RESEARCH SCHOLAR PROGRAM 2017
SUPERVISOR/PROJECT INFORMATION FORM

Due on or before October 21 2016. Forms received after this date will not be posted on the website.

SUPERVISOR INFORMATION

Supervisor Name: Dr. Gregory MT Hare

Mailing Address: Department of Anesthesia, St. Michael's Hospital, University of Toronto, 30 Bond Street, Toronto Ontario, Canada

Telephone Number: 416-864-5259

Email Address: HareG@smh.ca

Degree (MD, PhD, MD/PhD): MD/PhD

Academic Rank: Professor of Anesthesia and Physiology

Field of Research: Adaptive cardiovascular physiology and mechanisms which regulate tissue oxygen delivery and cellular oxygen homeostasis

Graduate School Appointment (IMS, IHPME etc..):
Professor of Physiology, Department of Physiology; Full member School of Graduate Studies, University of Toronto.
Please note that you must be appointed to the SGS in order to be a supervisor in the Scholar Program

Research Institute Affiliation (if applicable): Adjunct Scientist; Keenan Research Centre for Biomedical Science and Li Ka Shing Knowledge Institute

Allocation of student contact time (# of hours per week you are available to the student for any concerns or to review progress): As a clinician scientist, I have 2 to 3 academic days per week to be available to supervise the CREMS student; during the academic year and summer projects. I would commit an estimated 10 hours per week of available supervisory time.

PROJECT INFORMATION

Project Title: Defining the adaptive role of erythropoietin during acute and chronic anemia: Characterization of novel mechanisms of erythropoietin expression in the heart and brain.

Project Description (max 500 words):
Anemia is a global health issue affecting an estimated 1/3 of the world's population (*Kassebaum NJ Blood 2014*); and a leading contributor to the global burden of disease (*JAMA Pediatric 2016*). Regardless of the etiology; acute and chronic anemia are associated with increased morbidity (reduced quality of life, cognitive dysfunction, stroke, acute kidney injury, myocardial infarction) and mortality; including an increased risk of sudden death (*Shander A, Hare GM Br J Anaesth 2011*). These adverse outcomes occur by incompletely defined mechanisms. Our research has focused on defining the role of cardiovascular and cellular adaptation to acute anemia. We have demonstrated that oxygen homeostasis is maintained by adaptive cardiovascular responses to maintain adequate tissue oxygen delivery to vital organs and at the cellular levels through hypoxia signaling mechanism including hypoxia inducible factor (*HIF*). Deletion of these cellular responses results in increased mortality in experimental models of anemia. Erythropoietin (EPO) is the archetypal hypoxia (HIF) responsive protein with a clearly defined renal endocrine function which acts to restore hemoglobin concentration during anemia. However, recently defined autocrine and paracrine systems for EPO have been identified in the brain and heart, raising the possibility that the cellular regulation of EPO may contribute to adaptive mechanism during anemia. Recent research performed by our collaborators (*Allwood and Simpson, PhD Thesis 2016*), have assessed the tissue specific responses of EPO to graded atmospheric hypoxia. They have identified that local regulation of EPO in the brain and heart dramatically impact the cardiovascular and cellular response to hypoxia; utilizing tissue specific conditional EPO deletion. While the kidney is traditionally considered to be the sole producer of systemic EPO, new data have demonstrated that the kidney is not the primary EPO responder to graded levels of hypoxia in experimental models. This challenges the long standing belief that the kidney is the only site of EPO production in response to hypoxia. While anemia and systemic hypoxia share elements of inadequate delivery of oxygen to the tissue; our research has demonstrated anemia and hypoxia are fundamentally different (*Tsui AK, Hare GM, PNAS 2011*); therefore, the molecular response to hypoxia cannot be extended to anemia. As anemia is a prevalent health issue, there is an urgent need to better understand the importance of local expression of cardiac and brain EPO on the adaptive biology of anemia. We propose to test the **hypothesis** that local regulation of brain and cardiac EPO contribute to the adaptive cardiovascular and cellular responses to anemia and sustain organism survival. We propose to investigate: **Aim 1: What are the primary extra-renal tissue(s) responsible for EPO expression in response to graded anemia?** We will perform a whole-body, temporal, organ analysis of EPO expression following mild, moderate and severe anemia. **Aim 2: What is the physiological relevance of non-renal (brain and heart) EPO production during anemia?** Using the Cre-lox system, we will generate tissue-specific EPO knockout with independent deletion of brain (astrocyte; GFAP) and cardiac (cardiomyocyte; Mlc2v) derived EPO to investigate the significance of local EPO production in response to anemia. **Aim 3**: **What are the differences in renal and non-renal EPO expression in animals exposed to hypoxia and anemia**. Utilizing these approaches, we plan to further characterize the autocrine, paracrine and endocrine regulation of tissue specific EPO expression in response to anemia and determine their relative importance on organism adaptation and survival. These translational studies should inform clinical research assessing the role of EPO as a therapeutic to promote organ protection and survival in anemic patient.

If human subjects are involved, has Ethics been obtained?

☐YES ☐NO ☐Application Submitted ☒N/A

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

☒YES ☐NO ☐Uncertain

Student's Roles / Responsibilities (Please be as specific as possible) Please indicate who will serve as the student's direct report. (PI, PDF, PhD student, technician etc…):

- The CREMS student will work directly with and report to PI (Dr. Hare) during the 20 month term of the project. Interaction with additional local mentors (Dr. CD Mazer) and collaborators (Dr. J Simpson, U Guelph) will provide further supervision and student support.
- The student will be involved in all aspects of the study including animal care committee application, design and conduct of experiments and collection, analysis and interpretation of data.
- At the conclusion of the study, the student will be responsible for drafting the manuscript for publication