RESEARCH SCHOLAR PROGRAM – 2018

SUPERVISOR & PROJECT INFORMATION FORM

Please complete and return, via email only (crems.programs@utoronto.ca) by November 3rd 2017 (forms received after this date will not be posted).

Supervisor Information

Name: Claudia C dos Santos
Email: dossantosc@smh.ca

Degree: MD, MSc
SGS Appointment: IMS, LMP & (Physiology as of Jan 2018)

Academic Rank: Associate Professor
Field of Research: Critical Illness

Research Institution Affiliation (if applicable): Keenan Center for Biomedical Science Research

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): I do 75% research – so can make myself available 60-70% of my time
**Project Information**

**Title:** Functional Role of G9a Histone Methyltransferase in Acute Inflammation and Infection

**Description (max 500 words):**

Gene transcription following exposure to toll-like receptor (TLR) agonists is regulated by chromatin modifications induced by the inflammatory stimulus. Inhibition of members of the bromodomain family of histone acetylases prevents transcription of a distinct family of inflammatory genes, and improves survival in murine models of endotoxin challenge and polymicrobial infection, even when inhibition occurs after the insult. Through a collaboration with the Structural Genomics Consortium we have obtained two highly specific inhibitors of a key ‘writer’ - the H3K9 methyltransferase G9a and the closely-related G9a-like protein or GLP (UNCO638) - and a key ‘reader’- the BRD4 bromodomain transcriptional co-activator (PF-1). Each target has been linked to the regulation of inflammation. More importantly, both compounds completely reverse the in vitro inhibition of apoptosis of PMN harvested from patients with sepsis – a phenomenon we have previously only been able to partially accomplish with interventions that target elements of the septic PMN anti-apoptotic program.

We hypothesize that epigenetic mechanisms regulate the transcriptome of the activated PMN, enhancing the expression of genes that prolong PMN survival and inflammatory function in critically ill patients. Our overall goal is to identify novel strategies to limit the deleterious effects of PMN activation in acutely ill patients; our 3 specific Aims are:

1. To define the effects of G9a and BRD4 activity on the in vitro survival and inflammatory function of circulating PMN from patients with trauma and sepsis, and on in vivo survival and physiology in a murine model of sepsis
2. To define the transcriptional alterations associated with G9a and BRD4 modulation, and the intracellular mechanisms through which their function is modified by inflammation
3. To determine the effect of G9a Histone Methyltransferase in an in vivo clinically relevant model of polymicrobial sepsis

If human subjects are involved, have Ethics been obtained?

☒ YES ☐ NO ☐ Application Submitted ☐ N/A
Do you expect this work will be published within the 20 months?

☐ YES   ☐ NO   ☒ Uncertain

Student’s roles and responsibilities (please be specific)

Student will randomize male C57BL/6 mice to either polymicrobial sepsis by cecum ligation and puncture or sham surgery treated with placebo or G9a antagonists or agonists. Evaluation of mortality and organ injury will be performed as per standard protocols in the laboratory.

Mechanistic studies will be conducted in Human and Murine neutrophils isolated from septic and non-septic subjects to look at the effect of G9a modulation on Histone Methylation, target gene expression, and neutrophil apoptosis

*Please indicate who will serve as the student’s direct report (PI, PhD student, technician etc…)*

This project is an ongoing collaboration between my Lab and Dr, John Marshall’s Lab but the student will be reporting to ME and to my PDF.