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: Tereza Martinu

Email: tereza.martinu@uhn.ca

Degree: MD

SGS Appointment (IMS, IHPME, LMP etc..): IMS, Immunology

Academic Rank: Assistant Professor

Field of Research: Transplant immunology, lung transplantation, fibrosis

Research Institution Affiliation (if applicable): Toronto General Hospital Research Institute

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress):

I commit to at least one hour per week for a one-on-one meeting with the student. In addition, I will be available in person, by email, and by phone to the student at any time (within reason) for additional questions and discussions. I co-lead a lung transplant immunology research group (the CLAD Team) with my colleague Dr. Stephen Juvet. The

CREMS student will be an active participant in this group. Within the CLAD team, the student will have access to other investigators, multiple technicians, and students who will supervise and assist. There will also be 2-3 hours of lab meeting time each week for group discussions and feedback, in my presence. In these meetings, the student will have regular opportunities to present and get feedback on their work.

Project Information

Title:

Immunomodulatory role of the allograft microbiome in lung transplantation

Description (max 500 words):

Lung transplantation is a life-saving operation for patients with end-stage lung diseases. However, the median survival after lung transplantation is only about 6 years, significantly lower than for other solid organ transplants. The complex interaction between alloimmune (anti-donor) processes, innate immune activation, and the constant exposure to environmental stimuli is thought to be at the root of the high incidence of acute rejection and subsequent chronic lung allograft dysfunction (CLAD). The lung microbiome resides at the interface between the environment and mucosal immunity. Data from our and other laboratories indicate that bacterial composition and diversity in the lung graft correlate with inflammation and post-transplant outcomes. The microbiome is, in turn, influenced by environmental factors, including infections, pollution, gastroesophageal reflux disease (GERD) and microaspiration of gastric or oropharyngeal contents. However, these complex interactions are poorly understood. Therefore, a better understanding of how the microbiome is affected by environmental exposures and how it relates to rejection and inflammation is of paramount interest in transplantation. We postulate that microaspiration modulates the immune milieu in the lungs through its effects on the microbiome.

This project will leverage our group's combined expertise in lung transplant immunology and microbiology as well as access to a wealth of human samples from our large lung transplant program.

Overall Hypothesis: Microaspiration of gastric contents modifies the pulmonary microbiome, increasing the prevalence and relative abundance of upper gastrointestinal bacteria (such as *Prevotella, Gemella* and *Streptococcus*), which creates a proinflammatory microenvironment in the lung allograft and augments acute rejection.

Aim 1: Determine whether pulmonary bacterial composition and community diversity correlate with elevated markers of aspiration in lung samples obtained from patients with or without GERD. Microbial 16S rRNA sequencing will be correlated to patient lung fluid levels of bile acid and other markers of aspiration.

Aim 2: Determine whether microbial diversity and composition, with enrichment of upper gastrointestinal taxa, correlate with rejection and with increased lung innate immune activation. Rejection will be detected by regular biopsies performed in our patients. Innate immune activation will be quantified by measuring alarmins, neutrophil elastase, IL-6, and IL-8 and other cytokines in lung samples.

Under the guidance of MD researchers on the team, The CREMS student will collect clinical information about the patients from the Toronto Lung Transplant Program database supplemented by the medical record (this can begin during the orientation period). The student will participate in microbial gene sequencing and cytokine measurements, under the supervision of experienced technicians (aim 1 experiments will take place during summer 1 and aim 2 experiments during summer 2). During the academic years, the student will complete additional analyses required for the project, analyze data, and prepare a manuscript.

During this project, the CREMS student will become an integral part of our lung transplant immunology group (a.k.a. the CLAD team). They will interact with clinician-scientists, basic scientists, students, and technicians involved in cutting-edge microbiology, immunology and lung transplantation research. This will provide an ideal exposure to translational medical science and experience relevant to a clinician-scientist career path.

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)

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

The specific aims are outlined above. The CREMS student will be expected to acquire general knowledge about lung transplantation, transplant immunology, and the role of the microbiome. The student will perform data queries and clinical chart review in order to establish the presence of rejection or infection for each patient sample. They will also prepare and organize lung bronchoalveolar lavage samples for analysis. They will learn several analytic techniques, including ELISA and multiplex assays for cytokine detection and microbial gene sequencing. Significant focus will be placed on data analysis and interpretation in the context of the clinical scenario. The student will work directly with a medical research fellow (a clinician-scientist in training) as well as the PI. The student will also get direct technical supervision by students and technicians on the team. The student will be expected to interact with the project statistician and understand the concepts behind the statistical analyses.