laboratory environment, and the student may be involved in other projects in the lab if necessary.