



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: G. Angus McQuibban Email: angus.mcquibban@utoronto.ca

Degree: Ph.D. SGS Appointment (IMS, IHPME, LMP etc.):

Biochemistry

Academic Rank: Assoc. Prof. Field of Research: Parkinson Disease

Research Institution Affiliation (if applicable):

Allocation of student contact time (number of hours per week YOU are available to the student for any concerns or to review progress): as needed but 2 hours would be the maximum.

Project Information

Title: Identifying therapeutics for Parkinson Disease

Description (max 500 words):

Goal of proposed research: Currently there is no cure for Parkinson's disease (PD) but only limited applications to treat the devastating symptoms. We will identify and characterize small molecules that restore mitochondrial health by targeting the key pathologic etiology in PD.

Background: Mitochondria are essential organelles that are subject to a tightly regulated quality control system termed mitophagy. Mitophagy is the selective removal of damaged mitochondria by autophagy. Several recent studies have indicated a direct role for mitochondrial dysfunction in the etiology of Parkinson's disease. Interestingly, the proteins that orchestrate mitophagy are genetically-linked to PD, most notably a protein called Parkin. Recessive mutations in *PARK2*, the gene that encodes Parkin, account for ~50% of autosomal-recessive juvenile Parkinson's. Several lines of evidence have also demonstrated Parkin's involvement in the development of sporadic PD. Loss of dopaminergic neurons in the *substantia nigra* is the main pathological manifestation of PD, and Parkin has been shown to be neuroprotective in these cells and can restore synaptic function. Thus, Parkin-dependent mitochondrial quality control and neuronal survival pathways represent clear therapeutic targets for PD.

Research aims: We have engineered and optimized a phenotypic cell-based screen to identify small molecules that enhance the activity of wild type Parkin and/or restore the activity of specific disease-causing Parkin mutants. The basis of the screen is to identify compounds that accelerate the recruitment of wild-type or mutant Parkin to damaged mitochondria, where they can designate mitochondrial proteins for degradation. This project has 4 main aims representing methodologies and assays that are already in place in my lab.

1) Small molecule screening; We will screen several collections of small molecules, representing pathways that impinge on mitochondrial health and also collections of already approved FDA-drugs and drug-like molecules with the overall goal of repurposing.

2) Target/pathway validation; We have well established secondary assays in which to test the best hits from the primary screen. These include stabilization/clearance of mitophagy specific proteins, mitochondrial activity and most importantly Parkin activity

3) Efficacy testing in *Drosophila*; We have developed *Drosophila* models of PD that compliment the strategy of the primary screen. The efficacy of our best hits from aims 1 and 2 will be tested for their ability to reverse disease phenotypes in this well-established animal model of PD.

If human subjects are involved, have Ethics been obtained?

YES NO Application Submitted x N/A

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

YES NO x 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...)

PI will be student's direct report.

Student will be involved in all aspects of the project as described and based on interest. Skills include mammalian cell culture, microscopy, data analysis, Western blotting, Drosophila husbandry, behavioral assays.