Supervisor Information

Name: Minna Woo
Email: mwoo@uhnresearch.ca

Degree(s): MD FRCPC PhD SGS

Department: IMS and Immunology

Academic Rank: Professor
Field of Research: Metabolism and atherosclerosis

Research Institution Affiliation (if applicable): Toronto General Hospital Research Institute
Allocation of student contact time: one hour per wk but can be longer and more often if needed depending on the situation and the need of the student. I am usually in my lab office every day of the week and available anytime for all my lab trainees.

(number of hours per week YOU are available to the student for any concerns or to review progress)
Project Information (for posting on GDipHR website)

Title: Novel therapeutic strategies for cardiovascular disease

Description (max 500 words):

Atherosclerosis is the pathogenic process in the vasculature leading to ischemic heart disease and stroke, which remains the leading cause of death worldwide despite recent advances. Thus, understanding novel mechanisms of disease is mandated for prevention and effective therapy. Apart from conventional risk factors such as dyslipidemia, hypertension, smoking, and type 2 diabetes, inflammation plays a major emerging role in the disease process. Moreover, a recent landmark report has shown a critical role for hematopoietic clonal expansion to predispose not only to leukemia but also to cardiovascular disease!

The Woo lab has been investigating the role of Janus kinase (JAK2) signaling pathway in multiple tissues relevant for atherosclerosis. JAK2 is a major intracellular signaling node that mediates actions of many hormones and cytokines. Moreover, JAK2 is also implicated in clonal hematopoiesis. Macrophages have a pivotal role in both development and progression of the atherosclerotic lesion. We have recently found that mice lacking Jak2 specifically in macrophages have more pronounced atherosclerosis in comparison to control mice that harbour a wildtype Jak2. Similar results were found in mice lacking JAK2 specifically in the liver.

JAK2 inhibitors (specifically ruxolitinib) are already in clinical use for treatment of myeloproliferative disorders and certain autoimmune diseases, such as rheumatoid arthritis. These chronic diseases require long term therapy and affect older individuals who are often at high risk for cardiovascular disease. However, the effects of ruxolitinib on atherosclerosis is unknown. Given that deletion of JAK2 in hepatocytes or macrophages causes accelerated atherosclerosis, JAK2 inhibitors given systemically may also aggravate atherosclerosis.

A designated student will conduct experiments using macrophage cell lines and examine the effects of JAK2 inhibitors in vitro on various aspects of macrophage function, including inflammation, cholesterol uptake/efflux and apoptosis. Changes in gene and protein expression will be assessed. The student will also test the effects of JAK2 inhibition on bone marrow-derived macrophages from mice and perform experiments ex vivo. Additionally, JAK2 inhibitors will be tested in vivo in a mouse model of atherosclerosis. Ruxolitinib will be incorporated into a “western diet” for 16 weeks, and the effects on atherosclerosis will be compared to mice fed the same diet without ruxolitinib.

Overall these studies will provide translational, clinically relevant information and novel insight into molecular mechanisms of atherosclerosis. Moreover, results from proposed experiments may have relevance to individuals treated with JAK2 inhibitors. All of the research techniques to be learnt are generalizable and therefore will be widely applicable for other projects involving molecular biology and other disease models.

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

☐ YES  ☐ NO  ☐ Application Submitted  x ☐ N/A

Do you expect this work will be published within the 20 months?
 x ☐ YES  ☐ NO  ☐ Uncertain
**Student’s roles and responsibilities (please be as specific as possible):**

The student will be working closely with a senior postdoctoral research fellow (PDF). The PFD will be teaching the student all required basic techniques needed to carry out the proposed project. The student will also interact with other graduate students and fellows for support. The student will have his/her personal bench space and full access to the lab, which is equipped to perform standard molecular biology and biochemical experiments including protein, RNA and DNA analyses.

I am a senior scientist at the Toronto General Research Institute and my laboratory is located in the Princess Margaret Cancer Centre Research Tower in the MaRS complex. We have specialized equipment such as the metabolic caging system and quantitative real-time PCR machine, as well as access to the state-of-the-art microscopy facility. Our mice are housed in the same building and cared by veterinary technicians. My lab operation is currently well-supported by two grants from the Canadian Institute of Health Research and another two grants by Heart and Stroke Foundation of Canada.

The student will have his/her own desk and will have access to computers equipped with Internet, Office and required analytical software. I will meet the student weekly to review and discuss his/her experimental data and plans to ensure progress of the project. We have weekly lab meetings where a lab member presents his/her research progress and/or published research articles. The student can present at these lab meetings, which will help develop his/her scientific communication skills. The student can also have opportunities to attend other relevant seminars often given by invited national and international scholars at our research institute or at the university or other affiliated research institutes. The student may also have the opportunity to submit and present his/her work at local or international conference.

**Please indicate who will serve as the student’s direct report for daily oversight (PI, PhD student, technician, etc...):**

The student will work directly with our senior postdoctoral research fellow who will have a daily oversight of the student’s project. I will also meet with the student on a regular basis to discuss progress, interpretation of data and planning for next experiments.