



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: Dr. Martha Brown

Email: martha.brown@utoronto.ca

Degree: Ph.D.

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

Academic Rank: Associate professor

Field of Research: Virology

(Virus-cell interactions; adenovirus; antiviral agents)

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):

~5-6 hours per week



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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: Dr. Alan Cochrane

Email: alan.cochrane@utoronto.ca

Degree: Ph.D.

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

Academic Rank: Professor

Field of Research: Virology (HIV, antiviral agents)

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):

~5-6 hours per week from July 1, 2018 onwards

Project Information

Title: Antiviral Agents against Human Adenovirus

Description (max 500 words):

Despite the morbidity and mortality associated with viral infections, there are few antiviral agents available for treatment. Adenovirus is a common human pathogen which typically causes self-limited influenza-like illness but can cause severe pneumonia even in immunologically competent people and can spread to cause disseminated disease, including hepatitis, in immunocompromised patients. Mortality in severe cases can be 50%. Clearly, it would be beneficial to have an effective antiviral agent to use in these patients. We have been working with a number of agents that exhibit a potent antiviral effect against human adenovirus in cell culture, reducing the yield of progeny virus by more than 100-fold in the continuous A549 (lung epithelial) cell line. We are interested in characterizing the mechanism of antiviral action against adenovirus in A549 cells as well as in differentiated cultures of primary human nasal epithelial cells (hNEC) grown at air-liquid interface as a model for respiratory epithelium. One of the agents blocks infection early in the virus replication cycle, by reducing expression of viral genes encoding proteins essential for viral genome replication. With insufficient levels of those key proteins, subsequent viral genome replication and synthesis of virion capsid proteins is blocked. Another agent interferes at a step even earlier in the replication cycle, reducing the synthesis of even the first viral protein that normally is produced in infected cells. The apparent difference in mechanism of action of these two agents against adenovirus replication likely reflects their different targets within the host cell. Further experiments will look more closely at transcription of viral genes, processing of viral RNAs, and their translation. One of the antiviral agents inhibits spread of progeny virus within hNEC grown at air-liquid interface (ALI) as shown by fluorescence microscopy for detection of infected cells. A similar effect *in vivo* would be beneficial to the patient. Experiments in hNEC ALI cultures will examine the kinetics of virus replication and spread with and without drug. Overall, experiments in A549 cells and in hNEC cultures should further characterize the mechanisms by which these two agents block adenovirus replication and should provide a solid basis for translation to *in vivo* models and, ultimately, clinical trials.

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)

The student will do experiments, planned in consultation with the PIs, interpret results and participate in design of the subsequent experiments. The student will be trained in the appropriate techniques which will include cell culture, propagation and assay of adenovirus, protein gel electrophoresis, immunoblot analysis, RT-qPCR (reverse transcriptase – quantitative PCR). The student will have regular interactions with the PIs, to interpret results and design subsequent experiments.

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

For the first six months (Jan – June 2018), M. Brown will be the only PI while Alan Cochrane is on sabbatical. For the remaining time (July 2018 onwards), the student will report to both PIs.

Please sign and date below as acknowledgement of expectations and understanding of Program commitments.

MARTHA BROWN

Alan Cochran

Supervisor Name

Martha Brown

Signature

11/02/2017

Date