(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: David MALKIN

Email: david.malkin@sickkids.ca

Degree: MD

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

Academic Rank: Full Professor

Field of Research: Cancer Genetics

Research Institution Affiliation (if applicable): The Hospital for Sick Children

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

At least 10 hours/week in the lab (I am in the lab 4 days/week). In addition, the student will have contact time in my weekly pediatric cancer genetics/solid tumor clinic (~ 5.5 hours/clinic/week).
**Project Information**

Title: Pharmacologic prevention of cancer in Li-Fraumeni Syndrome

Description (max 500 words): Li-Fraumeni Syndrome (LFS) is a highly penetrant cancer predisposition syndrome caused by a germline mutation in the TP53 tumor suppressor gene. TP53 mutation carriers develop multiple early onset cancers across all organ sites. While surveillance protocols have proven effective in early tumor detection, primary prevention of cancer in these patients has not, to date, been achieved. In collaboration with Dr. Ran Kafri (Dept. Molecular Genetics), we have developed an innovative technology to assess the effect of agents that restore mutant p53 to ‘normal’ function in both skin-derived fibroblast cultures from LFS patients as well as trp53-mutant mice that recapitulate the human cancer phenotype. Through several international collaborators, we have access to five distinct agents (novel peptides and promising drugs) that have been shown to either modify the conformation of mutant p53 to bury its mutant epitope – allowing it to regain normal function, or that activate the mutant p53 allele to wildtype function.

Using these tools, the student will work closely with the PI(s), Research Associate and Graduate students to 1) learn the technologies of live cell microscopy and cell culture (this can be achieved within 4 weeks of starting the CREMS training); 2) treat fibroblasts with one of the specific p53 activators (this aim can be achieved through the 1st summer of the program); and 3) treat the mutant mice with the same activator (this latter aim will be achieved through the duration of the CREMS program). Specifically, the student will be assigned a unique project within the framework of current similar projects being carried out by 2 graduate students and one post-doc – each of whom is tackling a specific one of the agents available to us. In this manner, the student will be well-mentored in the use of the technologies, while at the same time having their own ‘project’ focusing on the agent that they are working with. Based on our preliminary data to date, it is anticipated that these agents will be effective in reversing or slowing the transforming effects of mutant p53 in these culture and in vivo systems. Thus, the potential to translate these studies into clinical utility is promising.

Throughout the project, the student will not only gain in depth understanding of the fundamental genetic and biologic basis of p53 and Li-Fraumeni syndrome, but he/she will also have the opportunity to meet and examine LFS patients in my weekly cancer genetics clinic (this would be most feasible during the summer based on the student’s school schedule). The insights gained here will complement the work in the lab – particularly with respect to discussions of therapeutic challenges for patients with LFS as well as the ongoing early tumor detection strategies based on the “Toronto Protocol” that we instituted,
and that is now used around the world, several years ago. Overall, the project provides the student experience in both the basic and clinical aspects of translational medicine.

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…)*

As described above, the student will work under close direct supervision by 2 graduate students, one research associate and one post-doctoral fellow on the project. Specifically, the graduate students will teach and supervise the generation and maintenance of cell cultures. During the school year, this will be particularly important as the grad students can maintain the cultures on days when the CREMS student is doing their medical school activities. The research associate has several years experience in live cell microscopy – particularly with the unique system established in our labs. Therefore, the CREMS student will be directly supervised by the RA for this technical aspect of the project. The post-doctoral student will directly supervise the aspects of the project related to the murine studies – treatment of the mice, evaluation of tumor latency and outcome.

The CREMS student will be responsible for establishing cell cultures from 3-5 skin derived LFS fibroblasts, learning how to treat the cells with the p53 activator, learning techniques of colony forming assay, induction of DNA damage, and measurements of growth arrest, apoptosis and other markers of p53 function. The student will also apply the live cell microscopy techniques to their cell treated cell lines. Beginning in the 1st summer, the student will learn how to treat the p53 mutant mice with the agent and monitor the mice for tumor formation – which can be done throughout the second year on a
weekly basis. Finally, and importantly, the student will be responsible as primary author on a manuscript to be generated describing their work, with the intention of submitting this to a peer-reviewed journal.

Within the context of the cancer genetics clinics, the student will be supervised directly by myself, occasionally with assistance from one of the senior pediatric oncology or cancer genetics fellows. During the clinics, the student will be able to see patients (supervised) to learn to take clinical history and physical examination – focusing particularly on unique aspects related to cancer risk. Depending on the nature of the clinic, the student may have an opportunity to write a case report, if the opportunity arises with a unique and informative clinical scenario.

Throughout the CREMS period, the student will meet with me weekly (usually before or after the clinic) and will attend weekly lab meetings. The student will also have the opportunity to attend and participate in other academic seminars/rounds that are relevant to their project and training.

At the end of April 2018, we are hosting the 4th International Li-Fraumeni Syndrome Symposium with 45 invited faculty including almost all of the major research scientists in the field of p53, Li-Fraumeni syndrome and cancer genetics. The student will have the opportunity to attend this symposium which will be ideal timing prior to starting to formally engage in the project.